



pan-Canadian Oncology Drug Review Final Economic Guidance Report

Bosutinib (Bosulif) for Chronic Myeloid Leukemia

April 21, 2015

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The submitter is requesting funding for bosutinib in patients with chronic, accelerated or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia 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. Two analyses were submitted:

- One of the economic analyses **submitted to pCODR by Pfizer** compared bosutinib to dasatinib or nilotinib, using a cost-minimization analysis, for the treatment of patients with chronic, accelerated or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia with resistance or intolerance to prior TKI therapy and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate. Bosutinib is administered orally, with a recommended dose of 500 mg for all phases (chronic phase (CP), accelerated phase (AP) and blast phase (BP)). Dasatinib is administered orally, with a recommended dose of 100 mg for the CP, and 140mg for the AP and BP. Nilotinib is administered orally, with a recommended dose of 800mg for the CP and AP; nilotinib was not considered for the BP in the economic analysis.
- The other economic analysis **submitted to pCODR by Pfizer**, compared bosutinib to hydroxyurea, interferon and stem cell transplant, using a cost-utility analysis, for the treatment of patients with chronic, accelerated or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia with resistance or intolerance to prior TKI therapy and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate. Bosutinib is administered orally, with a recommended dose of 500 mg daily for all phases (CP, AP and BP). Comparators considered in the three economic models include hydroxyurea, interferon-alpha and stem cell transplant. The recommended dose for hydroxyurea is 20-30 mg/kg daily and the dosing in the model is assumed to be 2g daily (25 mg/kg daily for an average weight of 80 kg). The recommended dose for interferon-alpha (known herewith as interferon), is 4 - 5 million units per m² body surface area daily.

According to the pCODR Clinical Guidance Panel (CGP):

- The cost-minimization analysis comparing bosutinib to dasatinib or nilotinib has limited appropriateness. The CGP acknowledged that there may be some clinical situations in which a patient would be deemed clinically inappropriate (ex. relative contraindications) for dasatinib, nilotinib and imatinib (as per submission), and yet would continue to receive these TKIs over best supportive care given physicians and patients preference to continue offering active treatment. In some of these situations, bosutinib would represent a more appropriate alternative to the TKIs currently available. In these circumstances dasatinib or nilotinib represent appropriate comparators for the economic analysis. The CGP also acknowledged that in some situations (ex. resistance and major intolerances) continued therapy with TKIs currently available would not be possible. In this circumstances, therapy with bosutinib may be possible and best supportive care would be the appropriate comparator. The Submitter has included best supportive care only as modification to the main economic analysis.
 - The submitter chose to initially submit a cost-minimization analysis. In a cost-minimization analysis, only costs are considered; estimates of efficacy, safety, and quality of life (or life years gained) are not considered. Further, this type of economic model assumes that patient important outcomes for the

effectiveness of treatments under consideration are similar. This type of model, therefore, only provides outputs in terms of costs; effectiveness in terms of life years gained or quality-adjusted life years are not considered. This type of analysis is appropriate in the instances where clinical effectiveness has been demonstrated in head-to-head trials, or through an indirect comparison. There are, however, no randomized controlled trials comparing the effectiveness and safety between currently available 2nd generation TKIs (i.e. dasatinib, nilotinib) and bosutinib. There are also no mixed treatment comparisons or meta-analyses available, that compare bosutinib to dasatinib or nilotinib.

- For the cost-utility analysis, the comparison of bosutinib to hydroxyurea, interferon-alpha or stem cell transplant is appropriate, under certain clinical conditions. For example, not all patients would be eligible for stem cell transplantation. The submitter has acknowledged these comparator issues and has thus provided several models in order to examine bosutinib under various clinical settings. The submitter has considered that hydroxyurea is a proxy to best supportive care, as confirmed by the CGP.

Patients considered the following factors important in the review of bosutinib, which are relevant to the economic analysis: access to additional treatments for those who have exhausted all available options, manageable side effect profile, increased survival and quality of life. Bosutinib does have a manageable side effect profile. In terms of overall survival and quality of life, again, these outcomes have not been compared in a head-to-head trial with any of the relevant comparators considered within the two economic analyses. While the CUA, which is the economic model used for the third and fourth line patients, has taken these factors into account, it is difficult to conclude whether safety profiles are equivalent for the comparison in the CMA analysis. Specifically, whether the safety profiles of bosutinib, dasatinib and nilotinib are equivalent. Conclusions on the relative efficacy, safety and quality of life of these drugs should be made with extreme caution.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for bosutinib, and which are relevant to the economic analysis:

- **Wastage:** There is a potential for wastage if patients are dispensed 500mg tablets but then need to reduce to 400mg tablets - as the 500 mg tablets are no longer usable. Wastage was not considered in the economic model. Further, the price for 400mg daily (based on 4x100mg tablets) is the same as 1x500mg tablet, resulting in no cost savings if the dose is reduced.
- **Use of bosutinib in the first line setting:** There is concern that bosutinib will be used in the first line setting. Based on feedback from the CGP, given the results of a recent clinical trial¹ that examined bosutinib in a first-line setting compared to imatinib, it is very unlikely that bosutinib will be used in the first-line.
- **Clinical benefits of bosutinib:** PAG highlighted that there is uncertainty around the clinical benefits of bosutinib given the data available and the lack of head-to-head trials with established comparators for CML (imatinib, nilotinib, and dasatinib, among others).

- Sequencing of treatment: PAG had concerns around the sequencing of treatment with previous TKI use. Various potential sequencing options were not considered in the economic model.
- Costs: PAG also noted that with the introduction of generic imatinib, the price of dasatinib and nilotinib has also shifted in some instances, which would have an impact on the incremental costs of bosutinib.

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 \$4097.52 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 \$182.95 per day and \$5122.60 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.)*

Dasatinib costs \$38.00 per 20mg tablet, \$76.4800 per 50mg tablet, \$84.2900 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 \$4280.08 per 28 day course. In AP and BP patients and at the recommended dose of 140mg, dasatinib costs \$168.58 per day and \$4720.24 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 \$158.88 per day and \$4448.64 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 \$2313.99 per 28 day cycle.

1.2 Summary of results

1.2.1 Summary of Results for the economic analysis comparing bosutinib to nilotinib or dasatinib (cost-minimization analysis)

Based on the current available data, the EGPs estimates differed from the submitted estimates. The EGP noted a high level of uncertainty around the inputs, which consequently impacted the results. A large part of the uncertainty is due to the lack of head to head clinical trials, which meant assuming that the efficacy and safety of dasatinib, nilotinib and bosutinib are equivalent. Should these assumptions of similar efficacy and safety be proven to be incorrect, then a cost-minimization analysis is no longer a valid approach and a standard cost-effectiveness/cost-utility analysis would need to be considered, in order to incorporate the differences in efficacy, safety and costs between the treatments under consideration.

Chronic phase

The EGP based their reanalysis estimates on the submitted model and using the submitted list price for bosutinib. The EGP's best estimate of the incremental cost for the chronic phase is between:

- \$0 (cost neutral) and \$26,707 when bosutinib is compared with dasatinib.
- \$1,960 and \$27,687 when bosutinib is compared with nilotinib

The incremental cost was based on an estimate of the extra cost (ΔC) only as this is a cost-minimization analysis. The EGP's best estimate of:

- the extra cost of bosutinib compared to dasatinib is between \$0 and \$26,707 (ΔC). The most important factor that influences the extra cost is the cost of the drugs.
- the extra cost of bosutinib compared to nilotinib is between \$1,960 and \$27,687 (ΔC). The most important factor that influences the extra cost is the cost of the drugs.

The EGP based these estimates on the model submitted by Pfizer and reanalyses conducted by the EGP using the list price for bosutinib. The reanalysis conducted by the EGP using the submitted model showed that when:

- The price of dasatinib decreased, the extra cost of bosutinib increased. Decreasing the price of dasatinib from 10% - 50% increased the incremental cost of bosutinib to between \$400 and \$26,707.
- The price of nilotinib decreased, the extra cost of bosutinib increased. Decreasing the price of nilotinib from 10%- 50 % increased the incremental cost of bosutinib to between \$7,105 and \$27,687.

The EGPs range of estimates differed from the submitted estimates due to uncertainty around drug prices actually paid by the provinces.

According to the economic analysis that was submitted by Pfizer, when bosutinib (using the list price) is compared with dasatinib:

- In the chronic phase, bosutinib is cost neutral (\$0), there are no incremental costs (ΔC). Costs considered in the main analysis included the cost of the drug.

According to the economic analysis that was submitted by Pfizer, when bosutinib (using the list price) is compared with nilotinib:

- In the chronic phase, bosutinib has an incremental cost of \$1,960 (ΔC). Costs considered in the main analysis included the cost of the drug.

Based on the list price of bosutinib, the Submitter estimated that bosutinib compared to dasatinib is cost neutral. The submitter also estimated that the cost increase of bosutinib compared to nilotinib is \$1,960.

Accelerated / blast phase

The EGP based their reanalysis estimates on the submitted model and using the submitted list price for bosutinib. The EGP's best estimate of the incremental cost for the accelerated phase is between:

- -\$5,490 (cost savings) and \$23,962 when bosutinib is compared with dasatinib.
- \$1,960 and \$27,687 when bosutinib is compared with nilotinib.

The EGP's best estimate of the incremental cost for the blast phase is between:

- -\$5,490 (cost savings) and \$23,962 when bosutinib is compared with dasatinib.
- Note that nilotinib was not considered in the economic analysis for the blast phase.

The incremental cost was based on an estimate of the extra cost (ΔC) only as this is a cost-minimization analysis. The EGP's best estimate of:

- the extra cost of bosutinib compared to dasatinib is between -\$5,490 (cost savings) and \$23,962 (ΔC). The most important factor that influences the extra cost is the cost of the drugs.
- the extra cost of bosutinib compared to nilotinib is between \$1,960 and \$27,687 (ΔC). The most important factor that influences the extra cost is the cost of the drugs.

The EGP based these estimates on the model submitted by Pfizer and reanalyses conducted by the EGP using the list price for bosutinib. The reanalysis conducted by the EGP using the submitted model showed that when:

- The price of dasatinib decreased, the extra cost of bosutinib in the accelerated & blast phase increased. Decreasing the price of dasatinib from 10% - 50% increased the incremental cost of bosutinib to between \$400 and \$23,962.
- The price of nilotinib decreased, the extra cost of bosutinib in the accelerated phase increased. Decreasing the price of nilotinib from 10%- 50 % increased the incremental cost of bosutinib to between \$7,105 and \$27,687.

The EGPs range of estimates differed from the submitted estimates due to uncertainty around drug prices actually paid by the provinces.

According to the economic analysis that was submitted by Pfizer, when bosutinib (using the list price) is compared with dasatinib:

- In the accelerated and blast phase, bosutinib has a cost savings of \$5,490 (ΔC). Costs considered in the main analysis included the cost of the drug.

According to the economic analysis that was submitted by Pfizer, when bosutinib (using the list price) is compared with nilotinib:

- In the accelerated phase, bosutinib has an incremental cost of \$1,960 (ΔC). Costs considered in the main analysis included the cost of the drug.

Based on the list price of bosutinib, the Submitter estimated that the cost savings of bosutinib compared to dasatinib was \$5,490. The Submitter also estimated that bosutinib compared to nilotinib has an incremental cost of \$1,960.

Scenario Analysis

A scenario analysis was provided looking at best-supportive care (BSC). However, this scenario analysis is inappropriate in a cost-minimization analysis as the incremental utilities and effects of bosutinib compared to best supportive care are not taken into consideration. The EGP requested a cost-utility analysis, in order to examine best supportive care as a comparator. The submitter provided a cost-utility analysis that examined the cost-effectiveness of bosutinib with hydroxyurea (as a proxy for best supportive care), interferon and stem cell transplantation.

Further, if best supportive care had been considered as a comparator, bosutinib would become an additional line of therapy and the resulting costs would not necessarily be an incremental cost (replacing an existing therapy) but an additional cost (adding a line of therapy) to treat CML patients.

1.2.2 Summary of Results for economic analysis comparing bosutinib to hydroxyurea, interferon or stem cell transplant (cost-utility analysis)

Chronic phase

Hydroxyurea

The EGP's best estimate of the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) is between \$56,529 and \$208,049 per QALY when bosutinib is compared with hydroxyurea in the chronic phase. This range of ICERs provided by the EGP reflects a large amount of uncertainty in the overall survival estimates used to inform the model due to both extrapolation of data and lack of head-to-head clinical trials.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- the extra cost of bosutinib is between \$85,744 and \$78,778. The greatest factors that influence the costs are the 95% confidence intervals for overall survival and the way that treatment discontinuation was modeled. It should be noted that treatment discontinuation was not included in the EGPs best estimate.
- the extra clinical effect of bosutinib is between 0.38 and 1.52 quality-adjusted life years (ΔE). The greatest factors that influence the effects are the 95% confidence intervals for overall survival and the time horizon.

The EGP based these estimates on the model submitted by Pfizer and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- the time horizon chosen was set to 5 years, based on feedback from the CGP to reflect survival of this patient population, the extra cost of bosutinib is \$86,032 (ΔC_1) and the extra effect is 1.01 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to \$85,163 (from \$54,290).

- the upper bound of the 95% confidence interval is used for overall survival, the extra cost of bosutinib is \$125,302 (ΔC_2) and the extra effect is 3.22 (ΔE_2), which decreases the estimated incremental cost-effectiveness ratio to \$38,943 (from \$54,290).
- The best case estimate of the above two parameters, forming the lower bound of the range of ICERs, is \$56,529, with an extra cost for bosutinib of \$85,744 (ΔC) and an extra clinical effect of bosutinib of 1.52 (ΔE).
- the lower bound of the 95% confidence interval is used for overall survival, the extra cost of bosutinib is \$105,620 (ΔC_3) and the extra effect is 1.20 (ΔE_3), which increases the estimated incremental cost-effectiveness ratio to \$87,850 (from \$54,290).
- The best case estimate of the lower bound of the 95% confidence interval for overall survival and a 5 year time horizon, forming the upper bound of the range of ICERs, is \$208,049, with an extra cost for bosutinib of \$78,778 (ΔC) and an extra clinical effect of bosutinib of 0.38 (ΔE)

The EGPs range of estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Pfizer, when bosutinib is compared with hydroxyurea in the chronic phase:

- the extra cost of bosutinib is \$119,113 (ΔC). Costs considered in the analysis included drug costs, health resource utilization costs, costs of death and costs for adverse events.
- the extra clinical effect of bosutinib is 2.19 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on overall survival, progression-free survival, treatment duration, and utilities.

So, the submitter estimated that the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) was \$54,290 per QALY.

Interferon

The EGP's best estimate of the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) is between \$44,198 and \$146,587 per QALY when bosutinib is compared with interferon in the chronic phase. This range of ICERs provided by the EGP reflects a large amount of uncertainty in the overall survival estimates used to inform the model due to both extrapolation of data and lack of head-to-head clinical trials.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- the extra cost of bosutinib is between \$60,013 and \$62,047. The greatest factors that influence the costs are the 95% confidence intervals for overall survival and the way that treatment discontinuation was modeled. It should be noted that treatment discontinuation was not included in the EGPs best estimate.
- the extra clinical effect of bosutinib is between 0.42 and 1.56 quality-adjusted life years (ΔE). The greatest factors that influence the effects are the 95% confidence intervals for overall survival and the time horizon.

The EGP based these estimates on the model submitted by Pfizer and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- the time horizon chosen was set to 5 years, based on feedback from the CGP to reflect survival of this patient population, the extra cost of bosutinib is \$69,301 (ΔC_1) and the extra effect is 1.05 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to \$65,599 (from \$45,955).
- the upper bound of the 95% confidence interval is used for overall survival, the extra cost of bosutinib is \$108,144 (ΔC_2) and the extra effect is 3.24 (ΔE_2), which decreases the estimated incremental cost-effectiveness ratio to \$33,356 (from \$45,955).
- The best case estimate of the above two parameters, forming the lower bound of the range of ICERs, is \$44,198, with an extra cost for bosutinib of \$69,013 (ΔC) and an extra clinical effect of bosutinib of 1.56 (ΔE).
- the lower bound of the 95% confidence interval is used for overall survival, the extra cost of bosutinib is \$88,461 (ΔC_3) and the extra effect is 1.23 (ΔE_3), which increases the estimated incremental cost-effectiveness ratio to \$72,106 (from \$45,955).
- The best case estimate of the lower bound of the 95% confidence interval for overall survival and a 5 year time horizon, forming the upper bound of the range of ICERs, is \$146,587, with an extra cost for bosutinib of \$62,047 (ΔC) and an extra clinical effect of bosutinib of 0.42 (ΔE)

The EGPs range of estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Pfizer, when bosutinib is compared with hydroxyurea in the chronic phase:

- the extra cost of bosutinib is \$101,954 (ΔC). Costs considered in the analysis included drug costs, health resource utilization costs, costs of death and costs for adverse events.
- the extra clinical effect of bosutinib is 2.22 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on overall survival, progression-free survival, treatment duration, and utilities.

So, the submitter estimated that the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) was \$45,955 per QALY.

Stem cell transplantation

The EGP did not provide a best estimate of bosutinib versus stem cell transplantation in the chronic phase, as in almost all scenarios, both the submitter and the EGP found that bosutinib costs less and is more effective than stem cell transplantation.

Summary of the Economic Guidance Panel's (EGP) and Submitted cost-effectiveness estimates for Patients in the Chronic Phase					
Bosutinib vs. Hydroxyurea					
EGP Estimate			Submitted Estimate		
ΔC (\$)	ΔE (QALY)	ICER (\$ per QALY)	ΔC (\$)	ΔE (QALY)	ICER (\$ per QALY)
\$85,744 and \$78,778	0.38 and 1.52	\$56,529 - \$208,049	\$119,113	2.19	\$54,290
Bosutinib vs. Interferon					
\$60,013 and \$62,047	0.42 and 1.56	\$44,198 and \$146,587	\$101,954	2.22	\$45,955
Bosutinib vs. SCT					
Almost always cheaper	Almost always more effective	Dominant	Almost always cheaper	Almost always more effective	Dominant

Accelerated phase

Hydroxyurea

The EGP's best estimate of the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) is \$149,141 per QALY when bosutinib is compared with hydroxyurea in the accelerated phase.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- the extra cost of bosutinib is \$103,262. The greatest factors that influence the costs is the time horizon and the length of time spent in the accelerated and blast phase.
- the extra clinical effect of bosutinib is 0.69 quality-adjusted life years (ΔE). The greatest factors that influence the effects is the time horizon.

NOTE: overall survival was not modeled in the accelerated phase. The amount of time spent in each phase was fixed and was based on an assumption

The EGP based these estimates on the model submitted by Pfizer and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- the time horizon chosen was set to 3 years, based on feedback from the CGP to reflect survival of this patient population in the accelerated phase, the extra cost of bosutinib is \$103,262 (ΔC_1) and the extra effect is 0.69 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to \$149,141 (from \$119,466).

The EGPs range of estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Pfizer, when bosutinib is compared with hydroxyurea in the accelerated phase:

- the extra cost of bosutinib is \$190,364 (ΔC). Costs considered in the analysis included drug costs, health resource utilization costs, costs of death and costs for adverse events.
- the extra clinical effect of bosutinib is 1.59 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on time spent in the phase, treatment duration, and utilities.

So, the submitter estimated that the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) was \$119,466 per QALY.

Stem cell transplantation

The EGP did not provide a best estimate of bosutinib versus stem cell transplantation in the accelerated phase, as in almost all scenarios, both the submitter and the EGP found that bosutinib costs less and is more effective than stem cell transplantation

Summary of the Economic Guidance Panel's (EGP) and Submitted cost-effectiveness estimates for Patients in the Accelerated Phase					
Bosutinib vs. Hydroxyurea					
EGP Estimate			Submitted Estimate		
ΔC (\$)	ΔE (QALY)	ICER (\$ per QALY)	ΔC (\$)	ΔE (QALY)	ICER (\$ per QALY)
\$103,262	0.69	\$149,141	\$190,364	1.59	\$119,466
Bosutinib vs. Interferon					
Estimates were not provided for interferon as it was not considered as a comparator in the accelerated phase model.					
Bosutinib vs. SCT					
Almost always cheaper	Almost always more effective	Dominant	Almost always cheaper	Almost always more effective	Dominant

Blast crisis phase

Hydroxyurea

The EGP's best estimate of the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) is \$163,868 per QALY when bosutinib is compared with hydroxyurea in the blast crisis phase.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- the extra cost of bosutinib is \$56,755. The greatest factors that influence the costs is the time horizon and the length of time spent in the accelerated and blast phase.

- the extra clinical effect of bosutinib is 0.35 quality-adjusted life years (ΔE). The greatest factors that influence the effects is the time horizon.

NOTE: overall survival was not modeled in the blast crisis phase. The amount of time spent in the phase was fixed and was based on an assumption

The EGP based these estimates on the model submitted by Pfizer and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- the time horizon chosen was set to 2 years, based on feedback from the CGP to reflect survival of this patient population in the blast crisis phase, the extra cost of bosutinib is \$56,755 (ΔC_1) and the extra effect is 0.35 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to \$163,868 (from \$141,542).

The EGPs range of estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Pfizer, when bosutinib is compared with hydroxyurea in the accelerated phase:

- the extra cost of bosutinib is \$83,431 (ΔC). Costs considered in the analysis included drug costs, health resource utilization costs, costs of death and costs for adverse events.
- the extra clinical effect of bosutinib is 0.59 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on time spent in the phase, treatment duration, and utilities.

So, the submitter estimated that the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) was \$141,542 per QALY.

Stem cell transplantation

The EGP did not provide a best estimate of bosutinib versus stem cell transplantation as in almost all scenarios, both the EGP and the submitter found bosutinib was cheaper but also less effective than stem cell transplantation in the chronic phase. An ICUR would not be informative, and would be misleading, as we have both a cost savings and a decrease in QALYs. In this case, it is not so much the magnitude of the numbers, but the direction that provide a spuriously false positive number (two negatives divided by each other), that would not at all reflect an incremental cost-effectiveness ratio, as defined previously as a ratio with incremental costs and incremental QALYs in the positive direction.

Summary of the Economic Guidance Panel's (EGP) and Submitted cost-effectiveness estimates for Patients in the Blast Phase					
Bosutinib vs. Hydroxyurea					
EGP Estimate			Submitted Estimate		
ΔC (\$)	ΔE (QALY)	ICER (\$ per QALY)	ΔC (\$)	ΔE (QALY)	ICER (\$ per QALY)
\$56,755	0.35	\$163,868	\$83,431	0.59	\$141,542
Bosutinib vs. Interferon					
Estimates were not provided for interferon as it was not considered as a comparator in the blast phase model.					
Bosutinib vs. SCT					
Almost always cheaper	Almost always less effective	N/A	Almost always cheaper	Almost always less effective	N/A

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC , ΔE and the ICER differ from the Submitter's, what are the key reasons?

Comparison to Dasatinib or Nilotinib:

The main reason for the difference in the estimates of cost is due to the EGPs inclusion of various scenarios for drug costs. As a generic imatinib has been introduced, this could decrease the cost of other agents, including dasatinib and nilotinib, thereby increasing the incremental cost of bosutinib.

Comparison to Hydroxyurea, Interferon or SCT:

The main reason for the difference in results is the lack of confidence in the overall survival estimates for the chronic phase and the EGP elected to use the upper and lower bounds of the 95% confidence interval for their best-case estimate to examine this uncertainty. The other main reason for the difference in estimates is the choice of a different time horizon based on phase. Based on feedback from the clinical guidance panel, a 10-year time horizon was not deemed appropriate for patients in the 3rd line. 5 years, 3 years and 2 years for the chronic, accelerated and blast phase models were used for the best estimate. The EGP also noted that the lack of head-to-head clinical trials further creates uncertainty in the estimates of efficacy between bosutinib and the listed comparators.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Patients identified that it was important to have access to additional treatments for those that have exhausted all available options. Although bosutinib would address this, neither the efficacy nor the safety of bosutinib in comparison to dasatinib and nilotinib have been demonstrated in head-to-head trials.

Patients have also identified survival and quality of life as important, which are considered in this cost-effectiveness analysis for the third and fourth line analysis. This was however

not considered in second line analysis using the cost-minimization analysis as the submitter has assumed that these would be equal across the three drugs considered.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Comparison to Dasatinib or Nilotinib:

No. The design and structure are inadequate. There have been no head-to-head trials comparing bosutinib to either dasatinib or nilotinib, nor have there been any meta-analyses/indirect comparisons. To assume equivalent efficacy and safety without the clinical data is a major limitation of the model. Further, patients have identified quality of life as an important factor to consider. A cost-minimization analysis incorporates only the costs, it does not consider survival, safety or quality of life.

Another limitation of the model beyond the structure is the choice of comparators. Best supportive care is an option for patients who have exhausted all other treatments. Best supportive care was examined in a modification of the main analysis only, but as this was a cost-minimization analysis, no other inputs were considered in this analysis other than cost.

The EGP was unable to account for these structural limitations of the model. Though re-analyses were done to account for cost limitations (such as potential changes in the cost of drugs), it was not possible to account for efficacy and safety data.

Comparison to Hydroxyurea, Interferon or SCT:

The choice and design of model were structurally adequate. The model was adapted from a UK population. Given the limited data in this area, the economic model captured the information available.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

Comparison to Dasatinib or Nilotinib:

The submitter made several key assumptions that had or could potentially have an impact on the results.

- Efficacy and safety of treatments under consideration are equivalent, despite the lack of data to confirm this. There are no head-to-head trials or appropriate indirect comparisons, which allow the conclusion that the efficacy and safety of dasatinib, nilotinib and bosutinib are equivalent.
- Choice of comparators did not include best supportive care, which is a viable option for the patients under consideration.
- Drug wastage was not considered, which may have an impact should the maximum dose be needed.
- Decrease in cost of dasatinib and nilotinib following the introduction of generic imatinib was not considered. Further, given the various contract pricing plans and agreements in place, should bosutinib get listed, it could be priced anywhere from 5-50% more. This was examined in a re-analysis by the EGP, by decreasing the costs of dasatinib and nilotinib.

- Sequencing of drugs, and specifically should dasatinib and nilotinib be given in the first line setting, instead of imatinib, which could have significant impacts on the extra cost of bosutinib. Various sequencing options were not examined in the economic model.
- Limited cost inputs were considered in the model. Pharmacy costs, costs of subsequent lines of therapy, and other resource utilization costs were not considered in the economic model.

Comparison to Hydroxyurea, Interferon or SCT:

The submitter made several key assumptions that had or could potentially have an impact on the results.

- All patients receive hydroxyurea following bosutinib.
- Patients across clinical trials are similar, given that there are no head-to-head trials.
- Time spent in the accelerated and blast phase period are fixed at 10 months and 6 months, respectively.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

Comparison to Dasatinib or Nilotinib:

No estimates of clinical effects were considered in the submitted economic model, as it is a cost-minimization analysis. There are no head-to-head trials or appropriate indirect comparisons, which allow the conclusion that the efficacy and safety of dasatinib, nilotinib and bosutinib are equivalent. Had a cost-utility analysis been considered, and had best supportive care been considered as a comparator, as suggested by the CGP, bosutinib would be an appropriate comparator. Bosutinib would become an additional line of therapy and the cost results presented would not necessarily be an incremental cost (replacing an existing therapy) but an additional cost (adding a line of therapy) to treat patients with CML.

Comparison to Hydroxyurea, Interferon or SCT:

Given the lack of head to head trials and the uncertainty of conducting a naïve comparison between multiple trials, the estimates of clinical effects were reasonable. There was a heavy reliance on assumptions, however, given the lack of clinical data. The CGP was however able to provide their input on all clinical inputs.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

In the submitted BIA which examines bosutinib versus other second generation TKIs, the most important factor that influences the BIA is drug cost. Also, varying the doses of the drugs (and thereby drug costs) influences the BIA. The number of patients treated with

CML has a limited impact on the BIA. The submitter did not provide a BIA examining bosutinib compared to hydroxyurea, interferon or stem cell transplantation.

What are the key limitations in the submitted budget impact analysis?

The submitted BIA examining bosutinib with other second generation TKIs did not consider any variation in the dosing of the drugs, which could result in higher costs. The BIA also did not examine a scenario where dasatinib and nilotinib would be used in the first line setting, instead of imatinib, which could impact costs. Finally, the BIA did not examine the impact on costs should dasatinib and nilotinib decrease in cost.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

Comparison to Dasatinib or Nilotinib:

The most appropriate model structure needs to be chosen when doing an economic analysis. In the case where there is no direct comparison, or appropriate indirect comparisons, of the data, a cost-minimization analysis should not be undertaken. Further, all relevant cost inputs should be considered.

Comparison to Hydroxyurea, Interferon or SCT:

The submitter could provide all estimates in Canadian dollars and source inputs from Canadian sources in order to increase the validity of the results.

Is there economic research that could be conducted in the future that would provide valuable information related to bosutinib for CML?

Economic models should be developed on what reflects most closely clinical practice. Further, randomized clinical trials should be developed to then test the efficacy and safety of the most appropriate comparators under consideration.

2 DETAILED TECHNICAL REPORT - Economic Analysis Comparing Bosutinib to Nilotinib or Dasatinib (Cost Minimization Analysis)

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 DETAILED TECHNICAL REPORT - Economic Analysis Comparing Bosutinib to Hydroxyurea, Interferon or Stem Cell transplant (Cost-Utility Analysis)

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

4 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Leukemia Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of bosutinib (Bosulif) for chronic myeloid leukemia. A full assessment of the clinical evidence of bosutinib (Bosulif) for chronic myeloid leukemia is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.pcodr.ca). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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