CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Cabozantinib (Cabometyx) for Hepatocellular Carcinoma

April 22, 2020

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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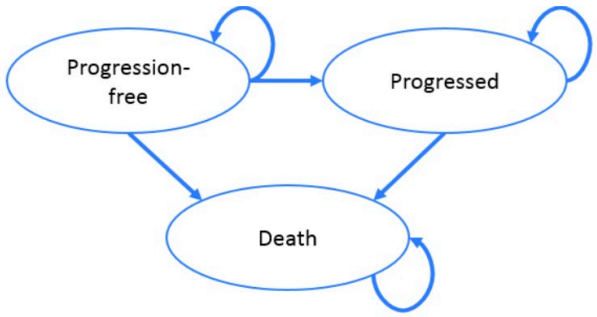
1 ECONOMIC GUIDANCE IN BRIEF

The economic analysis submitted to pCODR by Ipsen Pharmaceuticals Inc, compared cabozantinib plus best supportive care to placebo plus best supportive care for patients with hepatocellular carcinoma after prior therapy. The model specifies the following three populations for analysis: cabozantinib plus BSC versus placebo plus BSC for all 2nd and 3rd line patients, as per the CELESTIAL trial, cabozantinib plus BSC versus placebo plus BSC for sorafenib as only prior therapy population, and cabozantinib plus BSC versus regorafenib plus BSC for the sorafenib as only prior therapy population.

1.1 Submitted Economic Evaluation

Table 1: Submitted Economic Model	
The reimbursement request is for cabozantinib for patients with advanced hepatocellular carcinoma who have been previously treated.	The clinical data for the model is based on 2 main sources. For comparisons between cabozantinib and best supportive care, clinical input data were based on the CELESTIAL trial. For comparisons between cabozantinib and regorafenib, a matched adjusted indirect comparison (MAIC) was used to derive clinical data for the population of patients who received sorafenib as the only prior therapy. 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. Two populations were evaluated: a) Patients previously treated with sorafenib only (subgroup of CELESTIAL trial) • cabozantinib plus BSC versus best supportive care (BSC) • cabozantinib plus BSC versus regorafenib plus BSC b) 2nd and 3rd line patients (all patients in CELESTIAL) • cabozantinib plus BSC versus best supportive care Note that the sorafenib only population is not representative of the entire funding 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.
Type of Analysis	Cost utility analysis
Type of Model	Three state partitioned-survival model
Comparator	a) Patients previously treated with sorafenib only: BSC, regorafenib b) 2nd and 3rd line patients: BSC

Year of costs	*2019*
Time Horizon	*10 years*
Perspective	*Public Health Care Payer*
Cost of cabozantinib	• Unit cost $8800.00 per pack of 30, 20, 40 and 60mg pills. • Based on recommended fixed dosing of 60mg per day, the cost of cabozantinib is: a) $8,213.00 per 28 days b) $293.00 per day *As per the sponsor's submitted pharmacoeconomic model, the per day cost of cabozantinib is $250.80 is based on a dose interruption adjustment.
Cost of regorafenib	• Unit cost $6,100.00 per pack of 84 40mg pills, • Based on recommended dosing of 160mg daily for 3 weeks, then 1 week off medication, the cost of regorafenib alone is: • $6,100.00 per 3-week cycle • $6,100.00 per 28 days • $217.86 per day *As per the sponsor's submitted pharmacoeconomic model, the per day cost of regorafenib, based on a 21-day cycle, is $290.47.
Cost of best supportive care	Assumed to consist of the following per day: ODB based unit costs were applied to each daily dose. This resulted in best supportive care costs of: • $440.72 per 28 days • $15.74 per day
Model Structure	A proportion of patients are in one of 3 health states during each weekly cycle of the model: 1) alive and progression free; 2) alive with progressed disease; 3) dead. The proportion in each health state is determined by overall survival estimates and progression free survival estimates over time. 

Key Data Sources[1-3]	CELESTIAL, a randomized controlled trial, which compared cabozantinib to best supportive care in patients with advanced hepatocellular carcinoma who were previously treated. Data from this trial were used to derive the following for comparisons of cabozantinib versus, best supportive care: • Overall survival (OS) • Progression free survival (PFS) • Time to treatment discontinuation • Adverse events • Utility values ○ Same utility values applied in comparison of cabozantinib versus. regorafenib Match Adjusted Indirect Comparison, an indirect comparison using data from the CELESTIAL trial and the RESORCE trial. These data were used to derive the following for comparisons of cabozantinib and regorafenib. • Overall survival • Progression free survival • Adverse events

1.2 Clinical Considerations

- The CGP unanimously concluded that there is net clinical benefit for cabozantinib for advanced HCC patients, ECOG 0-1, with Child Pugh A liver function previously treated with an oral TKI (sorafenib or lenvatinib).

- The CGP concluded that cabozantinib demonstrated a benefit in PFS and OS in the subset of patients who had 2 prior systemic therapies and that patients with preserved performance status and liver function would derive clinical benefit from cabozantinib in this setting.

- The CGP noted that the matched indirect comparison (MAIC) of cabozantinib and regorafenib demonstrated similar OS with both agents.; however due to the limitations identified and the lack of statistical testing for OS, the CGP concluded that the comparative efficacy of cabozantinib versus regorafenib is uncertain.

Summary of registered clinician input relevant to the economic analysis

Clinicians providing input indicated that there is currently a significant unmet need for HCC patients. Based on the results of the CELESTIAL trial, clinicians agreed that cabozantinib is an effective treatment for patients with advanced HCC who have been previously treated with sorafenib. Cabozantinib has been demonstrated to have a larger survival benefit (OS) compared to regorafenib, along with significantly longer progression-free survival (PFS), and a similar adverse effect profile compared to other TKIs used in the HCC setting such as regorafenib and sorafenib.

- Overall survival, progression free survival, and adverse events are incorporated in the economic analysis.

Summary of patient input relevant to the economic analysis

From a patients' perspective, patients value increased survival and control of symptoms and side-effects, as HCC has a significant impact on the quality of life of patients. Patients expressed a desire for a sufficient level of independence to allow them to continue with their daily activities. HCC prognosis is generally poor as the disease is often diagnosed at a late 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 quality of life due to significant side-effects

- PFS, OS, adverse events and quality of life were incorporated into the model.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for cabozantinib which are relevant to the economic analysis:

- PAG noted that Cabozantinib is available in 20, 40, and 60mg tablets. The price per tablet is the same regardless of the dosage. The availability of three different strengths is an enabler for ease of dose adjustments. Dose adjustment can be accomplished by changing the tablet strength dispensed, PAG identified that this may result in drug wastage of previously dispensed tablets of a higher strength.
    - *The EGP reanalysis accounts for drug wastage of Cabozantinib by assuming that the 62% of patients who had a dose reduction in CELESTIAL would waste a half of a prescription period (assumed to be 28 days) worth of medication*
- PAG identified regorafenib as a relevant comparison and indicated interest in receiving data comparing cabozantinib with regorafenib for patients who had received prior treatment with sorafenib
    - The economic analysis includes a comparison between cabozantinib and regorafenib using data from a match adjusted Indirect comparison (MAIC)

1.3 Submitted and EGP Reanalysis Estimates

The main cost drivers of the sponsor's model were drug acquisition costs, and time on treatment. The main drivers of the clinical outcomes of the model (QALYs, Life Years) were: 1) overall survival estimates; 2) progression free survival estimates; 3) the time horizon used in the model, and 4) the utility values assigned to patients over the duration of the model's time horizon. Overall the approach taken in the economic evaluation was reasonable and appropriate.

Prior Treatment with Sorafenib Only Population

Table 2: Submitted and EGP Estimates: sorafenib only population: Cabozantinib plus BSC versus BSC Probabilistic (5000 Iterations)*

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
ICER estimate ($/QALY)	$238,889	$285, 931	$428, 706
ΔE (QALY)	0.343	0.34	0.20
ΔE (LY)	0.44	0.17	0.12
ΔC ($)	$81,939	$98, 041	$84, 896

*The proportion of simulations where incremental QALYs were negative (Cabozantinib had lower QALYs than best supportive care) were: 0.00 in the submitted model, 0.00 in the EGP best case scenario and 0.00 in the EGP worst case re-analysis

Table 3: Submitted and EGP Estimates: sorafenib only population: Cabozantinib plus BSC versus Regorafenib, Probabilistic (5000 Iterations)

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
ICER estimate ($/QALY)	$163,111	$250, 053	$320, 500
ΔE (QALY)	0.13	0.13	0.09
ΔE (LY)	0.17	0.20	0.12
ΔC ($)	$20,630	$32,015	$30,032

*The proportion of simulations where incremental QALYs were negative (Cabozantinib had lower QALYs than Regorafenib) were: 0.20 in the submitted model, 0.20 in the EGP best case scenario and 0.18 in the EGP worst case re-analysis

Table 4: Submitted and EGP Estimates: 2nd and 3rd line population (entire CELESTIAL population): Cabozantinib plus BSC versus BSC, Probabilistic (5000 Iterations)*

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
ICER estimate ($/QALY)	$253,626	$302,298	$442,810
ΔE (QALY)	0.287	0.29	0.17
ΔE (LY)	0.369	0.37	0.22
ΔC ($)	$72,752	$86,564	$77,422

*The proportion of simulations where incremental QALYs were negative (Cabozantinib had lower QALYs than best supportive care) were: 0.00 in the submitted model, 0.00 in the EGP best case scenario and 0.00 in the EGP worst case re-analysis

The main assumptions and limitations with the submitted economic evaluation were:

- Lack of comparative data between cabozantinib and regorafenib in the sorafenib only population : Direct comparative evidence was not used to estimate and project differences in overall survival or progression free survival between cabozantinib and regorafenib. Instead, a matched indirect comparison (MAIC) was used to estimate comparative efficacy. The Methods team and CGP identified a number of limitations with the MAIC. They noted that there were differences in patient characteristics between cabozantinib and regorafenib patients including ECOG performance status, number of prior treatments and duration of prior sorafenib treatments. Additionally, details were lacking on study eligibility criteria and study methods. Though statistically significant differences were found in progression free survival using the MAIC, the difference in overall survival was not statistically significant. This is reflected in the sponsor's base case analysis where 20% of the simulations showed cabozantinib to be less effective (lower QALYs) than regorafenib. Overall survival and progression free survival projections are a big driver when estimating relative QALYs and cost-effectiveness between comparative treatments. The lack of direct evidence of comparative overall survival and progression free survival creates high uncertainty around the cost-effectiveness of cabozantinib compared to regorafenib.

- Time Horizon: The submitted model uses a 10-year time horizon. Based on the CELESTIAL trial, the median survival with cabozantinib was approximately 1 year. Using such a long-time horizon can lead to erroneous predictions of long-term overall survival and progression free survival based on extrapolation of trial data with limited follow-up. Considering expected survival duration in this population of patients, the CGP felt that a 5-year time horizon was more appropriate. The 5 year overall survival rates for cabozantinib and BSC in the model was less than 10% and less than 5%, respectively.

- Overall survival model used to extrapolate overall survival in comparisons of cabozantinib and best supportive care: The log-logistic model was used to estimate overall survival in comparisons of cabozantinib and best supportive care (sorafenib only, 2nd and 3rd line population). As noted by the sponsor, both the generalized gamma and log-logistic model were appropriate based on statistical fit. The log-logistic model was chosen based on visual inspection and input from key opinion leaders. Though visual inspection and clinical validity should be taken into consideration, decisions based on them may be subjective. One of the reasons provided for dismissing the generalized gamma model was that the curves crossed over at around 4-5 years. However, this is not inconsistent with the observed Kaplan-Meir curves from CELESTIAL, in which OS curves of cabozantinib and best supportive care nearly converge after 2 years. The CGP compared the log

logistic and generalized gamma survival for clinical validity. The CGP thought that the generalized gamma OS survival curve was more realistic as it showed convergence of OS for cabozantinib and best supportive care between 4 and 5 years while the log logistic model showed continued comparative survival benefits up to 10 years.

- Overall survival model used to extrapolate overall survival in comparisons of cabozantinib and regorafenib: The log-logistic model was chosen to estimate overall survival in this comparison. The log normal model had the best statistical fit for regorafenib based on combined AIC and BIC. The Weibull model had the best statistical fit for the unweighted cabozantinib data. The manufacture stated that the log-normal performed poorly based on statistical fit for cabozantinib and that the Weibull model has a "mediocre fit" with regorafenib. The sponsor stated that the log-logistic model was chosen because it fit both the regorafenib and cabozantinib data well. The generalized gamma model was not considered despite having the best statistical fit for (AIC and BIC) the weighted cabozantinib data. The CGP reviewed the overall survival curves for clinical validity based on the following models: 1) log-logistic, 2) log normal,3)Weibull, 4) generalized gamma. The CGP did not that there was a specific OS model that was most clinically valid.

- Dose interruption acquisition cost discount: The model applies a 14.5% discount on the drug acquisition cost of cabozantinib to account for dose interruption. 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 4-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.

- Monthly half cycle drug acquisition cost adjustment: The submitted model has an adjustment for drug acquisition costs that reduces costs to account for patients stopping treatment before the end of each monthly cycle. However, the cycle length is short enough (1 month) that this adjustment should not be necessary.

- Potential drug wastage due to dose reduction with cabozantinib: PAG raised concerns about the potential for drug wastage due to dose switching. The concern is that if patients switch to a lower dose due to side effects, the remainder of the pills from their previous higher dosage prescription would be wasted.

- Time to Treatment discontinuation (TTD) in the cabozantinib versus regorafenib comparison: In the cabozantinib versus regorafenib comparison the model assumes TTD to be the same as PFS. However, in the CELESTIAL trial, patients could receive cabozantinib after radiological progression as long as patients derive clinical benefit (even after disease progression by RECIST). As a result, this assumption does not account for treatment beyond progression and the additional proportion of patients who would continue to take cabozantinib. or regorafenib. PFS was likely used due to lack of TTD data for regorafenib.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

- Time Horizon: As part of their re-analysis, the EGP shortened the time horizon from 10 years to a 5-year time horizon.

- Monthly half cycle correction drug acquisition cost adjustment: The EGP removed the sponsor's adjustment for drug stoppage occurring halfway each cycle from the model in its re-analysis.

- Cabozantinib cost discount for dose interruption: The EGP removed the 14.5% discount applied to cabozantinib for dose interruption.

- Overall survival curve used in comparisons between cabozantinib and best supportive care: The EGP evaluated the model using the generalized gamma overall survival model in the comparisons between cabozantinib and best supportive care (sorafenib only population, 2nd and 3rd line population. For this reanalysis, the model is adjusted so that the overall survival for best supportive care is never higher than overall survival for cabozantinib.

- Overall survival curve used in comparisons between cabozantinib and regorafenib: The EGP evaluated the model using a number of alternative overall survival models in the comparison between cabozantinib and regorafenib. These OS models include: 1) log-normal; 2) Weibull; 3) generalized gamma. Because the CGP did not feel that any specific OS model was the more clinically valid than the OS model used in the sponsors' base case (log-logistic), the alternative OS models are not used as part of the EGP's best or worst case scenarios. However, model results using each alternate OS model are shown in order to provide a more complete picture of the impact of OS model choice on cost-effectiveness results.

- Cabozantinib drug wastage from dose reductions: The EGP included drug wastage of cabozantinib due to dose reductions. In the CELESTIAL trial, 62% of cabozantinib patients had dose interruptions. In the re-analysis, we assume that cabozantinib is dispensed with 30-day prescriptions. Therefore, we assume that 62% of cabozantinib patients will have a total of 15 days of drug wastage.

Table 5 provides a summary of ICERs for the various populations and comparators using pairwise analysis. Table 6 presents a summary of ICERs for the sorafenib only population using sequential analysis.

Table 5: Summary of Submitted and EGP Estimates of ICER ($/QALY) by population and comparator-pairwise analysis, Probabilistic (5000 Iterations)

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
Sorafenib only			
cabozantinib plus BSC versus best supportive care	$238,889	$285,931	$428,706
cabozantinib plus BSC versus regorafenib plus best supportive care	$163,111	$250,053	$320,500
2nd and 3rd line population			
cabozantinib plus BSC versus best supportive care	$253,626	$302,298	$442,810

Table 6: Summary of Submitted and EGP Estimates of Sequential ICER ($/QALY) for sorafenib only population, Probabilistic (5000 Iterations)

Estimates	Submitted	EGP Reanalysis	
		Best Case Scenario	Worst Case Scenario
Sorafenib only			
Best supportive care	Reference	Reference	Reference
Regorafenib plus BSC	extendedly dominated	extendedly dominated	extendedly dominated
Cabozantinib plus BSC	$238,889	$285,931	$428,706

Detailed cost-effectiveness results from the EGP re-analysis are provided in Tables 7 to 9.

Table 7: Cost-effectiveness results from EGP reanalysis: Sorafenib only population. Cabozantinib plus BSC versus Best Supportive Care Probabilistic (5000 Iterations)

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1.Basecase	$81,939	0.35	$238,889	
2. Change time horizon from 10 years to 5 years	$76,306	0.29	$267,664	$28,775
3. Remove sponsor's half cycle drug acquisition cost adjustment	$85,633	0.34	$249,723	$10,834
4. Remove 14.5% dose interruption discount on cabozantinib acquisition cost	$93,699	0.34	$273,494	$34,605
5. Use generalized gamma overall survival model	$71,114	0.20	$360,262	$121,373
6. Add drug wastage adjustment to account for cabozantinib dose switching	$84,827	0.34	$246,320	$7,431
Best estimate				
Low range of best estimate of cost effectiveness (includes changes in 3, and 4)	$98,041	0.34	$285,931	$47,042
High range of best estimate of cost effectiveness (includes changes in 2, 3, 4 and 5)	$84,896	0.20	$428,706	$189,817

Table 8: Cost-effectiveness results from EGP reanalysis: Sorafenib only population. Cabozantinib +BSC versus Regorafenib + BSC Probabilistic (5000 Iterations)

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1.Basecase	$20,630	0.13	$163,111	
2. Change time horizon from 10 years to 5 years	$18,662	0.09	$197,629	$34,518
3. Remove sponsor's half cycle drug acquisition cost adjustment	$22,095	0.12	$178,792	$15,681
4. Remove 14.5% dose interruption discount on cabozantinib acquisition cost	$29,929	0.13	$231,886	$68,775
5. Use log-normal overall survival curve	$22,227	0.15	$146,875	-$16,236
6. Use Weibull overall survival curve	$21,790	0.14	$158,480	-$4,631
7. Use generalized gamma overall survival curve	$12,089	0.01	$877,951	$714,840
8. Add drug wastage adjustment to account for cabozantinib dose switching	$22,752	0.13	$175,084	$11,973
Best estimate				
Low range of best Estimate of cost effectiveness (includes changes in 3, and 4)	$32,015	0.13	$250,053	$86,942
High range of best estimate of cost effectiveness (includes changes in 2, 3, and 4)	$30,032	0.09	$320,500	$157,389

Table 9: Cost-effectiveness results from EGP reanalysis: 2nd and 3rd line population. Cabozantinib plus BSC versus Best Supportive Care, Probabilistic (5000 Iterations)

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1.Basecase	$72,752	0.28	$253,626	
2. Change time horizon from 10 years to 5 years	$67,649	0.23	$287,925	$34,299
3. Remove sponsor's half cycle drug acquisition cost adjustment	$75,901	0.29	$265,366	$11,740
4. Remove 14.5% dose interruption discount on cabozantinib acquisition cost	$83,011	0.29	$288,122	$34,496
5. Use generalized gamma overall survival model	$64,774	0.18	$352,208	$98,582
6. Add drug wastage adjustment to account for cabozantinib dose switching	$74,791	0.28	$266,403	$12,777
Best estimate				
Low range of best Estimate of cost effectiveness (includes changes in 3,4)	$86,564	0.29	$302,298	$48,672
High range of best estimate of cost effectiveness (includes changes in 2, 3, 4 and 5)	$77,422	0.17	$442,810	$189,184

1.5 Evaluation of Submitted Budget Impact Analysis

Table 10: Cost-effectiveness results varying discount on Cabozantinib price, Probabilistic (5000 Iterations)

	Best Case Incremental			Worst Case Incremental		
	Costs	QALYs	$/QALY	Costs	QALYs	$/QALY
Sorafenib only population						
Cabozantinib plus BSC versus best supportive care						
Rx price reduction						
25%	$77,865	0.34	$226,078	$64,427	0.19	$332,755
50%	$55,366	0.34	$161,792	$44,411	0.20	$226,184
75%	$36,206	0.34	$105,435	$24,416	0.19	$126,698
Cabozantinib plus BSC versus regorafenib plus BSC						
Rx price reduction						
25%	$14,229	0.13	$113,699	$11,952	0.09	$127,228
50%	-$3,493	0.13	Dominant	-$6,123	0.09	Dominant
75%	-$21,847	0.13	Dominant	-$23,261	0.10	Dominant
2nd and 3rd line population						
Cabozantinib plus BSC versus best supportive care						
Rx price reduction						
25%	$68,770	0.29	$239,386	$59,480	0.17	$342,968
50%	$49,528	0.29	$171,436	$41,223	0.18	$235,095
75%	$31,001	0.29	$106,631	$22,874	0.18	$129,638

The overall approach of the BIA appears to be reasonable. 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 (CELESTIAL) and regorafenib (RESORCE) to calculate medication budgetary costs. 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. Therefore, the budget impact may be underestimated. The sponsor used mean time on treatment as part of their sensitivity analysis.

1.6 Conclusions

Prior Sorafenib only population

Cabozantinib plus BSC versus Best supportive Care

- The EGP's best estimate of the incremental cost per QALY of cabozantinib compared to best supportive care ranges between $285,931 and $428,706.

- The EGP's best estimate of the incremental cost of cabozantinib compared to best supportive care ranges between $84,896 and $98,041. Incremental costs were most impacted by drug acquisition costs.

- The EGP's best estimate of the incremental QALY's gained of cabozantinib compared to best supportive care ranges between 0.20 and 0.34. Incremental QALYs were most impacted by overall survival estimates and time horizon.

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.

- The EGP's best estimate of the incremental cost of cabozantinib compared to regorafenib ranges between $30,032 to $32,015. Incremental costs were most impacted by drug acquisition costs.

- The EGP's best estimate of the incremental QALY's gained of cabozantinib compared to regorafenib ranges between 0.09 and 0.13. Incremental QALYs were most impacted by overall survival estimates and time horizon.

2nd and 3rd line population

Cabozantinib plus BSC versus Best Supportive Care plus BSC

- The EGP's best estimate of the incremental cost per QALY of cabozantinib compared to best supportive care ranges between $302,298 and $442,810.

- The EGP's best estimate of the incremental cost of cabozantinib compared to best supportive care ranges between $77,422 and $86,564. Incremental costs were most impacted by drug acquisition costs.

- The EGP's best estimate of the incremental QALY's gained of cabozantinib compared to best supportive care ranges between 0.17 and 0.29. Incremental QALYs were most impacted by overall survival estimates and time horizon.

Overall conclusions of the submitted model:

The overall structure and most assumptions in the model were appropriate. For the best-case scenario, the sponsor's chosen overall survival model 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. A major limitation of the cost-effectiveness analysis between cabozantinib and regorafenib was the reliance on an indirect comparison to derive overall and progression free survival estimates. 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. The time horizon and choice of overall survival models impacted incremental QALYs for both cost-effectiveness analyses.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Gastrointestinal Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of cabozantinib (Cabometyx) for hepatocellular carcinoma (HCC). A full assessment of the clinical evidence of cabozantinib (Cabometyx) for HCC is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no information redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revision was made in between posting of the Initial and Final Economic Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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