CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Midostaurin (Rydapt) for Systemic Mastocytosis

April 2, 2020

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Novartis Pharmaceuticals Canada Inc.** compared midostaurin (Rydapt™) to standard of care (SOC) defined as a combination of available therapies (e.g., interferon, hydroxyurea, cladribine, and cytarabine) used off-label for adult patients with aggressive systemic mastocytosis (ASM), systematic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL), collectively termed advanced systemic mastocytosis (advSM). Midostaurin is the only Health Canada approved treatment for patients with advSM regardless of KIT mutation status.

The clinical effectiveness of midostaurin for patients with advSM was primarily informed by an international, multicenter, open-label, single-arm, phase 2 study (CPKC412D2201, Gotlib et al., 2016)[1] reporting on the overall survival (OS), secondary endpoint, and the overall response rate (ORR), primary endpoint, for midostaurin (100 mg twice daily in 4-week continuous cycles).

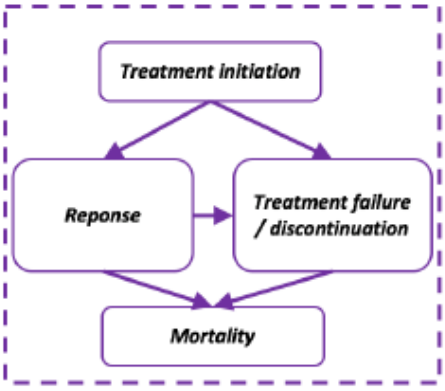
In the model, the OS curve for midostaurin was based on the Kaplan-Meier survival data reported in trial 2201 (Gotlib et al., 2016).[1] For SOC, the OS curve was determined by hazard mapping using the hazard ratio (HR) collected from a study that compared survival in patients on midostaurin (a French compassionate use program) vs. French historical control subjects, which were matched by disease class and age at diagnosis (Chandesris et al., 2016).[2] Survival beyond the study follow-up period in trial 2201(Gotlib et al., 2016)[1] was extrapolated using a piecewise lognormal parametric extrapolation. The parametric functional form was chosen based on overall fit by AIC/BIC.

The treatment duration (TD) curve for midostaurin was also determined by fitting a Kaplan-Meier plot to patient-level data from trial 2201, while the TD curve for SOC was determined though hazard mapping by using the ratio of ORRs for midostaurin vs. SOC (collected from studies of cladribine and interferon)[3,4] as a proxy for the hazard ratio (HR). The ORR was then applied to the proportion of patients "on treatment" to determine the proportion in the "responder on treatment" vs. "treatment discontinuation/failure" at each monthly cycle.

Health-related quality of life (HR-QoL) data were also obtained from trial 2201 (Gotlib et al., 2016)[1] for the health states considered in the model (**Figure 1**). Health state utilities (derived from the 2201 trial) were applied to both the SOC and midostaurin arms, therefore, differences between the two therapies with respect to HR-QoL were assumed to result only from the differences in the time spent in each health state (e.g., responder, treatment failure).

Table 1. Submitted Economic Model

Reimbursement Request/Patient Population Modelled	*The target population is assumed to be identical to that of the CPKC412D2201 trial population, which matches the reimbursement request* *Mean age: 64 (range: 25-82)* *Male: 57%* *No prior treatment: >50%* *Subtype: SM-AHN: 57/89, ASM:16/89, MCL:16/89* *Most common measurable C-findings:* • *Thrombocytopenia: 62%* • *Anemia: 31%* • *Transfusion-dependent anemia: 22%* • *Hypoalbuminemia: 54%* • *Hyperbilirubinemia: 28%*

Type of Analysis	*Cost-effectiveness (CEA) and cost-utility (CUA) analyses*
Type of Model	*Partitioned-survival model*
Comparator	*SOC (cladribine, interferon, cytarabine, hydroxyurea)*
Year of costs	*2019*
Time Horizon	*10 years*
Perspective	*Government (public payer perspective)*
Cost of Midostaurin	*Midostaurin (Rydapt™) costs $167.92 per 25 mg capsule.* *At a recommended dose of 100 mg twice daily, midostaurin costs $1,343.40 per day* *28-day cycle cost: $37,615.16*
Cost of standard care (SOC)	*Cladribine costs $4.00/1 mL vial (1 mg/mL)* *Cytarabine costs $0.06/500 mg vial)* *Interferon costs $33.99/0.5 ml vial (3 MMU/mL)* *Hydroxyurea costs $1.02/500 mg capsule* *Per 28-day cycle drug costs are:* *Cladribine costs $199.68* *Cytarabine costs $0.46* *Interferon costs $407.88* *Hydroxyurea costs $81.49* *28-day cycle costs of SOC (weighted average):* $308.73
Model Structure	*The model comprised of four health states:* *1) treatment initiation* *2) responder on treatment* *3) treatment failure/discontinuation* *4) mortality* ***Figure 1: Figure showing model structure, as taken from submission to pCODR:*** 
Key Data Sources	*Clinical data on OS, treatment duration and adverse events were collected from a single-arm CPKC412D2201 trial for midostaurin.[1] The ORR data was collected by pooling literature-based estimates for SOC and midostaurin. The Hazard ratio for*

	overall survival was collected from Chandesris et al,[2] where patients on midostaurin were matched to control subjects by age at diagnosis and disease subtype. Costs were obtained from the Ontario Case Costing Initiative (OCCI), Ontario health insurance plan (OHIP) and published Canadian costs where available. Utilities were determined by mapping SF-12 scores from the CPKC412D2201 clinical trial to EQ-5D utilities.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the mixture of standard of care options used for the comparison with midostaurin was not consistent with clinical practice in Canada (see bullet point 'Comparator' below for more details).

Relevant issues identified included:

- **Net clinical benefit:** The CGP concluded that there may be a net clinical benefit to midostaurin, compared with currently available chemotherapy options, in the treatment of adult patients with ASM, SM-AHN, or MCL as a first line option.
- **Comparator:** the submitted economic evaluation included as standard of care options a mix of cladribine, interferon, cytarabine, and hydroxyurea. The CGP noted that imatinib should also be considered as a relevant comparator to midostaurin in the first-line treatment of patients with advSM without the D816V c-KIT mutation (or unknown D816C c-KIT mutation status) in Canada (about 10% of cases). Furthermore, the CGP noted that hydroxyurea and cytarabine would be used very rarely in less than 5% of cases. *The EGP included the cost of imatinib in the EGP's reanalysis and excluded the cost of cytarabine and hydroxyurea.*
- **Sequencing:** While there is no clear consensus and insufficient data to guide sequencing of therapies, the CGP suggested that midostaurin is likely also appropriate as salvage treatment in patients progressing after interferon (IFN)-α, cladribine, or other cytoreductive therapy. *The submitted economic model addressed midostaurin only as first-line option.*
- **Clinical data sources:** Regarding the economic evaluation, the CGP noted that the data upon which the clinical inputs for OS and ORR were based were limited by study design (open-label single-arm trials and non-prospectively derived). Additionally, the methods team noted that trial 2201 was not powered to adequately assess OS.
- **Survival benefit:** The information on the survival benefit of midostaurin was derived from a review paper with limited methodological information (Chandesris et al., 2016).[2] This study matched French compassionate use subjects to historical control subjects by disease class and age at diagnosis to estimate the HR associated with OS. However, the CADTH Methods team identified differences in baseline characteristics of the patients in the two groups, most notably that they were not matched on prior therapies. The historical controls were more heavily pre-treated versus patients who received compassionate use midostaurin, which suggests that they may have been more refractory to treatment and thus predisposed to worse survival. In addition, the extent to which the standard care options for the historical control match the contemporary SOC options in Canada were also unclear. The CADTH Methods Team remarked that an alternative study by Reiter et al may be a better source for the HR estimate for OS versus the Chandesris study. This analysis matched patients on more factors (i.e., age at diagnosis, WHO-defined SM sub-type, prior treatments, and sex), and matched midostaurin treated patients (pooled from trial 2201 and 2213) to a more contemporary group of SOC patients. However, there was limited

information on SOC treatments received by the controls and the pooling of data from trials 2201 and 2213 despite differences in study design and follow-up was identified as a limitation. *The EGP used Reiter et al to source the HR in the reanalysis.*

- **HR-QoL:** The CGP and CADTH Methods Team also noted that HR-QoL weights, which were collected from trial 2201 were exploratory and only approximately 60% of patients were considered evaluable based on baseline scores and having assessments for at least 168 days. CGP noted that although no firm conclusions can be drawn due to these limitations, it appears likely that midostaurin does not negatively impact QoL in patients with advSM.
- **Clinical heterogeneity:** The CADTH Methods Review Team also commented that combining different classes of advSM patients into a single group could discount clinical heterogeneity in disease or prognostic heterogeneity by advSM sub-type. However, sufficient clinical data for the different subtypes particularly on OS are not available given the small number of patients involved.

Summary of registered clinician input relevant to the economic analysis:
One individual registered clinician considered standard care options, KIT mutation testing, and toxicities of SOC and midostaurin treatment. The clinician noted the lack of a standard of care for the treatment of adult patients with advSM and agreed that patients may receive cytoreductive therapies (e.g., imatinib, cladribine, cytarabine, azacitidine, hydroxyurea and fludarabine) plus mast cell stabilizers or inhibitors of release (e.g., antihistamines). *The SOC alternatives in Canada were confirmed by the CGP to include interferon, cladribine, and imatinib (10% based on KIT mutation status). However, while the submitted model included some of these alternatives (i.e., cytarabine, hydroxyurea, cladribine), the model did not include imatinib.* Therefore, in the reanalysis, SOC options as defined by the CGP were considered. The registered clinician noted that midostaurin would likely be used in all cases of advSM as first line therapy irrespective of KIT status. However, the guidance provided by the clinician also noted that some review articles suggest KIT mutation status guides treatment selection of midostaurin versus other therapies. *The current economic analysis did not consider this possibility. The analysis only considered midostaurin as first-line treatment regardless of KIT mutation.*

Summary of patient input relevant to the economic analysis:
Patient advocacy groups, the Mastocytosis Society Canada (MSC) and the Canadian Organization for Rare Disorders (CORD), noted that from a patient's perspective, SM is a very aggressive and debilitating condition with limited treatment options for patients. Patients considered symptom control to be their biggest concern, as the disease has significantly impacted their ability to carry on their daily activities. When presented with the drug profile of midostaurin, the majority of patients (93%) responded favourably and said that it should be made available through drug plans. An overarching theme in patient responses was the ability to maintain a level of independence to be able to carry on their daily tasks. Patients value new therapies that would provide better symptom management, improve quality of life and survival, and would have minimal or manageable side effects. *The submitted economic model considered adverse events, quality of life, and effectiveness (overall survival and response rates).*

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 reimbursement recommendation for midostaurin which are relevant to the economic analysis:

- **The high cost of midostaurin**: PAG noted that the high drug cost and affordability may be a barrier to implementation and would need to be addressed.
- **Additional pharmacy resources and clinic visits:** As midostaurin is administered orally, PAG identified that chemotherapy units and chair time would not be required compared to cytoreductive therapies. *The submitted model considered the higher administrative costs associated with the administering intravenous therapy vs oral.* PAG also considered that

dispensing midostaurin would require additional pharmacy resources and that additional health care resources (e.g., frequent clinic visits while patients are on therapy) are required for monitoring adverse effects and tolerability with midostaurin. *However, the CGP noted that clinical visits are unlikely to vary between the SOC and midostaurin therapy options. The submitted analysis did not consider differences in costs related to physician visits or pharmacy resources between SOC and midostaurin.*

- **KIT D816V mutation testing:** KIT D816V mutation status testing is required for the diagnosis of systemic mastocytosis. Midostaurin is indicated for the treatment of patients with advSM regardless of their KIT D816V mutation status. *The submitted economic model did not consider the cost of KIT D816V mutation testing as it applies to all patients regardless of whether they receive midostaurin or SOC.*

1.3 Submitted and EGP Reanalysis Estimates

The submitted base-case economic analyses indicated that when compared to SOC, midostaurin costs $696,495 more per patient and results in a gain of 1.90 life years and 1.46 QALYs on average (5,000 simulations were run). This translated to an incremental cost-utility ratio (ICUR) of $478,035 per QALY gained and an incremental cost-effectiveness ratio (ICER) $367,190 per life-years gained (**Table 2**).

The uncertainty in the ICUR is displayed using a cost-effectiveness plane (i.e., scatterplot with the incremental costs on the y-axis and the incremental QALYs in the x-axis) (**Figure 7**). The scatterplot revealed a large scatter across effectiveness estimates, likely related to the large confidence interval around the OS benefit. The probability of cost-effectiveness at a range of cost-effectiveness thresholds is displayed as a cost-effectiveness acceptability curve (CEAC) (**Figure 8**). The probability of cost-effectiveness at the conventional cost-effectiveness threshold of $100,000 per QALY gained is ~0.6% for midostaurin vs SOC.

Table 2. Submitted and EGP Estimates (probabilistic analysis)

Estimates (range/point)	Submitted*	EGP Reanalysis** (**Best estimate**)
ΔE (LY)	1.90	0.99
On treatment	-0.06	-0.08
Responder (on treatment)	0.26	0.26
Treatment failure/discontinuation	1.69	0.83
ΔE (QALY)	1.46	0.64
On treatment	-0.08	-0.07
Responder (on treatment)	0.24	0.20
Post-progression (treatment failure)	1.29	0.52
ΔC ($)	$696,495	$671,871
ICER estimate ($/QALY)	$478,035	$1,056,688

***10-year time horizon; **lifetime time horizon**

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

- The major limitations of the economic evaluation were related to the amount and quality of data available to inform important clinical inputs (e.g., OS, ORR, HR-QoL). The data sources were of limited quality as there was no direct head-to-head comparison of relevant comparators (midostaurin vs SOC).
- The ICUR and ICER estimates were most sensitive to estimated HR for OS. The HR used to map the OS in the midostaurin arm from trial 2201 (Gotlib et al., 2016)[1] to the SOC arm was collected from Chandesris et al., 2016.[2] This study is a review article where authors

matched 40 SOC (historical control) patients to 28 midostaurin (compassionate use) patients by age at diagnosis and disease class only with limited methodological detail. The extent to which the "control" arm represents the contemporary SOC alternatives in Canada is also unclear.

- The ORR associated with midostaurin was determined by pooling data from the single arm trial 2201 reported by Gotlib et al., 2016;[1] the single arm trial 2213 reported by DeAngelo et al., 2018 [5] and data reported by Chandesris et al., 2016.[2] The ORR associated with SOC was determined by pooling data from two studies evaluating the effectiveness of cladribine (Barete et al., 2015)[4] and interferon (Valent et al., 2003).[3] Because clinical inputs were not informed by randomized control trials comparing midostaurin and SOC, systematic differences in study conduct and patient selection may impact results.
- There is very limited data on HR-QoL on advSM. The HR-QoL data was only available from the 2201 trial of midostaurin reported by Gotlib et al., 2016.[1] This was applied to both the SOC and midostaurin arms. Therefore, the utilities used in the model did not fully capture the difference between midostaurin and SOC in terms of possible differences in the treatment-related adverse events. Moreover, it appears that the post-progression QoL data used in the model were based on the end of treatment visit, as patients who progressed no longer completed SF-12 assessments in study 2201. Therefore, no SF-12 scores are available for early or later phases of progressive disease. In addition, a large number of missing data exists at the end of treatment with less than 50% of the patients providing QoL data after cycle 12 and beyond. These limitations lead to high uncertainty in the utility values for the post-progression state. The application of a proxy for the current HR-QoL weights from a different disease was not considered appropriate by CGP due to the distinct disease profile of patients with advSM.
- Due to limited data availability, costing data relied heavily on assumptions regarding the prevalence of disease-related vs. treatment-related adverse events for SOC and midostaurin.
- Because there are no costing studies of advSM, medical resource use cost components were identified via structured interviews with clinical experts, as were monthly rate of resource utilization.
- The sponsor was unable to provide a stratified analysis of health economic outcomes based on SM subtypes (i.e., SM-AHN, ASM, MCL) due to lack of data and small number of patients in trials.
- The CGPs estimate of the SOC treatment options for advSM in Canada were identified as interferon (50%); cladribine (40%); imatinib (10%), for those without the D816V c-Kit mutation); <5% for hydroxyurea, cytarabine, and fludarabine. However, the sponsor defined SOC treatment based on KOL opinion as follows: interferon (60%); cladribine (30%); hydroxyurea (5%), cytarabine (5%).

1.4 Detailed Highlights of the EGP Reanalysis

Overall, model outcomes were most sensitive to the HR that maps OS for midostaurin vs. SOC (Chandesris et al., 2016), the model time horizon (with longer horizons resulting in lower ICERs) and the assumptions made regarding the functional form of extrapolating overall survival, as well as the choice of HR-QoL weights (SF-12 utility vs. EQ5D [SF-12 mapped to EQ5D]).

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

- **SOC comparators**: The review team noted that imatinib is a relevant comparator to midostaurin in patients with advSM without the D816V c-KIT mutation in Canada. Because the submitted economic base case does not include imatinib as a comparator, a reanalysis was performed considering the CGP's recommendations: 50% interferon, 40% cladribine, and 10% imatinib. However, this reanalysis only impacts the costs of SOC as the effectiveness in terms

of OS and ORR are derived from studies of historical cohorts and of interferon and cladribine, due to limitations in data availability.

- **Source of HR estimate for OS**: Sensitivity analysis presented by the sponsor indicated that the ICER and ICUR estimates were highly sensitive to the HR for OS derived from a review paper by Chandesris et al[2]. An alternative source of HR was identified: an unpublished study by Reiter et al[6], which used propensity score matching to match (by age at diagnosis, disease class, sex and prior lines of treatment) patients on midostaurin from the 2201/2213 trials to a German historical cohort. While the SOC options in the German cohort are not defined, matching may have been done to a contemporary group of patients (~95% were diagnosed after 2005) and with a longer median follow up (registry/historical control: 84.2 months [range, 22.3 -176.3] midostaurin pool: 79.5 months [range, 51.4 -234.0]). The later study also provides more methodological details and a better matching vs. the Chandesris study. Finally, the reported HR in the Reiteret al study was also more conservative vs. Chandesris et al: 1.57 (95% CI, 0.80-3.07) vs. 2.20 (95%CI, 1.08-4.47). For these reasons, the Reiter et al study was selected as the source of the HR used in the reanalysis.
- **Utility valuation**: A scenario analysis presented by the sponsor evaluated the application of SF-12 (SF-6D) utilities vs. EQ5D (mapped from SF-12). The analysis indicated that EQ5D values resulted in lower estimates of the ICER and ICUR. The probabilistic analysis did not consider uncertainty in the algorithm used to map the SF-12 scores to the EQ5D values and the derived algorithm may lack face validity and may have limited generalisability to the Canadian population as it was mainly derived from a US population sample with a high representation of Hispanic and black populations. Instead, the SF-12 (SF-6D) utilities were used in the re-analysis. The SF-6D values were derived from SF-12 scores using preference weights obtained from a sample of the UK general population using standard gamble valuation.
- **Time horizon:** The submitted base case analysis used a 10-year time horizon for the economic evaluation. However, based on the extrapolated data, ~15% of patients in the midostaurin arm and ~2% of patients in the SOC arm are still alive at the 10-year time horizon. A lifetime time horizon (corresponding to 30-years based on exponential extrapolations used in the EGP's best case, and 60-years based on extrapolations by sponsor) therefore was chosen in the re-analysis to fully capture all downstream consequences (i.e., costs and benefit) of the different treatment options as recommended by CADTH guidelines.[7]
- **Extrapolation**: The submitted analysis used a piecewise extrapolation of OS using a log-normal parametric tail. The EGP reanalysis considered a more conservative extrapolation given 1) the amount and quality of evidence around OS for advSM, 2) the high uncertainty in comparative effectiveness, 3) and that piecewise approach consists of long tails that may overestimate survival for this population of advSM patients with a median age 60 years. The reanalysis used an exponential parametric curve fit to the 2201 trial data to generate the best estimate of the ICUR. Under this scenario, ~0.85% of the patients in the SOC arm and 5% of those in midostaurin arm were still alive at 10-years. The CGP supported the exponential parametric curve fit used in the EGP's best case extrapolation. In addition, a log Normal parametric curve fit, which was the best fit function according to AIC and BIC statistics was also evaluated in a scenario analysis. Under this scenario, ~3% of the patients in the SOC arm and 10% of those in midostaurin arm were still alive at 10-years. In both scenarios, the curve was fit to the entire OS function rather than in a piece-wise manner, as was done in the submitted base case.

  In their feedback on the Initial Recommendation, the sponsor noted that *"the EGP reanalysis used an exponential function which is not the best fit according to AIC/BIC statistics. The choice of parametric function has a significant impact in the ICUR. Using the exponential function instead of log Normal function (best fit according to AIC/BIC statistics) has led to an overestimation of the EGP estimate."* The EGP reviewed the sponsor's feedback and agreed to uphold their initial reanalysis (i.e., using exponential instead of log Normal distribution) for

the reasons outlined previously. In addition, the application of a more conservative exponential extrapolation was preferred in the EGP's best-case analysis given that relying on trial-based survival data (as opposed to observational/longitudinal data) to benchmark survival within the model may overestimate survival. The log Normal parametric curve fit was considered in a scenario analysis for reasons outlined previously.

In view of these, EGP's best-case reanalysis included:
1) SOC comparators as recommended by CGP, 2) The HR estimate collected from Reiter et al, 3) SF-12 (SF-6D) utilities-unmapped, 4) a lifetime time horizon as recommended by CADTH HTA guidelines[7] for treatments having a differential effect on mortality, and 5) extrapolation of OS with an exponential parametric curve fit versus piecewise Log Normal parametric tail.

- The EGPs best case estimate of the ICUR resulted in a higher estimate when compared to the sponsors' best estimate ($1,056,688/QALY vs. $478,035/QALY).
- Additionally, in a scenario analysis on the EGP's best-case analysis, using a shorter 10-year time horizon resulted in an ICUR of $1,158,698/QALY. When several price reduction scenarios were considered on the EGP's best estimate, a 90% reduction in the cost of midostaurin ($16.79 vs. $167.92 per 25 mg capsule) resulted in an ICUR of $126,801/QALY, and a 95% reduction ($8.40 per 25 mg capsule) resulted in an ICUR of $76,911/QALY.

Table 3: Detailed Description of EGP Reanalysis

	∆C	∆E QALYs	∆E LYs	ICUR (QALY)	∆ from baseline submitted ICER
Sponsor's Best estimate					
Baseline (Sponsor's estimate) 1. Submitted SOC mix 2. OS HR based on Chandesris 3. EQ5D (mapped from SF-12) utilities 4. 10-year time horizon 5. Piecewise Log Normal parametric extrapolation of OS	$696,495	1.46	1.90	$478,035	--
Scenario analysis on Sponsor's Best estimate					
Comparators: SOC options based on CGP recommendation (costs only): - *50% interferon* - *40% cladribine* - *10% imatinib*	$695,148	1.46	1.90	$476,103	-$1,931
Source of OS HR estimate: HR based on Reiter et al. point estimate (HR: 1.57)	$672,380	0.96	1.25	$699,218	$221,183
Utility valuation: SF-12 (SF-6D) utilities	$697,001	1.21	1.91	$576,249	$98,214
Time horizon: Lifetime (60 years based on sponsor's choice of extrapolation)	$701,756	2.33	3.06	$300,860	-$177,175
EGP's Best estimate (including all scenario analyses above on Sponsor's Best estimate)					
EGP best estimate: 1. *SOC options bases on CGP recommendation* 2. *OS HR based on Reiter et al.*	$671,871	0.64	0.99	$1,056,688	$578,653

	∆C	∆E QALYs	∆E LYs	ICUR (QALY)	∆ from baseline submitted ICER
3. SF-12 (SF-6D) utilities *4. Lifetime time horizon (up to 30-years based on extrapolation used)* *5. Extrapolation of OS by exponential parametric curve fit*					
Scenario analyses on EGP's Best estimate					
Scenario analysis: EGP's best case with a lognormal extrapolation of OS: *1. SOC options based on CGP recommandation* *2. OS HR based on Reiter et al.* *3. SF-12 (SF-6D) utilities* *4. Lifetime time horizon (up to 60-years based on extrapolation used)* ***5. Extrapolation of OS by log normal parametric curve fit***	$674,539	1.09	1.72	$620,638	$142,603
Scenario analysis: EGP's best case with a 10-year time horizon matching the sponsor's base case: *1. SOC options based on CGP recommendation* *2. OS HR based on Reiter et al.* *3. SF-12 (SF-6D) utilities* ***4. 10-year time horizon*** ***5.*** *Extrapolation by exponential parametric curve fit*	$671,095	0.58	0.90	$1,158,698	$680,663
Scenario analysis: EGP's best case with a 90% price reduction of midostaurin: *1. SOC options based on CGP recommendation* *2. OS HR based on Reiter et al.* *3. SF-12 (SF-6D) utilities* *4. Lifetime time horizon (30-years)* *5. Extrapolation by exponential parametric curve fit* ***6. 90% reduction in the price of midostaurin ($33.59 vs. $167.92 per 25 mg capsule)***	$81,694	0.64	1.00	$126,801	-$351,234
Scenario analysis: EGP's best case with a 95% price reduction of midostaurin: *1. SOC options based on CGP recommendation* *2. OS HR based on Reiter et al.*	$49,175	0.64	1.00	$76,911	-$401,124

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
3. *SF-12 (SF-6D) utilities* 4. *Lifetime time horizon (30-years)* 5. *Extrapolation by exponential parametric curve fit* 6. ***95% reduction in the price of midostaurin ($8.40 vs. $167.92 per 25 mg capsule)***					

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influenced the budget impact analysis include 1) the proportion of public coverage, 2) the market uptake of midostaurin, 3) the incidence rates for SM, and 4) the treatment duration for midostaurin.

Key limitations of the BIA model are related to the fact that some important model inputs were based on assumptions. For example, Canadian epidemiology data was not available, and data from other countries in Europe were applied to estimate the incidence of disease. Data on treatment duration for all therapies were also not available and were estimated based on trial data. Baseline market share data for different treatment options were based on expert opinion. There were also limited data on market uptake and switching rates to midostaurin. The EGP modified the market share data for SOC to align with the recommended SOC option in Canada as defined by the CGP.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for midostaurin when compared to SOC:

- The best estimate of the ICUR is $1,056,688/QALY. Given the best estimate, there is a <0.5% probability that midostaurin is cost-effective at a conventional cost-effectiveness threshold of $100,000/QALY and a 0.3% and ~50% probability of cost effectiveness at a threshold of $500,000/QALY and $1,000,000/QALY respectively.
- The extra cost of midostaurin is $671,871 per person on average over the lifetime. The main factor that influences the costs is the cost of midostaurin. At least a ~90% reduction in the cost of midostaurin would likely reduce the ICUR to around $100,000/QALY
- The extra clinical effect of midostaurin is an average gain of 0.64 QALYs and 0.99 LYs per person over the lifetime. The main factors that influence the clinical gains associated with midostaurin is the benefit of midostaurin in terms of overall survival as indicated by the hazard ratio, and the HR-QoL values (utilities) associated with different avdSM health states (e.g., pre-progression, treatment response, post-progression).

Overall conclusions of the submitted model:

- Model results were most sensitive to clinical data around the survival benefit of midostaurin vs. SOC as well as the limited data on HR-QoL for advSM. Due to the lack of robust direct or indirect comparative efficacy data, there was substantial uncertainty in the comparative efficacy estimate used in the model.
- In terms of costs, the data is most sensitive to drug cost of midostaurin.
- Due to the rarity of the condition and limited literature on the clinical benefit (survival and HR-Qol) and on health care resource use for patients with advSM, the model does rely on a number of assumptions. These contribute to the uncertainty in the clinical and economic projections of the model.

- Better quality data on clinical effectiveness, natural history, HR-Qol and resource use to inform the model is limited based on currently available literature on advSM.

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 Systemic Mastocytosis 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 midostaurin for systemic mastocytosis. A full assessment of the clinical evidence of midostaurin for systemic mastocytosis 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 non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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.

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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