pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL 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.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with the *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Midostaurin (Rydapt)

Submitted Funding Request:
In combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed *FLT*3-mutated acute myeloid leukemia (AML)

Submitted by:
Novartis Pharmaceuticals Canada Inc.

Manufactured by:
Novartis Pharmaceuticals Canada Inc.

NOC Date:
July 21, 2017

Submission Date:
June 12, 2017

Initial Recommendation Issued:
November 30, 2017

Drug Costs

Approximate per Patient Drug Costs, per Month (28 days):

Submitted list price of $167.90 per 25 mg capsule

* Note: Costs are calculated based on an average weight of 70 kg and body surface area of 1.7m².

Midostaurin in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy costs:

- $496.98 per day
- $10,436.54 per 21-day course

pERC RECOMMENDATION

pERC recommends the reimbursement of midostaurin in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed FMS-like tyrosine kinase 3 (*FLT*3)-mutated acute myeloid leukemia (AML). Funding should be for patients who are deemed fit to receive standard chemotherapy induction and consolidation chemotherapy.

The Committee made this recommendation because it was satisfied that there is a net clinical benefit of the addition of midostaurin in this patient population compared with placebo based on a statistically significant and clinically meaningful improvement in overall survival (OS). pERC made this recommendation even though it acknowledged that there were no data on quality of life and that treatment with midostaurin is associated with manageable but not insignificant toxicities.

pERC agreed that midostaurin aligns with patient values of symptom

control, disease control, and the need for an effective treatment option that prolongs survival.

The Committee concluded that, based on the submitted economic analysis and at the submitted price, midostaurin in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy is cost-effective in patients with newly diagnosed *FLT*3-mutated AML when compared with standard of care. However, pERC concluded that the market uptake may be greater than estimated; therefore the submitted budget impact of the addition of midostaurin to standard of care may be underestimated and the actual budget impact may be substantially greater.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Budget Impact
Given that pERC was satisfied that there is a net clinical benefit of midostaurin in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed *FLT*3-mutated AML, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve affordability.

Time-Limited Need for Patients Currently Receiving Standard Induction and Consolidation Chemotherapy
At the time of implementing a funding recommendation for midostaurin in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed *FLT*3-mutated AML, jurisdictions may want to consider addressing the short-term, time-limited need for midostaurin in combination with standard induction and consolidation chemotherapy for patients who are currently receiving standard induction and consolidation chemotherapy and have not experienced disease progression or intolerance during the first-line treatment.

Accessibility and Feasibility of Companion Diagnostic Test
Given that midostaurin is administered beginning at day 8 of induction, *FLT*3-mutation testing results should be available prior to or within a week after commencing induction therapy. pERC noted that it would be desirable for jurisdictions to have validated, reliable *FLT*3 testing available in Canada both to identify the relevant patient population and to manage the budget impact. The Committee noted that centres in Canada that regularly treat adults with AML should have the capacity to obtain timely *FLT*3 results before initiating induction therapy. Midostaurin should be given by day 8 of induction therapy or as soon as possible thereafter. pERC noted that midostaurin should not be administered after the end of the consolidation phase of treatment.

Insufficient Evidence to Support the Use of Midostaurin in Combination With the FLAG-IDA Regimen
There is currently insufficient evidence to support the use of midostaurin in combination with the FLAG-IDA regimen in patients with *FLT*3-mutated AML. pERC noted that the dose and type of anthracycline used in induction may differ across centres (e.g., daunorubicin or idarubicin). However, pERC noted that midostaurin can be added to any 7+3 induction chemotherapy regimen. Furthermore, pERC noted that consolidation with high-dose cytarabine is given for two to four cycles in Canada and at varying doses of 9 g/m^2 to 18 g/m^2 total per cycle. pERC noted that midostaurin can be added to the consolidation phase of therapy, regardless of the varying dose and number of cycles.

Insufficient Evidence to Support the Use of Midostaurin in

Re-Induction and Re-Consolidation
There is currently insufficient evidence to support the use of midostaurin during re-induction and re-consolidation phases. The use of midostaurin in patients who are undergoing re-induction and re-consolidation is out of scope. Midostaurin is to be used in the induction and consolidation phases of treatment for newly diagnosed *FLT*3-mutated patients

Insufficient Evidence to Support the Use of Midostaurin in Patients With Therapy-Related AML
There is insufficient evidence to support the use of midostaurin in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy in patients who have developed therapy-related AML after prior radiation therapy or chemotherapy for another cancer or disorder.

SUMMARY OF pERC DELIBERATIONS

pERC's Deliberative Framework for drug-recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

In Canada, approximately 25% of adult cases of leukemia are AML. In 2016, there were 1,475 new cases of AML in Canada. A recently recognized AML prognostic subgroup is based on the molecular genetic signature of the leukemic cells activating mutations of the *FLT*3 gene, occurring in approximately 30% of newly diagnosed AML patients. Patients with *FLT*3 mutation experience higher relapse rates and poorer OS compared with *FLT*3-negative patients. The standard of care in Canada for adults younger than 70 years old is dual chemotherapy remission induction with an anthracycline for three days (daunorubicin or idarubicin) in combination with infusional cytarabine for seven days at intermediate doses (7+3). Registered clinicians also noted that FLAG-IDA is an option for curative therapy. If complete remission is achieved and a curative outcome remains the objective, post-remission therapy consisting of consolidation with high-dose cytarabine for two to four cycles is offered. For patients with *FLT*3 mutation, outcomes after high-dose cytarabine consolidation alone are disappointing. Consequently, curative allogeneic stem cell transplantation (SCT) is offered as soon as possible, provided a suitable donor can be identified. In patients with *FLT*3 mutations, apart from undergoing SCT in the first complete remission, targeted mutation-specific interventions are needed. Currently, there are no targeted treatments aimed at *FLT*3-mutated AML that demonstrate improvement in survival, thus representing an unmet need for this high-risk group of AML patients. Registered clinicians also noted that there is a need for therapy that may increase the rate of SCT in this patient population. Therefore, pERC agreed that there is an unmet need for patients with *FLT*3-mutated AML.

pERC deliberated on the results of one phase III, double-blind randomized controlled trial, RATIFY, which evaluated the efficacy and safety of midostaurin versus placebo, both in combination with standard cytarabine and daunorubicin induction and high-dose cytarabine consolidation chemotherapy in patients with newly diagnosed AML with *FLT*3 mutation. The Committee noted that the RATIFY trial included three phases of treatment: induction, consolidation, and maintenance. However, the request for reimbursement is only for the induction and consolidation phases of treatment, because Health Canada did not approve the use of midostaurin in the maintenance phase. pERC considered the use of midostaurin as an add-on to standard induction and consolidation treatment. The Committee noted that the RATIFY trial reported a statistically significant improvement in OS in favour of midostaurin plus standard chemotherapy compared with placebo in combination with standard chemotherapy. pERC also noted an additional analysis provided by the submitter that removed patients who received maintenance therapy, to reflect the reimbursement request, and noted a similar direction and magnitude of effect compared with the intention-to-treat population (all patients including those treated in the maintenance setting) with regard to OS. pERC noted that the Kaplan-Meier curves begin to separate at approximately one month, approximately after one cycle of induction, suggesting that the effect of midostaurin begins early in the treatment phase. The Committee also considered that the median duration of exposure to midostaurin was approximately 40 days. pERC also discussed the fact that the observed rate of patients receiving SCT was much higher in the RATIFY trial (57%) than planned during the study design. pERC noted that this may be due to variation in transplant practices across participating countries. The Committee also noted that the Clinical Guidance Panel (CGP) indicated that in clinical practice, more than 50% of *FLT*3-mutated AML patients will proceed to SCT in the first complete remission and would therefore not be exposed to midostaurin maintenance therapy. Therefore, considering these factors, pERC agreed with CGP that the benefit of midostaurin appears to begin early in the induction and consolidation phases of treatment.

pERC noted that patients enrolled in the RATIFY trial were much younger than the typical patient with *FLT*3-mutated AML presenting in clinical practice. pERC noted that CGP indicated that patients are offered curative standard induction and consolidation chemotherapy based on their ability to tolerate chemotherapy and not based on age alone. Therefore, pERC agreed with CGP that treatment with

midostaurin should be extended to patients who are deemed fit to receive intensive induction and consolidation, regardless of age.

pERC deliberated on the toxicity profile of midostaurin and noted that there were more frequent grade 3 or higher adverse events compared with the placebo. The most common grade 3 to grade 5 adverse events reported among patients receiving midostaurin included thrombocytopenia, neutropenia, anemia, febrile neutropenia, and infection. The Committee discussed that there may be the potential for drug interactions with midostaurin and antifungal drugs. While pERC noted that adverse events may have occurred in patients exposed to high levels of midostaurin, it also noted that adverse event rates for infection were expected in the trial and were managed by dose reductions. Overall, pERC agreed that although there was increased toxicity with midostaurin, the side effects are manageable through monitoring and appropriate dose adjustments.

pERC therefore concluded that there is a net clinical benefit of midostaurin in combination with standard induction and consolidation chemotherapy compared with placebo, based on the clinically meaningful results in OS and a manageable, but not insignificant, toxicity profile. pERC also concluded that midostaurin addresses an unmet need for patients with *FLT*3-mutated AML, as there is a need for effective targeted mutation-specific interventions that improve survival for this high-risk group of AML patients. In making this conclusion, the Committee also acknowledged the lack of evidence of the effect of midostaurin on patients' quality of life, since the RATIFY trial did not include quality of life as an outcome.

pERC deliberated on patient input from one patient advocacy group. Patient input indicated that patients value new, effective treatment options that offer disease control, longer remission, and improvement in quality of life and OS. The Committee noted that patients who have not had experience with midostaurin were willing and prepared to tolerate severe side effects attributed to treatment for improved survival. Although pERC was not able to comment on the impact of midostaurin on patients' quality of life from the RATIFY trial, the Committee noted that patients who had experience with midostaurin reported that they felt better overall and noted substantial improvement in the ability to take part in daily activities. Overall, pERC concluded that midostaurin aligns with patient values because it provides disease control, extends remission, and prolongs survival.

pERC deliberated on the cost-effectiveness of the addition of midostaurin to standard induction and consolidation chemotherapy compared with standard of care. The Committee considered the estimates provided by the submitter and noted that the pCODR Economic Guidance Panel (EGP) agreed with the submitter's estimate. pERC noted that a 15-year time horizon was considered reasonable in a cure model and that treatment with midostaurin would be short, being administered only in the induction and consolidation phases, and would be stopped if a patient went on to receive SCT. The submitted model assumed no relapse after SCT and no subsequent SCT. Furthermore, the Committee noted that utilities were estimated outside of the RATIFY trial, using a Time Trade Off technique in a sample of the general public in the UK. The Committee discussed that the EGP conducted several sensitivity analyses to explore uncertainty in the model, including modifying utility values for phases of treatment, mortality costs, routine care costs, duration of routine care, and SCT complication rate costs. However, pERC noted that the EGP concluded that none of the parameters tested significantly changed the base-case incremental cost-effectiveness ratio (ICER). pERC noted that the factors that most influenced the incremental cost included the cost of SCT and drug costs. The factors that most influenced the incremental effectiveness included the survival benefit of midostaurin. Overall, pERC noted that the true magnitude of the cost difference between the addition of midostaurin and standard of care is uncertain due to the use of resource utilization data for routine care from a study population different from that of the RATIFY trial and the use of unit costs that were not representative of the Canadian setting in the submitted model. pERC agreed with the EGP that the cost of routine care could have been overestimated and, therefore, the estimated ICER may be underestimated. However, pERC also considered sensitivity analyses conducted by the EGP indicating that the cost of routine care did not have a large impact on the ICER. Therefore, pERC concluded that at the submitted price and based on the submitted economic analysis, the addition of midostaurin to standard chemotherapy is cost-effective compared with standard of care.

pERC discussed the budget impact and noted that the factors that most influenced the budget-impact analysis included the proportion of patients expected to receive each cycle of treatment, the proportion

of patients receiving consolidation treatment, and the incidence of *FLT*3-mutated patients. pERC discussed that, if the addition of midostaurin were implemented, the market uptake of midostaurin could be much higher than estimated by the submitter and as high as 100% for eligible patients beginning in the first year. The Committee agreed that a higher market uptake was a reasonable assumption; therefore, the Committee felt that the submitted budget impact is likely underestimated. Therefore, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve affordability.

pERC deliberated on the feasibility of implementing a reimbursement recommendation for midostaurin in combination with standard induction and consolidation chemotherapy. pERC discussed the fact that a validated test is required to confirm the *FLT*3-mutation status of a patient. pERC noted that testing is done in most jurisdictions and that in provinces where *FLT*3 testing is not currently available, implementation of *FLT*3 testing would be required. pERC also noted that *FLT*3 test results should be available prior to or within one week after commencing induction therapy (7+3), as midostaurin would ideally commence eight days after beginning induction therapy. However, in cases where this is not possible, pERC noted that midostaurin should be given as soon as possible, but not administered after the consolidation phase of treatment.

pERC discussed the Provincial Advisory Group's request for guidance on a number of clinical scenarios to assist with implementation. The Committee noted that there would be a time-limited need for patients who have already started induction or consolidation therapy. In such cases, pERC agreed that it would be reasonable to offer midostaurin as an add-on therapy. The Committee also discussed that patients undergoing re-induction and re-consolidation should not be eligible for midostaurin and noted that midostaurin is to be used only in newly diagnosed, treatment-naive patients undergoing induction and consolidation therapy. Furthermore, the Committee discussed the fact that there is insufficient evidence from the available clinical trial to support the use of midostaurin in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy in patients who have developed therapy-related AML after prior radiation therapy or chemotherapy for another cancer or disorder.

pERC also noted that the dose and type of anthracycline used in induction may differ across centres (e.g., daunorubicin or idarubicin). However, pERC noted that midostaurin can be added to any 7+3 induction chemotherapy regimen. Furthermore, pERC noted that, in Canada, consolidation with high-dose cytarabine is given for two to four cycles and at varying doses of 9 g/m^2 to 18 g/m^2 total per cycle. pERC noted that midostaurin can be added to the consolidation phase of therapy regardless of the varying dose and number of cycles. The Committee discussed the fact that there are other induction regimens available in jurisdictions, including FLAG-IDA. pERC noted that clinicians representing Cancer Care Ontario's Hematology Drug Advisory Committee anticipate that midostaurin could be used with other induction regimens with curative intent in this population. However, pERC noted that, at this time, there is no evidence to support the use of midostaurin in other induction regimens other than induction with 7+3. Finally, pERC noted that although the RATIFY trial included the use of midostaurin in the maintenance phase, Health Canada did not include this phase as part of the indication. Therefore, midostaurin is to be used only in the Health Canada indicated phases of induction and consolidation.

EVIDENCE IN BRIEF

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

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget-impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient group: the Leukemia & Lymphoma Society of Canada (LLSC)
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of midostaurin in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed FMS-like tyrosine kinase 3 (*FLT3*)–mutated acute myeloid leukemia (AML).

Studies included: One randomized controlled trial

The pCODR systematic review included one open-label randomized controlled trial, the RATIFY trial. The RATIFY trial is a global, randomized, double-blind, phase III superiority trial comparing standard chemotherapy plus midostaurin to standard chemotherapy plus placebo in patients with newly diagnosed AML with *FLT3* mutation. Patients (n = 717) were randomized in block size of six, 1:1, stratified by *FLT3*-mutation subtype (tyrosine kinase domain, internal tandem duplication [ITD] high ratio, and ITD low ratio), to receive either standard chemotherapy plus midostaurin (n = 360) or standard chemotherapy plus placebo (n = 357) in induction, consolidation, and maintenance phases of therapy. pERC noted that the reimbursement request is for the use of midostaurin only in the induction and consolidation phases.

In the induction therapy stage, patients received daunorubicin (dosage of 60 mg/m^2 of body surface area per day administered by rapid IV injection on days 1, 2, and 3) and cytarabine (dosage of 200 mg/m^2 administered by continuous IV infusion on days 1 to 7). Midostaurin or placebo was administered at a dosage of 50 mg orally twice daily on days 8 to 21. On day 21, a bone marrow examination was performed. If definitive evidence of clinically significant residual leukemia was observed, a second cycle of induction therapy (identical to the first) was administered. If patients did not achieve complete remission after a second cycle of induction therapy, study treatment was discontinued.

In the consolidation therapy stage, patients who achieved complete remission after induction therapy received four 28-day cycles of consolidation therapy with high-dose cytarabine (dosage of 3,000 mg/m^2 over a period of three hours every 12 hours on days 1, 3, and 5). Midostaurin or placebo was administered at a dosage of 50 mg orally twice daily on days 8 to 21.

If patients remained in remission after completion of consolidation therapy, they received a maintenance phase of midostaurin or placebo (dosage of 50 mg orally twice daily for 12 28-day cycles). pERC noted that the maintenance phase was not considered in this review.

Transplantation was not mandated in the RATIFY trial protocol and was performed at the discretion of the investigator. If patients received SCT, midostaurin and/or placebo therapy was not resumed.

Patient populations: Patients aged 18 to 59 years with newly diagnosed acute myeloid leukemia with *FLT3* mutation

Baseline characteristics were generally well balanced between the treatment arms. Patients were eligible to participate in the RATIFY trial if they were between the ages of 18 and 59 years and had newly diagnosed AML with *FLT3*-positive mutation determined by analysis in a protocol-designated *FLT3* screening laboratory.

Overall, the median age of all patients was 48 years (range, 18 to 60). A higher proportion of females were randomized to the placebo group (n = 212, 60%) compared with the midostaurin group (n = 186, 52%). The majority of patients who reported race (n = 309) were Caucasian (89.0%); however, patients enrolled at European sites did not report race (n = 408). The subtypes of FLT3 mutation were balanced between both groups. Overall the proportions of patients with FLT3-mutation subtypes were 22.6% with TDK (n = 162), 47.6% with ITD with low allelic ratio (n = 341), and 30% with ITD with high allelic ratio (n = 214). In the midostaurin group, 90% (323 out of 360) were Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1, and in the placebo group, 87% (310 out of 357) were ECOG PS 0 or 1. The majority of the remaining patients were ECOG PS 2.

pERC noted that patients enrolled in the RATIFY trial were much younger than the typical *FLT*3-mutated AML patient seen in clinical practice. pERC noted that the Clinical Guidance Panel (CGP) indicated that patients are offered curative standard induction and consolidation chemotherapy based on their ability to tolerate chemotherapy and not based on age alone. Therefore, pERC agreed with CGP that treatment with midostaurin should be extended to patients who are deemed fit to receive intensive induction and consolidation, regardless of age.

Key efficacy results: No difference in median time to complete remission in both groups; statistically significant difference in overall survival in favour of midostaurin compared with placebo; high SCT rates

pERC deliberated on overall survival (OS), the primary outcome of the RATIFY trial, as well as key secondary outcomes. pERC noted that there was a statistically significant improvement in median OS in favour of midostaurin — specifically, 74.7 months (95% confidence interval [CI], 31.5 to not reported) compared with placebo at 25.6 months (95% CI, 18.6 to 42.9). Midostaurin, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, was associated with a significantly prolonged OS compared with placebo (hazard ratio 0.78; 95% CI, 0.63 to 0.96; *P* = 0.009). The four-year OS rate was 51.4% in the midostaurin group and 44.3% in the placebo group. The difference in four-year survival rate was 7.1%. Upon request from the pCODR Review Team, the submitter provided the hazard ratio for death removing patients (n = 205, 29%) who received maintenance to reflect the reimbursement request which includes only the induction and consolidation phases of treatment; as a result, 120 patients in the midostaurin group and 85 patients in the placebo group were removed. After removing the patients who received maintenance from the analysis, the reported hazard ratio was 0.82 (95% CI, 0.65 to 1.04). pERC noted a similar direction and magnitude of effect with regard to OS compared with the intention-to-treat population (all patients including those treated in the maintenance setting). As well, the Committee noted that the Kaplan–Meier curves begin to separate at approximately one month, approximately after one cycle of induction, suggesting that the effect of midostaurin begins early in the treatment phase. The Committee also noted that the median duration of exposure to midostaurin was approximately 40 days and that only a small proportion of patients (29%) entered the maintenance phase in the RATIFY trial. Therefore, considering these factors, pERC agreed with CGP that the benefit of midostaurin appears to begins early in the induction and consolidation phases of treatment.

pERC noted that there was no difference in the median time to complete remission in both groups (35 days; range 20 to 60 days). Similarly, the proportion of patients undergoing SCT after the first protocol-specified complete remission was 28.1% in the midostaurin group and 22.7% in the placebo group, respectively. pERC noted that the outcome of minimal residual disease was unknown between both groups.

Median event-free survival was 8.2 months (95% CI, 5.4 to 10.7) in the midostaurin group and 3.0 months (95% CI, 1.9 to 5.9) in the placebo group. The hazard ratio for an event was 0.78 (95% CI, 0.66 to 0.93; *P* = 0.002).

Overall, the proportion of patients undergoing SCT was much higher than the study design planned for: 59% of patients (213 out of 360) in the midostaurin group and 55% of patients (196 out of 357) in the placebo group compared with 15% which was the expected rate of transplantation in the study. pERC noted that the difference in SCT rates may be due to transplant practices across various centres.

Patient-reported outcomes: Not measured

Patient-reported outcomes, including quality of life, were not measured in the RATIFY trial; as such, pERC was not able to comment on the impact of midostaurin on patient quality of life.

Safety: Increased toxicity with midostaurin compared with placebo

pERC discussed the toxicity profile of midostaurin. The majority of patients enrolled in the trial experienced at least one grade 3 to grade 4 adverse event. The rate of grade 3, 4, or 5 anemia was higher in the midostaurin group than in the placebo group (92.7% versus 87.8%). Similarly, the rate of grade 3, 4, or 5 rash was also higher in the midostaurin group than in the placebo group (14.1% versus 7.6%). The rate of grade 3, 4, or 5 nausea was higher in the placebo group than in the midostaurin group (9.6% versus 5.6%). In the midostaurin group, 32 (9%) patients discontinued treatment due to an adverse event. In the placebo group, 22 (6.2%) patients discontinued treatment due to an adverse event. pERC noted that CGP indicated that the use of midostaurin in this setting appears to result in a toxicity profile similar to that of standard of care, with the exception of higher rates of skin reactions and anemia after exposure to midostaurin.

Registered clinician input: Unmet need, improve overall survival

Registered clinician input noted that midostaurin is to be used in combination with standard induction and consolidation chemotherapy for adult patients with newly diagnosed AML who are *FLT*3 mutation–positive. They noted that if remission is achieved, patients will proceed to allogenic SCT for curative treatment. Clinicians representing Cancer Care Ontario's Hematology Drug Advisory Committee anticipate that midostaurin could be used with other induction regimens with curative intent in this population. However, pERC noted that, at this time, there is no evidence to support the use of midostaurin in other induction regimens, including FLAG-IDA. A key benefit of midostaurin noted in the clinician input is that more eligible patients will be able to receive transplantation and survive longer. pERC noted that the proportions of patients who received SCT over time was not that different in the midostaurin group (59%) and the placebo group (55%), but further noted that there was a clinically meaningful improvement in OS. Registered clinicians also noted that there were few grade 3 to grade 4 adverse events attributed to midostaurin.

Need: Effective treatment options that improve survival

In Canada, approximately 25% of adult cases of leukemia are AML cases. In 2016, there were 1,475 new cases of AML in Canada. A more recently recognized AML prognostic subgroup is based on the molecular genetic signature of the leukemic cells activating mutations of the *FLT*3 gene occurring in approximately 30% of newly diagnosed AML patients. Patients with *FLT*3 mutation experience higher relapse rates and poorer OS compared with *FLT*3-negative patients. *FLT*3-mutation status is considered a poor risk biomarker. In patients with *FLT*3 mutations, apart from the recommendation to undergo hematopoietic cell transplantation in the first complete remission, targeted mutation-specific interventions are needed. Currently, there are no targeted treatments aimed at *FLT*3-mutated AML that demonstrate improvement in survival, thus representing an unmet need for this high-risk group of patients. Therefore, pERC agreed that there is an unmet need for patients with *FLT*3-mutated AML.

PATIENT-BASED VALUES

Experiences of patients with AML: High symptom burden, significant side effects with current treatment

Patient input from the Leukemia & Lymphoma Society of Canada (LLSC) indicated that a diagnosis of AML is a challenging and overwhelming experience for patients and their families, as it impacts their relationships with their communities and families and can have severe financial implications. The symptoms of AML experienced by patients include loss of appetite, fever and/or night sweats, fatigue, pain, bruising and/or bleeding, dizziness, and rashes/skin changes.

LLSC reported that standard treatment for AML patients includes induction chemotherapy with a cytarabine/anthracycline combination followed by up to four cycles of consolidation (post-remission) chemotherapy and either SCT. In some cases, radiation therapy and a bone marrow transplant are also necessary. LLSC reported that the majority of respondents stated that the current treatments available did a sufficient job in managing their cancer symptoms; however, there are significant side effects that come with treatment that patient respondents have to manage.

Patient values regarding treatment: Improve overall survival, disease control, manage symptoms

pERC deliberated on patient input from one patient advocacy group. Patient input indicated that patients value new, effective treatment options that offer disease control, longer remission, and improvement in

quality of life and OS. The Committee noted that patients who have not had experience with midostaurin were willing and prepared to tolerate severe side effects associated with treatment for improved survival. Patient input indicated that the most important symptoms to manage were pain, fatigue, loss of appetite/weight loss, and rashes/skin changes.

The Committee noted that the RATIFY trial did not collect quality-of-life data. Although pERC was not able to comment on the effect of midostaurin on patients' quality of life, the Committee noted that patients who had experience with midostaurin reported they felt better overall and noted substantial improvement in the ability to take part in daily activities. The Leukemia & Lymphoma Society of Canada indicated that the following were some of the benefits that respondents who received midostaurin reported: an increase in appetite and substantial improvement in daily activities but also fatigue and weakness.

ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel (EGP) assessed the submitter's cost-effectiveness and cost-utility analyses of midostaurin compared with standard of care, consisting of induction therapy with IV daunorubicin (60 mg/m^2 on days 1 to 3) and IV cytarabine (200 mg/m^2 on days 1 to 7) for adult patients with newly diagnosed *FLT*3 mutation–positive AML. If patients achieved complete remission after induction therapy, they then received four 28-day cycles of consolidation therapy with high-dose cytarabine (dosage of 3,000 mg/m^2 over a period of three hours every 12 hours on days 1, 3, and 5). Midostaurin or placebo was administered at a dosage of 50 mg orally twice daily on days 8 to 21. The maintenance phase of therapy was not considered in the pharmacoeconomic model.

Basis of the economic model: partitioned survival model comprised of five health states

The pharmacoeconomic model was comprised of five health states: AML diagnosis/induction, complete remission (including consolidation and beyond), relapse/refractory (secondary therapy/re-induction), SCT, and mortality.

All patients started from the initial AML diagnosis/induction state and moved to the complete remission state, the relapse state, or the death state. Patients in the complete remission state could move to relapse, SCT, or death states, but only these patients could receive SCT prior to relapse. SCT patients could move only to death (absorbing) state (i.e., no relapse/subsequent therapy after SCT was assumed).

Costs considered in the analysis included drug costs, SCT therapy costs, secondary therapy costs, mortality costs, routine care costs, adverse event costs, and SCT complication costs.

The clinical effect considered in the analysis was based on OS and event-free survival from the RATIFY trial reflective of six years of follow-up. The OS estimates were corrected to remove the efficacy of midostaurin during the maintenance phase. Extrapolation was used to model OS and event-free survival beyond the trial duration to 15 years using a cure model. Drug utilization information came from the trial with drug costs coming from Canadian sources. Resource utilization for routine care (all medical care costs except medications) came from a UK study. Unit costs for routine care came from Canadian sources, but the total costs did not reflect the Canadian fee-for-service reimbursement structure. The occurrence of adverse events came from the RATIFY trial with unit costs coming from Canadian sources. Utilities were estimated outside the trial, using a Time Trade Off technique in a sample of the general public in the UK.

Drug costs: High cost of midostaurin

The list price of midostaurin is $167.90 per 25 mg tablet. At the recommended dosage of 50 mg twice per day, the cost of adding on midostaurin to standard of care is $496.98 per day and $10,436.54 per 21-day course (used days 8 to 21 of each induction and consolidation cycle), assuming an average body weight of 70 kg.

The costs of standard-of-care treatment, assuming an average body weight of 70 kg, are as follows:

- Induction: Daunorubicin costs $93.00 per 20 mg vial. At the recommended dosage of 60 mg/m^2 on days 1 to 3 of a 21-day cycle, daunorubicin costs $67.75 per day or $1,422.90 per 21-day

course (used days 1 to 3 of each cycle). Cytarabine costs $6.75 per 100 mg vial. At the recommended dosage of 200 mg/m^2 daily by continuous IV for seven days of a 21-day cycle, cytarabine costs $7.65 per day or $160.65 per 21-day course.

- Consolidation: Cytarabine costs $6.75 per 100 mg vial. At the recommended dosage of 3,000 mg/m^2 over three hours every 12 hours on days 1, 3, and 5, cytarabine costs $49.18 per day or $1,032.75 per 21-day course.

Cost-effectiveness estimates: Cost-effective at the submitted price

pERC deliberated upon the cost-effectiveness of midostaurin compared with standard of care. pERC noted that the pCODR EGP's best estimate of $22,579 per quality-adjusted life-year was the same as the submitter's estimate. pERC noted that a 15-year time horizon was considered reasonable in a cure model and that treatment with midostaurin would be short, would be only in the induction and consolidation phases of treatment, and would be stopped if a patient went on to receive SCT. The submitted model assumed no relapse after SCT and no subsequent SCT. pERC discussed that the EGP noted a number of limitations with the submitted model, including but not limited to the use of a different population and different health care system from the Canadian setting to estimate routine care costs for AML patients; using utility estimates that did not come from AML patients and assuming no events (other than survival) after SCT; assumptions around the costs for mortality and routine care; and assumptions around the duration of routine care and SCT complication rates. The EGP conducted reanalyses to adjust for these limitations in the submitted model, including modifying the utility for the SCT procedure and the utility for the induction period, mortality costs, routine care costs, duration of routine care, SCT complication rate costs (actual SCT rates could not be modified), and reducing the unit cost of midostaurin. However, pERC noted that the EGP concluded that none of the parameters tested significantly changed the submitter's base-case incremental cost-effectiveness ratio (ICER). pERC noted that the factors that most influenced the incremental cost included the cost of SCT and drug costs. The factors that most influenced the incremental effectiveness included the survival benefit of midostaurin.

The EGP noted that the model structure had limited flexibility in modifying the underlying hazard ratios for OS and event-free survival. However, the EGP noted that the submitter conducted sensitivity analyses using confidence intervals around the hazard ratios and different survival distributions, which had a minimal impact on the submitter's base-case ICER. Overall, pERC noted that the true magnitude of the cost difference between the addition of midostaurin and standard of care is uncertain due to the use of resource utilization data for routine care from a study population different from the RATIFY trial and the use of unit costs that were not representative of the Canadian setting. pERC agreed with the EGP that the cost of routine care may have been overestimated and, therefore, that the ICER may be underestimated. However, pERC considered that the EGP noted that the cost of routine care did not have a large impact on the ICER. Therefore, pERC concluded that, based on the submitted economic analysis and the submitted price, the addition of midostaurin is cost-effective compared with standard of care.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Access to *FLT*3-mutation testing; add-on oral therapy to IV chemotherapy during induction and consolidation therapy; budget impact likely underestimated

The Committee discussed factors affecting the feasibility of implementing a reimbursement recommendation for midostaurin. Input from PAG highlighted various considerations around implementing midostaurin. The Committee noted that there would be a time-limited need for patients who have already started induction or consolidation therapy. In these cases, pERC agreed that it would be reasonable to offer midostaurin as an add-on therapy. The Committee also discussed the fact that patients undergoing re-induction and re-consolidation would not be eligible for midostaurin and noted that midostaurin is to be used in newly diagnosed, treatment-naive patients undergoing induction and consolidation therapy. Furthermore, the Committee discussed that there is insufficient evidence from the available clinical trial to support the use of midostaurin in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy in patients who have developed therapy-related AML after prior radiation therapy or chemotherapy for another cancer or disorder. Finally, pERC noted that although the RATIFY trial included the use of midostaurin in the maintenance phase, Health Canada did not include this phase as part of the indication. Therefore, midostaurin is to be used only in the indicated phases of induction and consolidation.

pERC deliberated on the feasibility of implementing a reimbursement recommendation for midostaurin in combination with standard induction and consolidation chemotherapy. pERC noted that a validated test is required to confirm the *FLT*3-mutation status of a patient. pERC noted that testing is done in most jurisdictions and that, in provinces where *FLT*3 testing is not currently available, implementation of *FLT*3 testing would be required. pERC also noted that *FLT*3 test results should be made available before or within one week after commencing induction therapy, as midostaurin would ideally commence eight days after beginning induction therapy. However, in instances where this is not possible, pERC noted that midostaurin should be given as soon as possible but not administered after the consolidation phase of treatment.

pERC noted that the dose and type of anthracycline used in induction may differ across centres (e.g., daunorubicin or idarubicin). However, pERC noted that midostaurin can be added to any 7+3 induction chemotherapy regimen. Furthermore, pERC noted that, in Canada, consolidation with high-dose cytarabine is given for two to four cycles and at varying doses of 9 g/m^2 to 18 g/m^2 total per cycle. pERC noted that midostaurin can be added to the consolidation phase of therapy regardless of the varying dose and number of cycles. The Committee discussed the fact that there are other induction regimens available in jurisdictions, including FLAG-IDA. pERC noted that clinicians representing Cancer Care Ontario's Hematology Drug Advisory Committee anticipate that midostaurin could be used with other induction regimens with curative intent in this population. However, pERC noted that, at this time, there is no evidence to support the use of midostaurin in other induction regimens, including FLAG-IDA. Finally, pERC noted that although the RATIFY trial included the use of midostaurin in the maintenance phase, Health Canada did not include this phase as part of the indication. Therefore, midostaurin is to be used only in the indicated phases of induction and consolidation. Furthermore, the Committee noted that midostaurin would need to be started while the patient is in hospital for induction and consolidation therapy. pERC noted that in some provinces, drugs used while in hospital are not funded by the provincial cancer agency nor by the provincial public drug program.

The factors that most influence the budget-impact analysis include the percentage of patients expected to receive each cycle of treatment, the percentage of midostaurin patients expected to receive consolidation therapy, and the incidence of AML patients with the *FLT*3 mutation. pERC noted that, if the addition of midostaurin were implemented, the market uptake of midostaurin could be much higher than estimated by the submitter and as high as 100% for eligible patients beginning in the first year. The Committee agreed that a higher market uptake was a reasonable assumption; therefore, the Committee felt that the submitted budget impact is likely underestimated. Therefore, jurisdictions may want to consider pricing arrangements or cost structures that would improve affordability.

DRUG AND CONDITION INFORMATION

Drug Information	• Midostaurin is available as 25 mg soft gelatin capsules. • The recommended dose of midostaurin is 50 mg twice daily on days 8 to 21 of each cycle of induction with cytarabine and daunorubicin and on days 8 to 21 of each cycle of consolidation with cytarabine.
Cancer Treated	• Adult patients with newly diagnosed *FLT*3-mutated acute myeloid leukemia (AML)
Burden of Illness	• Approximately 30% of newly diagnosed AML patients are *FLT*3 mutation-positive. • *FLT*3-positive patients experience higher relapse rates and poorer overall survival than *FLT*3-negative patients.
Current Standard Treatment	• Standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy
Limitations of Current Therapy	• Currently, there are no targeted treatments aimed at *FLT*3-mutated AML that demonstrate improvement in survival, thus representing an unmet need for this high-risk group of patients.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

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

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Mike Doyle, Health Economist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Dr. Craig Earle and Lauren Flay Charbonneau, who were not present for the meeting
- Cameron Lane, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of pERC 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 acute myeloid leukemia, through their declarations, no members had a real, potential, or perceived conflict. Based on the application of the *pCODR Conflict of Interest Guidelines*, no members were excluded from voting.

Information sources used

To inform its deliberations, pERC was provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which included input from a patient advocacy group, a registered clinician, and the Provincial Advisory Group, as well as original patient advocacy group input submissions. 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 pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

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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