pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

This is a revised Final Recommendation which supersedes the Final Recommendation for this drug and indication dated April 21, 2015. The revision was made to specifically address the Request for Advice question from CADTH's pan-Canadian Oncology Drug Review (pCODR) Provincial Advisory Group (PAG) on a clinical issue that did not impact pCODR's Expert Review Committee (pERC's) previous comments on cost-effectiveness, patient values, or adoption feasibility.

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-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is amended based on a request for advice question submitted by PAG and feedback from eligible stakeholders. Subject to the economic evaluation, patient values, and adoption feasibility, this pERC Final Recommendation supersedes the previous Final Recommendation issued on April 21, 2015.

Drug: Bosutinib (Bosulif)

Submitter's Reimbursement Request: For the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior tyrosine kinase inhibitor (TKI) therapy, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate.

Request for Advice: Is there evidence of clinical benefit sufficient to extend reimbursement eligibility of bosutinib "for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior TKI therapy" without limiting it further to those "for whom subsequent treatment with imatinib, nilotinib, and dasatinib is not clinically appropriate?"

Submitted By: Pfizer Canada Inc.	**Manufactured By:** Pfizer Canada Inc.
NOC Date: March 7, 2014	**Submission Date:** May 30, 2014
Initial Recommendation: April 2, 2015	**Final Recommendation:** April 21, 2015 **Revised:** August 1, 2019

pERC RECOMMENDATION on REQUEST FOR ADVICE	Following a Request for Advice, the pCODR Expert Review Committee (pERC) recommends reimbursement of bosutinib (Bosulif) for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior TKI therapy. pERC made this recommendation because there was sufficient evidence from the systematic review to extend the reimbursement eligibility of bosutinib "for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) CML in adult patients with resistance or intolerance to prior TKI therapy" without limiting it further to those "for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate." pERC noted that the major cytogenetic remission (MCyR), major molecular response (MMR) and clinical significance of complete cytogenetic response (CCyR) rates for bosutinib in the second line (post-imatinib failure or intolerance) were similar to those achieved with dasatinib or nilotinib, with a comparable rate of discontinuation due to toxicity. pERC also noted the long-term follow-up quality of life (QoL) data were consistent with what was reviewed in the original submission. pERC noted that the request to extend reimbursement eligibility of bosutinib aligns with patient values of safe, effective treatments and improved quality of life (QoL) as well as the need to manage side-effects. pERC noted that these were consistent with the pERC recommendation from 2015. pERC could not assess the adoption feasibility, and cost-effectiveness of bosutinib in this expanded population, as the request for advice question submitted by the pCODR's PAG was specific to the clinical issue. For detailed information about the patient values, adoption feasibility, and the economic evaluation, please refer to: https://www.cadth.ca/sites/default/files/pcodr/pcodr_bosutinib_bosulif_cml_fn_rec.pdf
	No next steps for stakeholders were identified by pERC

SUMMARY OF pERC DELIBERATIONS ON REQUEST FOR ADVICE

On April 21, 2015, pERC issued a reimbursement recommendation for bosutinib (Bosulif) for chronic myeloid leukemia. On April 8, 2019, the pCODR Provincial Advisory Group (PAG) submitted the following Request for Advice (RFA):

- Is there evidence of clinical benefit sufficient to extend reimbursement eligibility of bosutinib "for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior TKI therapy" without limiting it further to those "for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate?"

pERC noted that the original 2015 reimbursement indication was restricted due to the Health Canada specifications in the Notice of Compliance with conditions (NOC/c) for longer follow-up data. pERC noted that the conditions on the NOC/c were removed as of a Health Canada Product Monograph dates December 10, 2018.

pERC considered updated findings from a single arm phase I/II trial, Study 200, investigating the safety and efficacy of bosutinib.. Alongside Study 200, pERC also reviewed evidence from a Japanese Study (NCT00811070), the ongoing Phase IV (BYOND) post-authorization study, and the match-adjusted indirect treatment comparisons (MAICs) of bosutinib versus ponatinib, dasatinib and nilotinib. pERC noted that the overall results were consistent with what was observed with other second-line TKIs studies and there is sufficient evidence to support expanding the bosutinib indication to the second-line setting. pERC acknowledged that there are additional studies evaluating the use of bosutinib in patients progressing after a second-line TKI treatment; however, the use of bosutinib in this patient population was recommended in the 2015 pERC reimbursement recommendation. As such, pERC noted that the evidence for the use of bosutinib beyond second-line had been previously deliberated upon in 2015 with a favorable reimbursement recommendation and is still applicable to the RFA patient population. pERC noted that evidence to support the use of other second-line TKIs is similar to the evidence available for bosutinib. pERC was satisfied with the evidence to support the choice of bosutinib as an option for patients with comorbidities, concomitant medications and/or those with drug specific BCR/ABL mutations. pERC noted that the progression-free survival (PFS) and overall survival (OS) results of the MAICs demonstrate that comparative efficacy of bosutinib, dasatinib, and nilotinib in the treatment of second-line CP-CML were consistent; however, pERC noted the limitations of the study design and that conclusions on comparative efficacy could not be drawn.

pERC commented that the level of evidence for the Request for Advice is similar to what was presented in 2015. pERC noted that the favourable cytogenetic response rates reported in 2015 demonstrated durable responses in the longer term follow-up results presented in the RFA. pERC also noted that these cytogenetic response rates are considered acceptable surrogates for long-term benefit. pERC discussed that although the level of evidence between the second-line TKIs is similar, there is uncertainty in the comparative effectiveness of agents, as no randomized controlled trials (RCTs) directly comparing TKIs in the second-line setting were identified by the pCODR systematic review. Furthermore, pERC acknowledged input from the pCODR Clinical Guidance Panel (CGP) that it was highly unlikely that an RCT comparing the effectiveness of these second-line treatment options in this patient population would be conducted.

In addition, pERC noted that the safety profile of bosutinib is different than other second-line TKIs. The most commonly reported adverse event (AE) was mostly gastrointestinal (diarrhea) and was manageable; this AE occurred mostly in the first year of bosutinib treatment. pERC also noted that there is a lower risk of cardiovascular events and pleural effusions with bosutinib compared to other second-line TKIs, and bosutinib could be an option for patients with certain comorbidities where other TKIs are not an option. pERC noted that cross-intolerance (defined as discontinuation of bosutinib for the same adverse events that lead to discontinuation for imatinib) was low for rash/edema and pleural effusions. pERC noted that rates of discontinuation between the TKIs were similar.

pERC commented that the quality of life (QoL) data for EQ-5D for second- and third-line chronic phase CML patients was collected up to 264 weeks while on bosutinib treatment and improvements from

baseline were reported. pERC also noted that the subgroup of patients with diarrhea had similar QoL improvement as the overall group. In addition, pERC noted that EQ-5D utility scores were stable throughout bosutinib treatment in the advanced phase CML patients and some improvements were observed in the blast phase patients.

pERC agreed with the CGP that the expanded indication for bosutinib would not imply that all patients would receive bosutinib, but that patients would have the option of bosutinib andto receive the other currently funded second-line TKI options. pERC commented that other than the side-effect profiles, the available treatments (dasatinib, nilotinib, and bosutinib) are comparable with respect to clinical effectiveness.

pERC also discussed whether an economic evaluation was warranted considering that the Request for Adviec (RFA) is based on a clinical issue. pERC noted that currently, it is not anticipated that the cost-effectiveness of bosutinib would be impacted by the RFA reimbursement recommendation. However, pERC did note that generic drug products may impact the anticipated cost-effectiveness of bosutinib.

pERC discussed that patients value having an effective, safe, treatment option which improves quality of life. pERC noted that having an additional treatment option for extending life with a different side effect profile would be of value to patients. pERC also noted that these values are consistent with what was noted for the original bosutinib review in 2015. pERC also discussed the concerns about generic drugs raised by individual patients who contributed to the RFA patient input. pERC agreed with the patient advocacy group that patient education on the safety and efficacy of generic drugs is needed for patients.

CONTEXT FOR REQUEST FOR ADVICE

PAG is seeking advice on extending the reimbursement eligibility of bosutinib “for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) CML in adults with resistance or intolerance to prior TKI therapy” without limiting it further to those “for whom subsequent treatment with imatinib, nilotinib, and dasatinib is not clinically appropriate.”

The pCODR recommendation from April 2015 was in line with the Health Canada Notice of Compliance with Conditions (NOC/c) issued in March 2014. In December 2018, Health Canada removed the conditions on the NOC/c, noting that the submitter (Pfizer Canada Inc.) had provided the final phase I/ II results of Study 200 along with supportive safety data which was required to meet the conditions for bosutinib (Bosulif)’s NOC. As such, the restrictions of use of bosutinib in patients with CML for whom subsequent treatment with imatinib, nilotinib, and dasatinib is not clinically appropriate were removed.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon the following to address the Provincial Advisory Group’s (PAG’s Request for Advice:

- a pCODR systematic review
- input from one patient advocacy group (CML Society of Canada)
- input from the manufacturer of bosutinib (Bosulif) (Pfizer Canada Inc.)

CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of bosutinib on patient outcomes, and where available, compared with dasatinib, nilotinib, and ponatinib for the second-line treatment of patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) CML in adults with resistance or intolerance to prior TKI therapy.

Studies included: 18 studies as an update to Study 200, two MAIC, and four observational studies

The pCODR systematic review included twenty-seven studies; the original pCODR submission for bosutinib for CML, eighteen updates to the phase I/II Study 200, the Japanese study (NCT00811070), phase 4 post-authorization study (BYOND), two match adjusted indirect treatment comparisons, and four observational studies.

The update to Study 200 reported the eight-years update for major cytogenetic remission (MCyR) with a probability of maintaining MCyR at eight years at 65%, clinical significance of complete cytogenetic response (CCyR) at 61%, treatment discontinuation due to AEs at 24%, and overall survival at eight years at 79%.

The Japanese study (NCT00811070) reported the five-year update with MCyR rate of 73%, CCyR rate of 67%, and major molecular response (MMR) rate of 53%. The PFS rate was 91% at 240 weeks and the overall survival (OS) rate was 98% at five years. Specifically, for the AP/BP populations, the MCyR rate was 50%, CCyR was 38%, and OS rate at two years of 58%.

The ongoing phase IV (BYOND) study reported the MCyR rate of 72% at one year, CCyR rate of 81%, and MMR rate of 83% for patients who had received one prior TKI.

pERC discussed the MAICs and noted several limitations for each. While the committee had concerns regarding the potential for bias in the MAICs, pERC felt that the consistency of results between all included studies in the systematic review was notable.

Patient populations: Majority of patients received prior imatinib

A total of 284 patients were included in the update for Study 200, of which 195 patients were imatinib refractory and 89 patients were imatinib intolerant. Additionally, patients selected for the MAIC were from the pivotal trials for each of the dasatinib, nilotinib, and bosutinib studies. Additional details are available in Table 5 of the pCODR Request for Advice Clinical Guidance Report.

Key efficacy results: Second-line OS, PFS, MCyR, and CCyR

Overall Survival

For Study 200, after eight years from the last patient enrolled, the OS rate was 79% (95% CI, 73 to 84) for the Second Line Chronic Phase CML (CP2L) subgroup. There was a decline in OS rate, where at year two the OS rate was 91.2% (95% CI, 87 to 94.0),[3] at year five the OS rate was 83.5% (95% CI, 78.1 to 87.7).

For Study NCT00811070, at years two and five the OS rates were both 98%. In addition, the OS rate at one year for the phase IV BYOND study was reported as 98%.

Progression-Free Survival

There were no updated results for Study 200 for PFS rates for CP2L. As previously reported, based on 24-month follow-up, the PFS rate at two years was 81% and the median PFS had not been reached.

For Study NCT00811070, at years two and five the PFS rates were 91%.

Cytogenetic Response (Major and Complete)

For Study 200, for the CP2L cohort the newly attained or maintained MCyR was 59% and the CCyR was 48%. Subsequent follow-up results reported similar results at minimum follow-ups of 48 months, 60 months, 96 months, six years, and seven years from the last patient enrolled. The majority of MCyR and CCyR had occurred in two years or less. After six years of follow-up the median MCyR duration had not been reached. pERC also noted that after eight years of follow-up, for patients with a valid baseline assessment (n = 262), that MCyR was achieved by 60% and CCyR by 50% of patients.

For Study NCT00811070, the CP2L cohort at baseline had a CCyR in 11 patients (24%), where MCyR was 73% and CCyR was 67%.

For the ongoing phase IV study, abstract level data were reported for the cytogenetic response rates. For the 144 evaluable patients, the cumulative confirmed MCyR by one year was 71.5% (63.4 to 78.7) and the cumulative complete cytogenetic response rate anytime on treatment was 81.3% (73.9 to 87.3).

Molecular Response

For Study 200, based on a median follow-up of 54.8 months (range 0.6 to 96.3), at year five for the CP2L cohort, the cumulative MMR was 42% (n = 82 of 197; 95% CI, 34.7 to 48.8).

For Study NCT00811070, only one CP2L patient had a Complete molecular response (CMR)at baseline, MMR was 53%, and CMR was 49%.

For the ongoing phase IV study, abstract level data were reported for the 46 evaluable patients who had received one prior TKI. The cumulative rate at any time on treatment for MMR was 82.6% (68.6 to 92.2).

Hematologic Response

There were no updated results for Study 200 for complete hematological remission (CHR). As previously reported, based on 24 months of follow-up, the CHR was 85 (n = 244 of 287; 95% CI, 80 to 89) for the CP2L cohort.

CHR occurred in 32 (71%) of patients in Study NCT00811070 CP2L cohort.

Quality of Life

Quality of Life for Chronic Phase Patients

EQ-5D

The mean EQ-5D visual analogue scale scores were 71.31 (95% CI, 68.32 to 74.29) and 72.56 (95% CI, 67.92 to 77.21) in the CP2L and third-line chronic phase CML (CP3L) cohorts, respectively. Similar results to the EQ-5D scores were observed, improvements were observed at weeks eight to 96, 120, 144, and 168 to 264 in the CP2L cohort and at weeks 48 to 96, 120, 168, and 240 in the CP3L cohort.

Fact-Leu

Baseline mean Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu) scores were similar between the CP2L and CP3L cohorts. Minimal important differences (MID) denoting benefit were observed for the CP2L cohort at weeks 168, 216, and 264 for emotional well being (EWB); at weeks 168 and 216 for FACT-G Total and FACT-Leu Total.

Fact-Leu in patients with chronic diarrhea

For patients with chronic diarrhea, 101 and 30 patients were in the CP2L and CP3L cohorts, respectively. Overall, baseline FACT-Leu general and summary scales were similar across cohorts and compared with the larger CP2L and CP3L cohorts.

Quality of Life for Accelerated and Blast Phase Patients

Baseline assessments were completed for FACT-Leu and EQ-5D for 76.3% and 77.6% of patients in the AP cohort and for 85.9% and 87.5% of patients in the BP cohort, respectively. There were sharp declines in completion rates in the BP and AP CML cohorts (FACT-Leu Total scores were 50.0% and 28% [week 24] and 16% and 3% [week 96]; EQ-5D utility scale scores were 51% and 25% [week 24] and 18% and 3% [week 96]).

EQ-5D

Health status as measured by EQ-5D utility scores were stable throughout treatment in AP CML patients; scores were significantly improved versus baseline at weeks 4, 8, 12, and 36 in Blast Phase (BP) CML patients. For mean visual analogue scale scores, there were significant improvements at weeks 8, 36, and 48 for AP CML patients; there were significant improvements at weeks 4, 8, 12, 24, 36, and 96 in BP CML patients.

FACT-Leu

Mean FACT-Leu Total scores met MIDs denoting benefit at weeks 24, 36, and 48 in both AP and BP cohorts; there were additional time points where MID were reached for BP (at weeks 4, 8, 12, and 96).

Harms Outcomes

For Study 200, newly occurring AEs for years one to four were assessed by cohort of CP2L, CP3L, and Advanced (Advanced Phase and Blast Phase). In year one, the most commonly reported AE with bosutinib was diarrhea with 239 (84%) patients with CP2L, 82 (69%) with CP3L, 67 (85%) with AP, and 41 (64%) with BP. In subsequent years, there were none or low newly occurring diarrhea AEs across all cohorts; rates of cardiac, vascular, and renal events were low at year one and throughout to year four.

Limitations

Comparator Information: Uncertainty in results of indirect treatment comparisons

The main limitation identified by pERC, which was previously identified in the original pCODR submission, is that there are no randomized controlled trials directly comparing bosutinib with nilotinib, dasatinib, or ponatinib in this patient population. Therefore, the comparative efficacy is unknown. pERC also noted that there are no planned or ongoing trials that will compare these TKIs in the second-line setting or beyond. pERC discussed the inherent limitations of observational studies and MAICs such as the inability to correct for unreported differences between the study populations, differences in outcome definitions between trials, as well as the lack of statistical analyses of the observational studies. However, pERC noted that the results of the observational studies as well as the MAICs were consistent with the included clinical studies.

In the absence of trials directly comparing bosutinib with dasatinib, nilotinib, and ponatinib for patients who have progressed or are intolerant to imatinib, pERC discussed observational studies as well as two MAICs and the limitations as well as biases associated with these studies. pERC noted that the comparison populations used were not gathered from national cohorts or registry data but instead, the nilotinib/dasatinib populations in the respective pivotal trials were used for comparison.

Furthermore, pERC noted that the limited methodological details provided in the included abstracts precluded an adequate critical appraisal.

Need: Alignment between Health Canada indication and reimbursement request

pERC noted that on April 21, 2015 bosutinib was recommended for reimbursement by pCODR for "treatment of patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) CML who have resistance or intolerance to prior TKI therapy, and for whom subsequent treatment with imatinib, nilotinib, and dasatinib is not clinically appropriate." At that time, the reimbursement request aligned with the Health Canada Notice of Compliance with Conditions (NOC/c) dated March 6, 2014. pERC discussed that on December 10, 2018, the Health Canada Product Monograph was revised to remove these conditions, and bosutinib is indicated "for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) CML in adult patients with resistance or intolerance to prior TKI therapy;" however, as of December 2018, jurisdictions participating in the pCODR process funded bosutinib for CML based on the original submitted criteria.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, 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. Kelvin Chan, who was not present for the meeting
- Daryl Bell, who did not vote due to his role as a patient member alternate

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 request for advice of bosutinib (Bosulif) for CML, through their declarations, six members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Request for Advice Report*, as well as the original stakeholder submissions to inform their deliberations.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (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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