

pCODR EXPERT REVIEW COMMITTEE (pERC) INITIAL RECOMMENDATION

The 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.

Providing Feedback on this Initial Recommendation

Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *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:
Bosutinib (Bosulif)

Submitted Funding 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 TKI therapy, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate.

Submitted By:
Pfizer Canada Inc.

Manufactured By:
Pfizer Canada Inc.

NOC/c Date:
March 07, 2014

Submission Date:
May 30, 2014

Initial Recommendation Issued:
April 2, 2015

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding bosutinib conditional on the cost effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) who have resistance or intolerance to prior TKI therapy, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate. Funding should be in patients who have a good performance status

The Committee made this recommendation because it concluded there was a net clinical benefit of bosutinib based on clinically meaningful major cytogenetic response rates, 1 and 2 year progression free survival and overall survival rates, a manageable toxicity profile and because it aligns with patient values. pERC, however, acknowledged that because of the non-comparative study design, there was considerable uncertainty around the magnitude of the net clinical benefit in comparison to other treatment options and, therefore, in the cost-effectiveness of bosutinib. This led to a wide range in the incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, bosutinib could not be considered cost-effective using either the manufacturer's or the Economic Guidance Panel's reanalysis estimates.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Collecting Evidence to Reduce Uncertainty in the Clinical Benefit and Cost-Effectiveness of Bosutinib

Given the considerable uncertainty in the magnitude of clinical benefit of bosutinib in patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous

leukemia (CML), pERC concluded that any additional prospective evidence that could be collected to decrease the uncertainty in the incremental effect would be of benefit in understanding the true cost-effectiveness of bosutinib. Specific information on efficacy, safety and quality of life would be of particular value.

Pricing Arrangements to Limit Budget Impact

Given that pERC was satisfied that there is a net clinical benefit of bosutinib in patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML), jurisdictions may want to consider pricing arrangements and/or cost structures that may help reduce the uncertainty in the budget impact of bosutinib.

SUMMARY OF pERC DELIBERATIONS

Chronic Myelogenous Leukemia (CML) is an uncommon clonal bone marrow stem cell disorder. There are approximately 450 cases of CML diagnosed annually in Canada with the majority of patients diagnosed in the chronic phase (CP) of the illness. The majority of CML patients are ineligible for potentially curative therapy with allogenic stem cell transplantation (ASCT). pERC noted that for those patients who are not candidates for ASCT, current therapies include the BCR-ABL tyrosine kinase inhibitor (TKI), imatinib in the first-line setting, or second generation TKIs, dasatinib and nilotinib, used as first or second-line treatment. Patients may be considered inappropriate for dasatinib or nilotinib treatment if they have a genetic mutation that predicts for reduced efficacy of a second-line agent or if patients have co-morbidities that may predispose them to a drug-related adverse events. Patients may also receive interferon in the third-line setting while patients with disease in the accelerated phase (AP) and blast phase (BP) setting may receive palliative treatment with hydroxyurea. Some of these available treatments are associated with significant toxicities, and have limited clinical benefit. Having considered that patients with CML can receive treatment for as long as 10 years, pERC noted the importance of new agents that are active with less toxicity and less risk of exacerbating existing co-morbidities.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

The pCODR systematic review included one non-comparative study (SKI-200), which examined the use of bosutinib in patients who were intolerant or resistant to imatinib, dasatinib or nilotinib. pERC concluded that there is a net clinical benefit of bosutinib in patients with chronic, accelerated or blast phase CML who have been treated with at least one previous TKI and are deemed to be intolerant or resistant to imatinib, dasatinib and nilotinib treatment. pERC considered the magnitude of major cytogenetic response (MCyR) experienced by a large proportion of patients in the SKI-200 study to be clinically meaningful. pERC accepted the Clinical Guidance Panel's conclusion that MCyR is a reasonable surrogate for overall survival and acknowledged that the substantial benefit in the one and two year progression free survival (PFS) and overall survival (OS) further supported the conclusion of a net clinical benefit. pERC discussed the quality of life (QoL) of patients in the study and noted that statistically significant improvements were observed from baseline for a number of scales in all subgroups of patients. While the patients in the trial were reflective of the clinical population and had a good QoL, the added improvement in QoL following treatment with bosutinib, particularly in the AP and BP population, were noted by pERC as improvements in QoL are not usually observed in this advanced disease setting. pERC also commended the collection and availability of long term QoL data in this study. pERC discussed the limitations of non-randomized studies and considered that, although the SKI-200 trial was appropriately conducted, the conclusions that can be drawn from non-comparative data are not as robust as those that can be drawn from randomized controlled trials. Therefore while pERC acknowledged that bosutinib demonstrates clinical benefit in patients, there was considerable uncertainty in the magnitude of benefit with bosutinib as randomized controlled trials comparing bosutinib to dasatinib, nilotinib and/or other relevant comparators including best supportive care (BSC) were not available. pERC also discussed the Clinical Guidance Panel's conclusions that a randomised controlled trial would not be feasible in this patient population. Following a robust discussion the Committee had contrary thoughts on feasibility issues and equipoise in the second-line setting as there were sufficient numbers of patients in the second-line setting who could have been randomised among currently available treatments to determine comparative efficacy. pERC, however, agreed that a randomised controlled trial would not be feasible beyond the second-line setting.

pERC discussed the toxicity profile of bosutinib and noted it to be different from currently available TKI's. Toxicities associated with bosutinib consisted mainly of gastrointestinal events (diarrhea, nausea and vomiting) and thrombocytopenia. These were noted to be more manageable in comparison to the toxicities associated with the other available TKI's (exacerbation of diabetes or peripheral vascular disease with nilotinib and asthma or prior/existing pleural effusion with dasatinib). In discussing treatment options other than TKIs, pERC noted that patients currently receive other treatments that are

associated with a negative impact on quality of life and significant toxicities (interferon in third-line CP patients and hydroxyurea in AP). Having discussed these multiple factors, pERC concluded that, subject to improved cost-effectiveness, bosutinib should be available for adult patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance or intolerance to prior TKI therapy, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate. pERC acknowledged that this population will predominantly be comprised of those who have exhausted funded TKI treatment options (ie. in the third-line setting) but there will also be rare circumstances in which patients will have pre-existing comorbidities or resistance/intolerance to dasatinib or nilotinib and may benefit from treatment with bosutinib (ie. in the second-line setting).

pERC deliberated on patient advocacy group input, which indicated that patients with CML value the addition of new treatment options that provide manageable toxicity profiles and improve quality of life. pERC agreed that bosutinib aligned with patient values based on the improvement in MCyR which is an acceptable surrogate for overall survival, one and two year progression-free survival rates, a manageable toxicity profile, and notable improvements in quality of life. pERC noted input from patients who had experience with bosutinib indicating that in some instances patients were able to return to work. This was consistent with the study results which showed notable improvements in quality of life (QoL).

pERC deliberated upon two economic analyses submitted by the manufacturer providing estimates on the cost-effectiveness of bosutinib compared with relevant treatment options. pERC discussed a comparison of bosutinib to dasatinib or nilotinib through a cost-minimization analysis (CMA). pERC noted that this type of economic analysis is only appropriate in instances where all efficacy outcomes (clinical effect, safety and QoL) have been demonstrated to be similar through a randomized controlled trial or an appropriately conducted network meta-analysis. In this submission, pERC noted that there is no direct or indirect evidence to validate assumptions of similar efficacy between bosutinib and dasatinib or nilotinib. pERC additionally considered that bosutinib has a different toxicity profile than the currently available TKIs and agreed with the Economic Guidance Panel (EGP) that the use of a CMA is inappropriate in this circumstance. A cost utility analysis addressing differences in cost and effectiveness is needed to determine the true cost-effectiveness of bosutinib compared to dasatinib or nilotinib. pERC was, therefore, unable to determine the cost-effectiveness of bosutinib. pERC acknowledged that the first deliberation by pERC on this review was deferred pending the provision of a cost-utility analysis to address the limitations discussed above. Additionally, the EGP had requested a cost-utilization analysis from the submitter on a number of occasions, in order to examine best supportive care as a comparator but this was not provided at the time.

pERC also discussed the results of a cost utility analysis it requested from the submitter, comparing bosutinib to hydroxyurea, interferon or stem cell transplant (SCT). In the absence of direct or indirect comparative data, pERC noted that multiple data sources from the literature and/or assumptions were used to populate clinical inputs within the cost utility analysis, all of which were confounded by factors that would be controlled for in an RCT. pERC, therefore, noted that due to the limitations of relying on non-comparative evidence from the SKI-200 study, there was substantial uncertainty in the magnitude of the clinical benefit associated with bosutinib. This made it challenging to estimate the incremental effect of treatment with bosutinib and, therefore, the resulting incremental cost-effectiveness estimates for bosutinib. This considerable uncertainty in the magnitude of clinical benefit of bosutinib led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, bosutinib could not be considered cost-effective at the submitted price.

pERC discussed the feasibility of implementing a positive funding recommendation for bosutinib. Input from the pCODR's Provincial Advisory Group indicated that there were concerns about indication creep into the first and second-line setting. Based upon discussion of the clinical evidence and the need for alternative treatment options in patients that have pre-existing conditions that make currently available second-line treatments, pERC agreed that it would be reasonable to use bosutinib in patients that have failed at least one previous TKI. pERC agreed that this would likely occur only in rare circumstances and that the patient population which will predominantly be treated with bosutinib are those who will have exhausted all available treatment options. pERC acknowledged that jurisdictions will need to consider the potential budgetary impact of making bosutinib available in the second or third-line setting. pERC noted that the first line use of bosutinib is not likely as there is no evidence that bosutinib is superior to imatinib. Having considered that patients are likely to be on life long treatment and will receive available

TKIs in sequence, pERC discussed the potential sequencing of treatment with bosutinib and other currently available TKIs. pERC acknowledged that data on sequencing of TKIs are limited and not informed by controlled clinical trials. pERC, however, agreed with the Clinical Guidance Panel that decisions beyond first-line therapy will likely be guided by the agents available for first-line therapy, clinical judgment, CML mutation status, and patient comorbidities. pERC discussed PAG's input highlighting the absence of a comparator arm in the study and acknowledging that although bosutinib shows meaningful clinical benefit, pERC was unable to determine the magnitude of the benefit as comparative data were not available.

EVIDENCE IN BRIEF

pERC deliberated upon a pCODR systematic review, other literature in the Clinical Guidance Report providing 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 advocacy group (The Chronic Myelogenous Leukemia Society of Canada) and input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

The objective of this review is to evaluate the effectiveness of bosutinib monotherapy 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, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate.

Studies included

The pCODR systematic review included one phase 1/2, open label study (SKI-200) examining the use of bosutinib in patients who were intolerant or resistant to imatinib, dasatinib or nilotinib. Bosutinib was given at a dose of 500mg/day. The dose could be adjusted to 600mg/day if patients were not responding and lowered to 300mg/day if patient's experienced severe drug related adverse events. pERC noted that a significant minority of patients who did not achieve response at the 500mg dose received an increase in dose to 600mg. pERC agreed that jurisdictions will need to consider the budgetary impact of this dose increase during implementation.

No randomized controlled trials were identified that met the eligibility criteria of this systematic review. pERC discussed the limitations of non-comparative data and the feasibility of conducting a randomized controlled trial in this population. Having noted the Clinical Guidance Panel's conclusion that a randomized controlled trial is likely not feasible, members expressed a variety of opinions regarding equipoise. Although previous regulatory approvals in CML have been made using non-comparative data, pERC noted that the second-line cohort within the study may have had sufficient patient numbers for randomization among appropriate comparators. pERC however agreed that a randomised trial would not be feasible for patients in the setting of third-line setting and beyond.

The pCODR review also provided contextual information on results from the BELA study (Cortes et al 2012 and Brummendorf et al 2014), an open-label randomized multinational phase III trial funded by Pfizer comparing bosutinib to imatinib for adult patients with a new (≤ 6 months) diagnosis of Ph-positive CP CML who had received no prior anti-leukemia treatment (except ≤ 6 months of anagrelide or hydroxyurea). pERC discussed the summary of results provided on the BELA study and agreed with the Clinical Guidance Panel's conclusion that the use of bosutinib as first-line therapy would be unlikely as the trial data did not support the superior efficacy of bosutinib compared to imatinib in this setting.

Patient populations: Heterogeneous CML population

The SKI-200 study included 546 patients receiving treatment in the following lines;

- 288 second-line CP (n=200 imatinib resistant and n=88 imatinib intolerant), of these 115 patients had mutations at baseline;
- 144 third-line CP (n=37 imatinib resistant or intolerant and dasatinib resistant, n=50 imatinib resistant or intolerant and dasatinib intolerant, n=27 imatinib resistant or intolerant and nilotinib resistant), of these 39 patients had mutations at baseline;
- 4 fourth line CP;
- 76 AP and 64 BP patients

The median age of patients was 53, 56, 50.5 and 48.5 in the second-line CP, third/fourth line CP, AP and BP arms of the trial, respectively. The majority of patients had an ECOG PS of 0 or 1 in the second-line CP (77% or 23%), third/fourth line CP (72% or 27), AP (54% or 43%) and BP (34% or 44%) arms, respectively. Twenty two percent of patients in the BP arm also had an ECOG PS of 2.

Key efficacy results: Clinically meaningful improvement in MCyR, 1 and 2 year OS

Key efficacy outcomes deliberated on by pERC included major cytogenetic response (MCyR) and progression free survival (PFS). MCyR was achieved in 59%, 32%, 35% and 30% of second line CP, third/fourth line CP, AP and BP patients, respectively. Although response rates decreased as the disease became more aggressive, pERC noted that the proportions of patients responding in each line of therapy did not differ among patients based upon resistance or intolerance to previous therapies. Similar rates of MCyR were also observed between patients with and without BCR-ABL mutations, with the exception of the T315I mutation. pERC also discussed improvements in 1 and 2 year PFS rates of 91% and 81% in the second-line CP patients and a 2 year OS rate of 91% in the second line cohort. This further supported the conclusion of net clinical benefit. One and two year OS rates were also 91% and 83% in the third and fourth-line cohorts.

pERC discussed the magnitude of MCyR experienced by patients and concluded it to be clinically meaningful. Although median OS data was not available, pERC considered the CGP's rationale regarding the association of OS with cytogenetic response in previous CML studies assessing second line therapy. Although recognizing that there is no direct evidence to support this correlation for bosutinib, pERC considered the high MCyR rates observed with bosutinib across all patient subgroups, the preservation of overall survival over one and two years and the magnitude of one and two year PFS supported the CGP's conclusion that bosutinib likely provides an OS benefit over BSC, hydroxyurea or interferon. pERC was, however, unable to determine the magnitude of benefit in comparison to other available therapies (dasatinib or nilotinib). Additionally, pERC noted the use of cytogenetic response in informing regulatory approvals for other drugs in this setting and the consensus within the CML treating community regarding MCyR being a surrogate for OS after over 10 years' experience of using TKI's in clinical practice. Having considered these factors, pERC accepted that the Clinical Guidance Panel's conclusion that MCyR is a reasonable surrogate for OS.

Quality of life: Improved quality of life during treatment

pERC noted input from patients highlighting the importance of a good quality of life during therapy. Patients indicated that this is important aspect for long term therapy as it would enable them to consistently stay on this therapy. pERC discussed that bosutinib provided improvements in quality of life to patients in most subgroups. Significant changes were observed as early as four weeks in both imatinib resistant and intolerant 2nd line CP patients. There were minimally important differences observed in the imatinib intolerant group only. Significant changes were also measured in 3rd line patients using the leukemia symptoms tool (LEUS) in dasatinib intolerant patients at weeks 12 and 24 ($p<0.01$), and in nilotinib-resistant subjects at weeks 4 and 8 ($p<0.05$). In AP and BP patients, clinically meaningful improvements in excess of the minimally important difference (MID) were observed at weeks 24 and 48 in the accelerated phase patients and in week 48 in the blast phase patients. pERC noted this to be of importance as improvements in quality of life are not routinely observed in patients with CML while on treatment, particularly in the AP and BP stage of their disease. Patients also reported that there can be exacerbations of pre-existing conditions with currently available TKI's (eg asthma, diabetes)'s, and a negative impact on quality of life due to the toxicities associated with agents such as interferon in third-line setting. They also noted that for CML patients in the acute blast phase, therapy is largely supportive care. Further to this, pERC noted that patients entered into the trial, although reflective of the clinical population, generally had a good QoL. The added improvement in quality of life further supported the benefit of bosutinib in preserving and improving the quality of life of patients. pERC also commended the collection and availability of long term QoL data in this study as it is of great importance to patients.

Safety: Manageable toxicity profile

pERC noted that the side effect profile of bosutinib differed from dasatinib and imatinib. Bosutinib toxicities consisted mainly of gastrointestinal effects (nausea, vomiting, diarrhea) and myelosuppression which may be successfully managed with dose interruptions and/or dose reductions without an apparent loss of benefit. Adverse events for patients with AP and BP CML were also similar to chronic phase patients. pERC contrasted this with the toxicities associated with the other available TKI's, including the exacerbation of underlying conditions (eg nilotinib: diabetes or peripheral vascular disease; dasatinib: asthma or prior/existing pleural effusion). Although comparative evidence is not available, pERC considered that bosutinib related toxicities are generally more manageable.

Limitations: No direct comparison with currently available TKIs for use in 2nd line and beyond setting and no ongoing trials

pERC noted the absence of a direct comparison to other TKI's to be a limitation in the presented evidence for bosutinib. pERC discussed the limitations of non-randomized, non-comparative studies and considered that, although the SKI-200 trial was appropriately conducted, the conclusions that can be drawn from non-randomized, non-comparative data are not as robust as those that can be drawn from randomized controlled trials. pERC considered that, given the lack of randomized comparative studies, there is considerable uncertainty surrounding the magnitude of clinical benefit of bosutinib. pERC also discussed the feasibility of conducting a randomized controlled trial and had varying opinions. pERC noted that the pivotal study recruited 288 second line patients and considered that randomization may have been reasonable and equipoise may have been present. pERC also noted that there are no planned or ongoing trials that will compare bosutinib with relevant comparators in this setting. pERC, however, acknowledged that the limited prevalence of patients in third line setting and beyond does not make randomization feasible.

Need: Resistant and intolerant patients

Chronic Myelogenous Leukemia is an uncommon clonal bone marrow stem cell disorder with approximately 450 cases diagnosed annually in Canada with a median age of diagnosis 65 years. The majority of patients are diagnosed in the chronic phase (CP) of the illness. pERC noted that, although curative therapy is available with allogeneic stem cell transplant (ASCT), only approximately 20-25% of patients are eligible for this treatment. Currently available therapies in patients ineligible for ASCT include the BCR-ABL tyrosine kinase inhibitor (TKI) imatinib in the first-line setting as well as the second generation TKIs, dasatinib and nilotinib, agents which are used as first or second-line treatment for CML. pERC noted that there is no information on the optimal sequencing of therapies and the inclusion of bosutinib into this algorithm will likely be influenced by the agents available for first-line therapy and second-line settings, clinical judgment, CML mutation status and patient comorbidities.

pERC noted that patients face life long treatment that can be as long as 10 years or greater and adherence to treatment is acknowledged to be an important factor in optimizing outcomes in chronic phase CML. While intolerance and resistance to second-line TKIs occurs in some patients, allogeneic stem cell transplantation, an available treatment option at that progressed stage of disease, has very limited applicability and carries a risk of treatment-related mortality of 20-30% in the first year. pERC agreed that, in patients who develop resistance or intolerance to current therapies, there remains an unmet need for more effective and tolerable therapies in the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML).

PATIENT-BASED VALUES

Values of patients with Chronic Myelogenous Leukemia: Quality of life, disease control, treatment option

pERC deliberated on patient advocacy group input and noted that quality of life and the availability of new treatment options were important to patients. pERC noted that for a smaller population of CML patients, the available treatments are either not well tolerated and/or their disease becomes resistant. Patients thus reported experiencing fear and anxiety of not having their disease well controlled and the possibility of progressing into the accelerated or blast phase, for which few treatments currently exist.

Patient values on treatment: treatment options, tolerable side effect profile

pERC noted that patients place importance on access to new treatment options that provide manageable toxicity profiles and improve quality of life. pERC agreed that in providing improvements in MCyR rates, which is an acceptable surrogate for overall survival, improving 1 and 2 year progression-free survival, providing a manageable toxicity profile and notable improvements in quality of life, bosutinib aligned with patient values. pERC also noted that the importance of having treatments that have a safer toxicity profile and do not exacerbate any pre-existing conditions (e.g. asthma, COPD) was highlighted by patients. In alignment with these patient values, pERC agreed that bosutinib provided a treatment option with notable improvements in QoL, an observation not generally seen in this setting. pERC also noted that the toxicity profile of bosutinib was unlike other TKI's and was easier to manage. Overall, pERC concluded that bosutinib aligned with patient values. pERC noted input from patients who had experience with

bosutinib which indicated that the side effects of bosutinib were easier to manage compared to those associated with the currently available treatment options. In some instances patients were able to return to work which pERC noted to be in aligned with the results of the study reporting notable improvements in QoL.

ECONOMIC EVALUATION

Economic model submitted: Cost-minimization and cost utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-minimization analysis comparing the cost of bosutinib with dasatinib or nilotinib 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, and for whom subsequent treatment with imatinib, nilotinib and dasatinib was not clinically appropriate (advanced treatment lines, i.e. second-line therapy and beyond). pERC expressed disappointment in the provision of an economic analysis that was inappropriate for the available clinical data and deferred making a recommendation during the first deliberations on this submission. pERC requested a cost-utility analysis to address the limitations discussed above. Additionally, the EGP had requested a cost-utilization analysis from the submitter, on a number of occasions in order to examine best supportive care as a comparator but this was not provided.

The EGP also assessed a cost-utility analysis, requested by pERC, comparing the cost of bosutinib with hydroxyurea, interferon or stem cell transplant 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, and for whom subsequent treatment with imatinib, nilotinib and dasatinib was not clinically appropriate (advanced treatment lines, i.e. second-line therapy and beyond).

Basis of the economic model: Non-Comparative data used in a Cost Minimization and Cost Utility analysis

Costs considered in the cost-minimization analysis included only the drug cost. pERC noted that there were likely additional costs associated with the management of adverse events but these were not included.

Costs considered in the cost-utility analysis included drug costs, health care resource utilization costs, costs for adverse events and end of life care costs. The clinical effect considered in the cost utility analysis was based on overall survival (CP patients), progression-free survival (CP patients), time spent in the phase (AP and BP patients), treatment duration, and utilities.

Drug costs: submitted confidential price

At the list price, bosutinib costs \$36.59 per 100mg tablet or \$146.34 per 500mg tablet. At the recommended daily dose of 500mg for all phases (CP, AP, BP), bosutinib costs \$146.34 per day and \$4,097.52 per 28 day course. Depending on the combination of tablets used to provide a 500mg dose (5 x 100mg or 1 x 500mg), the price of bosutinib may be as high as \$182.93 per day and \$5,122.04 per 28 day course. At the recommended dose of 500mg for all phases (CP, AP, BP), and using the confidential price, bosutinib costs \$[REDACTED] per day and \$[REDACTED] per 28-day course. (*The cost of bosutinib is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the pCODR Disclosure of Information guidelines.*)

pERC noted potential concerns for drug wastage in patients who may be dispensed the 500mg tablets but do not tolerate it and then have their dose reduced to 400mg. pERC also noted that 15% of imatinib resistant chronic phase patients and 17% of third-line patients had an inadequate response to the initial 500mg dose and received an escalated dose of 600mg, with no apparent increase in adverse events. pERC noted that this increase in dosage will likely result in increased drug cost and should be considered in jurisdiction's budget impact analysis.

Dasatinib costs \$38.00 per 20mg tablet, \$76.48 per 50mg tablet, \$84.29 per 70mg tablet and \$152.86 per 100mg tablet. At the recommended daily dose of 100mg in the CP patients, dasatinib costs \$152.86 per

day and \$4,280.08 per 28 day course. In AP and BP patients and at the recommended dose of 140mg, dasatinib costs \$168.58 per day and \$4,720.24 per 28 day course.

Nilotinib costs \$28.72, per 150mg tablet and \$39.72 per 200mg tablet. At the recommended daily dose of 800mg for the CP and AP (nilotinib was not examined for the BP), nilotinib costs \$158.88 per day and \$4,448.64 per 28 day for both phases.

Hydroxyurea costs \$1.0203 per 500 mg capsule. At the recommended average daily dose of 20-30 mg/kg, hydroxyurea costs \$3.06 - \$4.08 per day and \$85.71 - \$114.27 per 28 day cycle.

Interferon costs \$218.76, \$364.60 and \$729.19 per 18mu, 30mu, and 60mu, respectively. At the recommended average daily dose of 4-5 million units/m², interferon costs \$82.64 per day and \$2,313.99 per 28 day cycle.

Cost-effectiveness estimates: Substantial uncertainty in incremental effect and resulting estimates of cost effectiveness due to limitations of non-randomized, non-comparative data

pERC deliberated upon the two economic analyses submitted by the manufacturer providing estimates on the cost-effectiveness of bosutinib compared with relevant treatment options. The first involved a cost-minimization analysis based on the assumption of similar efficacy and toxicity between bosutinib and currently available second generation TKIs (dasatinib or nilotinib). This analysis only took into consideration differences in drug cost. pERC discussed the appropriateness of this approach and agreed that, in the absence of direct or indirect evidence, there was considerable uncertainty in the assumption of similar efficacy and toxicity between dasatinib, nilotinib and bosutinib. Additionally, pERC noted that bosutinib demonstrated a side effect profile that is different from currently available second generation TKI's and agreed that a cost-minimization analysis was inadequate to explore the impact these differences may have on the cost effectiveness of bosutinib. pERC concluded that, until the assumptions of similar efficacy and safety have been validated, a cost-minimization analysis is not a valid approach and a standard cost-effectiveness/cost-utility analysis is required, which incorporates differences in efficacy, safety, quality of life and costs between the treatments under consideration. pERC requested this additional economic information from the submitter.

pERC also discussed the results of a cost-utility analysis provided by the submitter comparing bosutinib to hydroxyurea, interferon or stem cell transplant (SCT). In the absence of direct or indirect comparative data, pERC noted that multiple data sources from the literature and/or assumptions were used to populate clinical inputs within the cost-utility analysis, which was understandable. pERC, however, noted that due to the limitations of relying on non-randomized evidence from the SKI-200 study, there was substantial uncertainty in the magnitude of the clinical benefit associated with bosutinib. This made it challenging to estimate the incremental effect of treatment with bosutinib and, therefore, the resulting incremental cost-effectiveness estimates for bosutinib. This considerable uncertainty in the magnitude of clinical benefit of bosutinib led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. The Committee noted that in order to improve the cost-effectiveness of bosutinib and offset the considerable uncertainty in the incremental effect, a substantial reduction in drug price would likely be required. pERC also considered that, if feasible, the collection of additional prospective data on the clinical benefit of bosutinib would reduce the uncertainty around the magnitude of the benefit and improve the cost-effectiveness estimates. Therefore, pERC considered that bosutinib could not be considered cost-effective at the list or submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Second line population, unknown magnitude of clinical benefit, budget impact

pERC discussed factors affecting the feasibility of implementing a positive funding recommendation for bosutinib.

Input from the pCODR's Provincial Advisory Group indicated concerns for indication creep into the first and second line setting. Given the available options which have evidence demonstrating efficacy for first line treatment and the evidence demonstrating no additional clinical benefit to support the use of bosutinib in the first-line setting, pERC noted that it is unlikely bosutinib will be used in the first-line

setting. Within the second-line setting, pERC discussed the available evidence and agreed that bosutinib offers a therapeutic option in patients that have preexisting conditions making them inappropriate for treatment or patients that have mutations conferring resistance to currently available TKI's. Having agreed that it would be reasonable to use bosutinib in patients that have failed at least one previous TKI, pERC acknowledged that jurisdictions will need to consider the potential budgetary impact of making bosutinib available in the second or third-line setting. pERC also discussed PAG's request on clarity around the sequence of previous TKI use. pERC acknowledged that data on sequencing of TKIs are limited and not informed by controlled clinical trials. pERC however agreed with the Clinical Guidance Panel that decisions beyond first-line therapy will likely be guided by the agents available for front-line therapy, clinical judgment, CML mutation status and patient comorbidities. pERC discussed PAG's concern about the absence of a comparator arm in the study. pERC discussed the limitations associated with non-randomized studies and noted that, although not feasible in the third-line setting and beyond, a randomized study could have been conducted within the second-line cohort to determine comparative efficacy against currently available treatment options. Due to the absence of this comparative evidence, pERC was unable to determine the magnitude of the benefit associated with bosutinib.

pERC considered several factors related to drug cost and dosing that may affect the feasibility of implementing a positive funding recommendation. pERC noted that the potential for dose adjustments (increase and decrease of doses) will need to be considered by provinces as this could affect the incremental cost of bosutinib relative to the other second generation TKI's. pERC acknowledged that a significant minority of patients received dose escalations to 600mg due to inadequate response to the initial 500mg dose, noting that this may have an impact on the cost of bosutinib as an additional 100mg tablet will be required to achieve this dose. While bosutinib is priced per tablet, when considering the per mg cost, pERC noted that the cost of five 100mg tablet is more expensive than the one 500mg tablet and a dose reduction to 400mg would not result in no cost savings over the cost of the 500mg tablet. Lastly, pERC acknowledged the introduction of generic imatinib and noted that this may shift the pricing of other tyrosine kinase inhibitors.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> • Oral, dual Src/Abl Tyrosine Kinase Inhibitor • 100mg tablet and 500mg tablet reviewed by pCODR • Recommended dosage of 500 mg administered orally, once daily
Cancer Treated	<ul style="list-style-type: none"> • Chronic Myelogenous Leukemia
Burden of Illness	<ul style="list-style-type: none"> • Chronic Myelogenous Leukemia accounts for approximately 10-15% of cases of leukemia diagnosed in Canada, with an incidence rate of 1-2cases/100,000/year. • Approximately 450 cases are diagnosed annually in Canada with a median age at diagnosis of 65 • The majority of patients (>95%) with CML are in chronic phase (CP) at diagnosis • Approximately 1/3 of patients treated with imatinib for CP CML discontinue therapy because of disease progression (10%) or intolerance (25%)
Current Standard Treatment	<ul style="list-style-type: none"> • In patients with resistance or intolerant intolerance to currently available treatments <ul style="list-style-type: none"> ○ Dasatinib ○ Nilotinib • Hydroxyurea • Interferon • Allogenic stem cell transplant • Best supportive care
Limitations of Current Therapy	<ul style="list-style-type: none"> • interferon and palliative treatment with hydroxyurea, are associated with significant toxicities, and limited clinical benefit • A large number of mutations have been described in the BCR-ABL kinase domain that lead to drug resistance • Presence of a mutation may predict for reduced efficacy of a second-line agent; patients may have co-morbidities that predict for drug-related adverse events and make the use of dasatinib or nilotinib inappropriate. • Agents that are active without the risk of exacerbating significant comorbidities are needed in the treatment of CML.

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. Anthony Fields, Oncologist (Chair)	Dr. Bill Evans, Oncologist
Dr. Maureen Trudeau, Oncologist (Vice-Chair)	Dr. Allan Grill, Family Physician
Dr. Scott Berry, Oncologist	Dr. Paul Hoskins, Oncologist
Bryson Brown, Patient Member	Danica Wasney, Pharmacist
Dr. Matthew Cheung, Oncologist	Carole McMahon, Patient Member Alternate
Mario de Lemos, Pharmacist	Jo Nanson, Patient Member
Dr. Sunil Desai, Oncologist	Dr. Tallal Younis, Oncologist
Mike Doyle, Economist	Dr. Kelvin Chan

All members participated in deliberations and voting on the initial recommendation except:

- Scott Berry and Mario De Lemos who were not present for the meeting
- Carole McMahon who did not vote due to her 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 review of bosutinib (Bosulif) for chronic myeloid leukemia, through their declarations, five members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, and none of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee 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 their 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*. Pfizer Canada Inc., as the primary data owner, did not agree to the disclosure of economic information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

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 policymakers 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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