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
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Midostaurin (Rydapt) Submitted Reimbursement Request: For the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).	
Submitted By: Novartis Pharmaceuticals Canada Inc.	**Manufactured By:** Novartis Pharmaceuticals Canada Inc.
NOC Date: October 3, 2018	**Submission Date:** August 13, 2019
Initial Recommendation: January 30, 2020	**Final Recommendation:** April 2, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	Midostaurin costs $167.92 per 25 mg capsule. At the recommended dose of 100 mg twice daily, midostaurin costs $1,343.40 per day and $37,615.16 per 28-day cycle.

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 does not recommend reimbursement of midostaurin for the treatment of adult patients with advanced systemic mastocytosis (SM), which is comprised of aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

pERC made this Recommendation because it was not satisfied that there is a net clinical benefit of midostaurin compared with available cytoreductive treatment options given the limitations in the evidence from the available phase II clinical trials. While pERC acknowledged that there is an unmet need for an approved treatment option for this uncommon disease and that midostaurin produces antitumour activity, the Committee concluded that there was considerable uncertainty in the magnitude of clinical benefit of midostaurin compared with appropriate comparators with regard to outcomes important to decision-making such as overall survival (OS), progression-free survival (PFS), and quality of life (QoL).

pERC concluded that midostaurin aligns with patient values in that it may offer symptom management and has the potential to maintain QoL in this rare disease with a significant unmet need.

pERC concluded that, at the submitted price, midostaurin was not cost-effective compared with available cytoreductive treatment options. Midostaurin is a high-cost therapy. There was considerable uncertainty in the cost-effectiveness estimates because of a lack of robust direct or indirect comparative data in the submitted economic evaluation.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC considered that new clinical data comparing midostaurin with currently available treatments in Canada for adult patients with SM could form the basis of a resubmission to CADTH, including efficacy data important to decision-making, such as OS, PFS, and QoL.

SUMMARY OF pERC DELIBERATIONS

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Advanced systemic mastocytosis (SM) comprises three rare mast cell neoplasms: ASM, SM-AHM, and MCL. No epidemiological data specific to Canada are available with respect to Canadian incidence and prevalence statistics. A Danish population-based study (Cohen et al. [2014]) estimates a combined incidence of 0.06 per 100,000 for advanced SM (0.01 for ASM, 0.04 for SM-AHN, and 0.01 for MCL); the estimated prevalence of advanced SM in this study was 0.4 per 100,000. Advanced SM is an aggressive disease with high morbidity and mortality. Disease-related symptoms include bone disease, ascites, liver dysfunction, and skin disease. The median OS is three-and-a-half years in patients with ASM, two years in those with SM-AHN, and less than six months in those with MCL. There is no standard of care for the treatment of advanced SM in Canada; cytoreductive therapies currently used off-label in Canada include interferon, cladribine, imatinib, hydroxyurea, and cytarabine. pERC agreed with the CADTH Clinical Guidance Panel (CGP) and registered clinicians providing input for this submission that response rates to currently available cytoreductive therapies are low and that there is an unmet need in this setting for effective and tolerable treatments that reduce disease symptoms and extend survival. In their feedback on the Initial Recommendation, the sponsor, the patient group Mastocytosis Society Canada (MSC) with support from the Canadian Organization for Rare Disorders (CORD), and the CGP highlighted the high unmet need in the present target population. pERC agreed that there is an unmet need in this rare disease and acknowledged the CGP's response in the final CADTH Clinical Guidance Report that midostaurin appears to have relatively high efficacy and low toxicity compared with currently available cytoreductive therapy. However, pERC reiterated that, given the numerous limitations in the evidence from the available phase II clinical trials with midostaurin, the Committee was not satisfied that there was a net clinical benefit with midostaurin compared with available cytoreductive treatment options or that midostaurin adequately addresses the need for more effective therapies for patients with advanced SM.

pERC deliberated on two non-comparative, open-label, phase II trials (Study 2201 and Study 2213) that evaluated the efficacy and safety of midostaurin for the treatment of adult patients with ASM, SM-AHN, or MCL. pERC noted that Study 2201 provided the main evidence for the submission and was supplemented by the much smaller patient population in Study 2213. Although pERC considered that the magnitude and durable nature of objective tumour responses observed with midostaurin in these trials were important, the Committee discussed that there was a high level of uncertainty around the magnitude of the clinical benefit given the limitations in the evidence from the non-comparative phase II clinical trials. pERC was concerned about the reliance on tumour response as the primary measure of benefit, the assessment of efficacy outcomes being based on data cuts that were not pre-specified or adjusted for multiple testing, efficacy results being pooled across three disease subtypes (i.e., ASM, SM-AHN, and MCL) that have different survival outcomes, and the studies not being designed to detect statistical significance in secondary end points (e.g., PFS or OS). pERC noted that overall response rate (ORR) is an uncertain surrogate for survival in SM. pERC agreed that the magnitude of clinical effect of midostaurin compared with available therapies was uncertain, given the lack of comparative outcomes data important to decision-making and patients, such as OS, PFS, and QoL.

Upon reconsideration, pERC discussed feedback from the sponsor, the patient group MSC with support from CORD, and the CGP regarding a risk-sharing agreement for midostaurin between the public payers and the sponsor where the sponsor would collect further data for a subsequent submission to CADTH. pERC noted that its mandate is to provide cancer drug funding recommendations, including conditions and/or criteria for coverage where appropriate, to the participating provincial and territorial Ministries of Health, provincial cancer agencies and federal drug programs, based on Submissions or Resubmissions. Providing recommendations to jurisdictions regarding new mechanisms to support access to treatments for patient with rare diseases is out of the current scope of the CADTH pCODR mandate. pERC also acknowledged the CGP's response in the final Clinical Guidance Report, noting that the National Comprehensive Cancer Network (NCCN) recommendations include midostaurin as a first-line treatment option for advanced SM. pERC noted that organizations producing clinical practice guidelines have

different objectives than health technology assessment (HTA) bodies. The purpose of clinical practice guidelines is to optimize patient care informed by the safety and efficacy of alternative care options as well as expert opinion. HTA is broader in that it examines the comparative effectiveness of different treatment strategies looking at multiple dimensions, while aiming to provide a balance between the values, needs, preferences, and perspectives of patients and those of society based on evidence.

pERC deliberated on the toxicity of midostaurin. It noted a high proportion of adverse events (AEs) suspected to be drug-related and that the majority of patients required dose interruptions and/or reductions. pERC was also concerned about the high proportion of patients who withdrew due to AEs. The most frequent AEs suspected to be drug-related were gastrointestinal (GI)-related (e.g., nausea, vomiting, and diarrhea). The most frequent grade 3 to 4 AEs were due to myelosuppression (e.g., anemia, thrombocytopenia, and neutropenia). pERC noted that the single-arm, non-randomized design of the available phase II trials made interpreting the safety events attributable to midostaurin challenging, given that all patients received the same treatment.

pERC discussed the exploratory patient-reported outcomes data from Study 2201 and noted that the results suggested that midostaurin may not have a detrimental effect on QoL. However, it noted that the number of patients providing QoL scores declined substantially over the course of the first year. pERC concluded that given the open-label design of the trial, the lack of a comparator group, and the declining number of patients providing responses, there is considerable uncertainty in the QoL results.

In addition, pERC discussed that phase II trials are mainly hypothesis-generating and their intent is to determine whether there is sufficient promise to proceed to a phase III confirmatory trial. While pERC agreed that conducting a phase III trial with midostaurin compared with currently available cytogenetic therapies would likely not be feasible, it could not confidently conclude that midostaurin addresses the need for effective and tolerable treatment options, given the uncertainty in the results from the available phase II trials, which had considerable limitations in their design and statistical analysis plans.
pERC deliberated on input from one patient group that was provided with support from another patient group. Given the rarity of advanced SM, pERC was very appreciative of the contribution of the small number of patients who had direct experience with midostaurin and of the balanced presentation of their responses by the patient groups. While some patients who had experience with midostaurin spoke very favourably of midostaurin in terms of improvements in QoL, others spoke of its benefits but were also challenged by the drug regimen and side effects. Some patients reported that they discontinued the therapy with midostaurin due to side effects. pERC considered that patients value treatments that provide better symptom management and improve QoL and survival. Although pERC acknowledged that midostaurin produces antitumour activity, it was uncertain whether the current evidence demonstrates that midostaurin improves response rates and survival compared with current treatment options. Upon reconsideration, pERC acknowledged feedback from the patient group MSC with support from CORD, regarding a few of the patients they surveyed, who did experience positive benefits with midostaurin in this setting. Specifically, the patient group noted that these patients experienced very positive benefits in symptom management, QoL, and side effects. pERC concluded that midostaurin aligned with patient values in that it may offer symptom management and has the potential to maintain QoL in this rare disease with an unmet need.

pERC deliberated on the cost-effectiveness of midostaurin in patients with ASM, SM-AHN, or MCL and concluded that midostaurin is not cost-effective compared with currently available cytoreductive therapy options (i.e., interferon, hydroxyurea, cladribine, and cytarabine). pERC noted that midostaurin is a high-cost therapy and that the factor that most influenced the incremental cost of midostaurin compared with cytoreductive therapy was the cost of the drug itself. Based on the CADTH Economic Guidance Panel's (EGP's) best estimate, the probability of midostaurin being cost-effective at any of the conventional cost-effectiveness thresholds was negligible. The incremental benefits of midostaurin were most sensitive to the OS hazard ratio (HR) and the utility estimates. pERC noted that in the absence of comparative trials, the sponsor sourced comparative estimates for OS and ORR from the literature, which was considered to be of low-quality evidence (e.g., small sample sizes, limited data reporting, retrospective analyses, and missing data elements). pERC agreed with the CADTH Methods team and the EGP that a key limitation of a naive treatment comparison is that it is not possible to determine if any observed difference or similarity in efficacy between therapies is solely due to the treatment or rather due to bias or confounding factors (e.g., differences in study populations, definitions of outcomes, or study designs). pERC agreed that given the limitations with the naive treatment comparison, the comparative effectiveness of midostaurin versus available cytoreductive therapies remains uncertain. Because of the considerable limitations in the available clinical data of midostaurin from the non-comparative phase II studies and the lack of robust indirect comparative effectiveness estimates, pERC concluded that there was considerable uncertainty in

the cost-effectiveness estimates.

pERC considered the feasibility of implementing a reimbursement recommendation for midostaurin for the treatment of adult patients with ASM, SM-AHN, or MCL. The Provincial Advisory Group (PAG) identified that the high cost and affordability of midostaurin may be a barrier to implementation and would need to be addressed, that there is a potential for pill burden with a total of eight capsules daily along with concomitant medications, and that some jurisdictions do not have KIT D816V mutation testing available in their provinces. pERC also considered that midostaurin is a high-cost therapy and that the submitted Canada-wide budget impact was high. Factors that had the largest impact on the budget impact analysis included the proportion of public coverage, the market uptake of midostaurin, the incidence rates for SM, and the treatment duration for midostaurin. pERC noted that a key limitation of the budget impact analysis was that important model inputs were based primarily on assumptions.

EVIDENCE IN BRIEF

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

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the sponsor's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group: Mastocytosis Society Canada (MSC), with support of the Canadian Organization for Rare Disorders (CORD)
- input from one individual registered clinician
- input from PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group: Mastocytosis Society Canada (MSC), with support of the Canadian Organization for Rare Disorders (CORD)
- One individual registered clinician
- The PAG
- The sponsor Novartis Pharmaceuticals Canada Inc.

The pERC Initial Recommendation was to not recommend the reimbursement of midostaurin for the treatment of adult patients with advanced SM, which is comprised of aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

Feedback on the pERC Initial Recommendation indicated that the PAG and the individual registered clinician agreed, while the sponsor and patient advocacy group disagreed, with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the efficacy and safety of midostaurin for the treatment of adult patients with ASM, SM-AHN, or MCL.

Studies included: Two non-comparative phase II trials

The pCODR systematic review included two non-randomized trials: Study 2201, a non-comparative phase II trial (full analysis set [FAS]: N = 116; primary efficacy population [PEP]: N = 89) and Study 2213 (FAS and PEP: N = 26), a non-comparative phase II trial.

Study 2201 was a phase II, single-arm, open-label, international, multi-centre, non-randomized trial that evaluated the efficacy and safety of midostaurin in patients with ASM, SM-AHN, or MCL. Study 2213 was an investigator-initiated and manufacturer-sponsored, single-arm, open-label, multi-centre trial that also included adult patients with ASM, SM-AHN, or MCL.

The intervention in both trials was oral midostaurin 100 mg twice daily administered over continuous four-week cycles. In Study 2201, patients received up to six cycles of midostaurin after which they entered an extension phase. In Study 2213, patients received up to 12 cycles of midostaurin after which they also entered an extension phase, although if patients did not achieve a major response (MR) or partial response (PR) in the first two months, then treatment was discontinued. Otherwise in both trials, midostaurin treatment continued during the extension phases until disease progression, unacceptable toxicity, or patient withdrawal. Assessment of efficacy and harms included patients enrolled in the initial stages of the trials and the extension phases.

Both trials enrolled patients irrespective of KIT D816V mutation status and required that patients have one or more C-findings, European Cooperative Oncology Group (ECOG) performance status between 0 to 3, and adequate renal and hepatic function.

Key exclusion criteria in both trials were serious cardiovascular disease such as congestive heart failure and use of hematopoietic growth factor support within two weeks of study entry. Study 2201 also excluded patients who had relapsed after three or more SM treatments or had eosinophilia and known positivity for FIP1L1-PDGFR alpha fusion, unless the patient had relapsed or had disease progression on imatinib.

Patient population: Median age 64 years; majority of patients with SM-AHN subtype, and large proportion of patients with ECOG performance status 2 or 3

In Study 2201 (PEP) (N = 89), the median age was 64 years (range: 25 to 82), 64% of patients were male, and 36% of patients had an ECOG performance score of 2 or 3. More than 50% of patients had not received any prior treatment for SM and most (87% in the PEP) were positive for a KIT D816 mutation. The PEP included 16 (18%) patients with ASM, 57 (64%) patients with SM-AHN, and 16 (18%) patients with MCL (of which six [7%] had MCL associated with AHN). All patients had at least one sign of organ damage and most (43% in the PEP) had three or more C-findings. Baseline median tryptase levels were 236 ng/mL (range: 27 to 12,069) and median bone marrow mast cell burden was 50% (range: 8 to 98) in the PEP.
In Study 2213, median age was 64.5 years (range: 24 to 79), 58% of patients were male, and 54% of patients had an ECOG performance score of 2 or 3. Most patients (more than 80%) had received prior treatment and were positive (77%) for a KIT D816 mutation. Of the 26 patients in the FAS, three (12%) were diagnosed with ASM, 17 (65%) with SM-AHN, and six (23%) with MCL. All patients had at least one sign of organ damage with the largest category of patients (39%) having at least two C-findings. Baseline median tryptase levels were 323 ng/mL (range: 22 to 1255) and median bone marrow mast cell burden was 50% (range: 5 to 95).

Key efficacy results: Important but uncertain response rates

The primary efficacy outcome in Study 2201 was ORR, defined as the proportion of patients classified as confirmed responders (i.e., having a MR or PR during the first six cycles of midostaurin treatment as adjudicated by the study steering committee according to modified Valent and Cheson criteria and confirmed for eight weeks or more in the PEP). Secondary outcomes included duration of response, time to response, PFS, OS, safety and tolerability, and histopathologic response based on bone marrow mast cell infiltration and serum tryptase levels. Exploratory outcomes included the assessment of patient-reported outcomes (PROs) using the Memorial Symptom Assessment Scale (MSAS) and the Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12).

The primary outcome in Study 2213 was ORR, defined as the proportion of patients with a best overall response of MR or PR by investigator assessment over the first two cycles of midostaurin treatment according to Valent criteria and confirmed for eight or more weeks. Secondary outcomes included safety and tolerability, pharmacokinetic parameters, KIT mutation status, OS, and PFS. PROs were not measured in Study 2213.

In Study 2201, based on the December 1, 2014, data cut-off, 54 patients (60.7%) in the PEP had died, corresponding with a median OS of 26.8 months (95% CI, 17.6 to 34.7). In the final OS analysis (data cut-off August 24, 2017), median OS was similar: 26.8 months (95% CI, 17.6 to 34.4) in the PEP. Based on the December 1, 2014, data cut-off date, median PFS was 17.0 months (95% CI, 10.2 to 24.8). For the primary efficacy outcome of ORR by study steering committee adjudication in the PEP, at the same data cut-off, 53 patients had a confirmed best response of MR (n = 40) or PR (n = 13) corresponding with an ORR of 59.6% (95% CI, 48.6 to 69.8). The responses lasted for 31.4 months (95% CI, 10.8 to not estimable [NE]).

In Study 2213, [redacted] ([redacted]), whereas at the data cut-off of March 1, 2017, 22 patients (84.6%) had died and median OS was 40.0 (95% CI, 27.3 to 52.7) in the FAS. (*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* Median PFS was 38.6 months (95% CI, 11.3 to NE) and 41.0 months (95% CI, 4.4 to 77.6) for the two data cut-offs, respectively, in the FAS. For the December 3, 2012, data cut-off, 13 patients (50.0%) had an MR and six patients (23.1%) had a PR corresponding with an ORR by investigator assessment (primary efficacy outcome) of 73.1% (95% CI, 52.2 to 88.4). For the March 1, 2017, data cut-off, ORR was 69% (95% CI, 50 to 88).

PROs: Potential to maintain QoL

PROs were measured using the MSAS and SF-12 and were included in Study 2201 as exploratory outcomes. The questionnaires were administered every cycle during the first 12 cycles, and every three cycles thereafter until disease progression, development of unacceptable toxic effects, or the end of the study, whichever occurred first. A decreased MSAS score indicates an improvement or reduction in symptoms. An increased score on the SF-12 indicates improvement (better health-related QoL [HRQoL]). The number of patients providing QoL scores declined substantially over the course of the first year.

SF-12 assessment: Of the 89 patients in the PEP, 53 patients (with non-missing baseline values or baseline scores higher than 0) were evaluable for at least 168 days. Of the 53 evaluable patients, 10 patients (18.9%) and three patients (5.7%) had a 50% or greater increase in Physical Component Score and Mental Component Scale scores, respectively, relative to baseline.

MSAS assessment: Of the 89 patients in the PEP, 52 patients were evaluable for 168 days or more per five cycles. Overall, 20 out of 52 patients (38.5%) had 50% or higher decrease in total MSAS score relative to baseline for at least 168 days.

The CADTH Methods team noted that the decline in the number of eligible patients over the first 12 treatment cycles leads to uncertainty in the PRO results beyond cycle 12 and possibly in earlier cycles. PRO estimates up to cycle 12 may not represent an accurate picture of the patients' experiences with midostaurin for a longer period of time. Additionally, the trial was non-randomized and the impact of midostaurin on PROs in relation to other therapies is unknown. PRO data were reported based on descriptive exploratory analyses. Due to these limitations, no firm conclusions can be drawn on midostaurin's impact on QoL based on the PRO results.

Safety: High proportion of AEs suspected to be related to study drug

Based on a pooled safety analysis of harms outcomes from Study 2201 and Study 2213, all (100%) patients in both studies experienced an AE and, of these, 93.1% and 96.2%, respectively, were suspected to be treatment related. The most frequent AEs suspected to be treatment related were GI-related (e.g., nausea, vomiting, and diarrhea), the majority of which were of grade 1 or 2 severity. Furthermore, 88.8% (Study 2201) and 61.5% (Study 2213) of patients experienced AEs of grade 3 to 4 severity. The most frequent grade 3 to 4 AEs were due to myelosuppression (e.g., anemia, thrombocytopenia, and neutropenia)

Serious AEs occurred in 68.3% of patients in the pooled data set and common reasons included primarily pneumonia (7.0%), sepsis (7.0%), and urinary tract infection (4.2%). The most frequent hematologic AEs reported as serious AEs were febrile neutropenia (4.9%) and anemia (4.2%).

AEs leading to discontinuation were reported by 34 (23.9%) of patients. The most frequent reasons were nausea (2.1%), ascites (2.1%), and electrocardiogram QT interval prolongation (2.1%).

Dose interruptions were reported for 67 patients (47.2%): 29 patients (20.4%) had one dose interruption and 38 patients (26.8%) had more than one dose interruption. Dose reductions were reported for 84 patients (59.2%): 38 patients (26.8%) had one dose reduction and 46 patients (32.4%) had more than one dose reduction. AEs were the most frequent reason for dose interruptions (59 of 67 interruptions) and dose reductions (63 of 84 reductions), followed by dosing error. AEs leading to dose interruption or adjustment were most commonly related to GI events.

There was a total of 26 (18.3%) on-treatment deaths (i.e., deaths occurring on treatment and up to 28 days after the last dose of study drug) across both trials. Ten deaths were directly attributed to disease progression; other frequent primary causes were sepsis (n = 5), cardiac disorders (n = 5), and multi-organ failure (n = 3). Furthermore, seven additional on-treatment deaths were reported after the cut-off dates of the individual studies up to April 30, 2016 (i.e., four deaths in Study 2201 and three deaths in Study 2213, of which four were due to disease progression). None of the deaths were judged to be related to the study drug by investigators.

Limitations: No direct comparative data to current treatment options

A critical appraisal was performed for the submitted naive treatment comparison of midostaurin and standard of care (SOC) for the treatment of advanced SM. The submitted comparative OS HR used in the economic model was sourced from a study by Chandesris et al. (2016/2017), while the EGP used an alternative OS HR from a study by Reiter et al. (2019). Both studies (i.e., Chandesris et al. and Reiter et al.) attempted to match patients receiving midostaurin to a historical cohort. A comparative ORR

estimate for the economic model was obtained by pooling objective response estimates across two studies (Barete et al. [2015] and Valent et al. [2003]) that reported on ORR with cladribine and interferon, respectively. The CADTH Methods team and the EGP identified several limitations with the naive treatment comparison. Most notably, when using a naive treatment comparison, it is not possible to determine if any observed differences or similarities in efficacy between therapies are solely due to the treatment or rather due to bias or confounding factors such as differences in study populations, definitions of outcomes, or study designs. Other factors that increased the uncertainty in the effect estimates included insufficient reporting of study methodologies, small sample sizes, limited data reporting, retrospective analyses, missing data elements, and the absence of indirect comparisons for safety and QoL data. pERC agreed with the Methods team and EGP that, given these limitations, the comparative effectiveness of midostaurin versus available treatment options remains highly uncertain.

Need and burden of illness: Need for effective treatment options Advanced SM comprises three rare mast cell neoplasms: ASM, SM-AHM, and MCL. Based on extrapolating the results from a Danish population study (Cohen et al. [2014]) to Canada's population of 37 million, the CGP estimated that there would be approximately 20 new patients per year with advanced SM (this may increase as SM is increasingly recognized). Advanced SM is an aggressive disease with high morbidity and mortality. Disease-related symptoms include bone disease, ascites, liver dysfunction, and skin disease. The median OS is three-and-a-half years in patients with ASM, two years in those with SM-AHN, and less than six months in those with MCL. There is no SOC for the treatment of advanced SM in Canada and cytoreductive therapies currently used off-label in Canada include interferon, cladribine, imatinib, hydroxyurea, and cytarabine. Cytoreductive therapy aims to achieve mast cell debulking in the setting of aggressive disease. pERC agreed with the CGP that response rates to currently available cytoreductive theories are low and that there is an unmet need for effective and tolerable treatments that reduce disease symptoms and extend survival.

Registered clinician input: Unmet need, very symptomatic disease with poor outcomes
One individual clinician input was provided by a hematologist/oncologist from Cancer Care Ontario Hematology Drug Advisory Committee for the review of midostaurin for the treatment of adult patients with ASM, SM-AHN, and MCL. The clinician asserted an unmet medical need considering that SM is a very symptomatic disease with poor outcomes. Midostaurin was recommended as a first-line treatment as it appears to have better responses than other treatments and seems to be tolerable.

PATIENT-BASED VALUES

Values of patients with advanced SM: Better symptom management and improved QoL and survival.
One patient group, MSC, with support from CORD, provided input on midostaurin for SM.

From a patient's perspective, SM is a very aggressive and debilitating condition with limited treatment options. Patients considered symptom control to be their biggest concern, as the disease has significantly impacted their ability to carry out their daily activities. Some of the most debilitating symptoms reported by patients include fatigue, headaches, lightheadedness, GI problems, and skin-related issues (such as lesions, hives, rashes and itching, and allergic reactions). MSC and CORD commented that overall, current therapies do not appear to halt the progression of disease or control bouts of symptoms. Some of the most common therapies that have been used by patients to control symptoms included antihistamines (for skin and abdominal reactions), allergen immunotherapy or epinephrine (for allergic reactions), steroids, and chemotherapy.

Patients valued having alternative treatment options that focused on better symptom management and improved QoL and survival.

Patient values on treatment: Experience reflects both the benefits of the therapy as well as the challenges
The patient groups provided the perspective of five patients with experience with midostaurin. The patients' experiences with midostaurin reflected both the benefits of the therapy as well as its challenges. According to MSC and CORD, two patients who had experience with midostaurin felt overall very positive, primarily because they felt that the therapy reduced the burden of disease and perhaps, most importantly,

allowed them to return to "normal, daily life." Several patients who had experience with midostaurin spoke of the benefits and hope for future disease management but were also challenged by the drug regimen and side effects. As reported by MSC and CORD, in one case, the patient adapted the drug schedule and, in another situation, the patient said that issues were resolved with pre-treatment or concomitant therapy. Two patients chose not to continue therapy with midostaurin because of its side effects. MSC and CORD cautioned that because the number of patients who have experience with midostaurin is small, it may be difficult to generalize their reactions to a larger patient population.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The EGP assessed one cost-utility analysis (cost per quality-adjusted life-year gained) of midostaurin compared with SOC, defined as a combination of available therapies (e.g., interferon, hydroxyurea, cladribine, and cytarabine) in adult patients with ASM, SM-AHN, or MCL.

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were OS, treatment duration, ORR, and utilities.

Costs considered in the analysis included those related to drug acquisition and administration, disease management health care resource utilization, and costs of AEs, subsequent treatment, and terminal care.

Drug costs: Treatment cost of midostaurin and comparators

- Midostaurin costs $167.92 per 25 mg capsule
  Dosage schedule: 100 mg twice daily
  Cost per 28-day cycle: $37,615.16

Standard of care:

- Cladribine costs $4.00/1 mL vial (1 mg/mL)
  Cost per 28-day cycle: $199.68
- Cytarabine costs $0.06/500 mg vial
  Cost per 28-day cycle: $0.46
- Interferon costs $33.99/0.5 mL vial (3 MMU/mL)
  Cost per 28-day cycle: $407.88
- Hydroxyurea costs $1.02/500 mg capsule
  Cost per 28-day cycle: $81.49
- 28-day cycle costs of SOC (weighted average by estimated market shares in Canada): $308.73.

Cost-utility estimates: Substantial uncertainty in clinical effectiveness estimates

The submitted base-case incremental cost-utility ratios (ICURs) were lower than the EGP's ICUR estimates (submitted probabilistic ICUR versus reanalyzed probabilistic ICUR: $478,035 versus $1,056,688). This was primarily due to the following factors:

- Sourcing an alternative OS HR from a non–peer-reviewed oral presentation by Reiter et al. (2019) instead of from Chandesris et al. (2016/2017): Reiter et al. 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. The EGP felt that the Reiter et al. study appeared to provide more methodological details, better matching than the Chandesris et al. study, and a more conservative HR.

- Choosing SF-12 (Short-Form Health Survey with a six-item descriptive system [SF-6D]) values rather than EuroQol 5-Dimensions scores: The EGP felt that using SF-12 (SF-6D) values may increase face validity and enable better generalizability to the Canadian population.

- Using an alternative mix of cytoreductive treatments for the SOC option: The CGP's estimate of the SOC treatment options for advanced SM in Canada were identified as interferon (50%), cladribine (40%), and imatinib (10%); the latter for those without the KIT D816V mutation.

- Increasing the lifetime horizon from 10 years to a lifetime horizon of 30 years: The EGP chose a lifetime time horizon (corresponding to 30 years based on exponential extrapolations) to fully

capture all downstream consequences (i.e., costs and benefit) of the different treatment options, as recommended by CADTH guidelines.

- Selecting an exponential parametric curve fit for OS rather than a piecewise extrapolation using a log-normal parametric tail: The EGP chose a more conservative extrapolation given the amount and quality of evidence around OS for advanced SM, the high uncertainty in comparative effectiveness, and that the piecewise approach consists of long tails that may overestimate survival for this population of patients with advanced SM with a median age of 60 years old. The CGP supported the exponential parametric curve fit.

  Upon reconsideration of the Initial Recommendation, pERC considered feedback from the sponsor regarding the use of an exponential rather than a log-normal function for the extrapolation of OS by the EGP. Given the lack of robust long-term survival evidence, pERC agreed with the EGP on upholding its initial analysis, which was more conservative than using trial-based survival to benchmark survival in the economic model. Overall, pERC reiterated that, at the submitted price, midostaurin is not cost-effective.

The EGP noted several limitations in the submitted economic evaluation, particularly the lack of a direct head-to-head comparison of relevant comparators (midostaurin versus SOC) and high-level quality data to inform important clinical inputs (e.g., OS, ORR, HRQoL), as well as costs. The EGP also highlighted that the heterogeneity in disease subclass could not be evaluated due to the rarity of the condition. The main factor that influenced the incremental cost of midostaurin was the cost of midostaurin. The main factors that influenced the clinical gains associated with midostaurin were the OS HR, and the HRQoL values (utilities) associated with different health states. The EGP agreed with the CADTH Methods team and the CGP that, given the limitations associated with the naive treatment comparison of midostaurin compared with SOC, the comparative effectiveness of midostaurin versus available treatment options remained highly uncertain (see Limitations in the Evidence in Brief section for more details on the naive treatment comparison).

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact likely underestimated

PAG identified that the high cost and affordability of midostaurin may be a barrier to implementation, there is a potential for pill burden with a total of eight capsules daily along with concomitant medications, and some jurisdictions do not have KIT D816V mutation testing available in their provinces. Factors that had the largest impact on the budget impact analysis included the proportion of public coverage, the market uptake of midostaurin, the incidence rates for SM, and the treatment duration for midostaurin. The EGP noted that a key limitation of the budget impact analysis was that important model inputs were based primarily on assumptions.

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:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. 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:

- Drs. Michael Crump and Catherine Moltzan, who were not present for the meeting.
- Dr. Maureen Trudeau, who did not vote due to her role as the pERC chair.
- Dr. Kelvin Chan, who was absent for the deliberation on midostaurin.

pERC Membership During Deliberation of the Final Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. 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 Final Recommendation, except:

- Dr. Avram Denburg, who was not present for the meeting
- Dr. Christopher Longo, who was not present for discussion and deliberation for this review
- Dr. Maureen Trudeau, who did not vote because of her role as the pERC Chair.

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 midostaurin (Rydapt) for advanced systematic mastocytosis, through their declarations, no member had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were 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*. Novartis Pharmaceuticals

Canada Inc., as the primary data owner, did not agree to the disclosure of clinical information, therefore, this information has been redacted in this Recommendation and publicly available guidance reports.

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.

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