PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Ponatinib (Iclusig) for Chronic Myeloid Leukemia / Acute Lymphoblastic Leukemia

October 1, 2015

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by ARIAD Pharmaceuticals, Inc.** compared ponatinib to several comparators for patients with either CML or Ph+ ALL for whom other TKI therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance. The comparators considered include the following:

- CP-CML: dasatinib, nilotinib, hydroxyurea, interferon-alfa, and allogenic stem cell transplantation
- AP-/BP-CML: hydroxyurea, allogenic stem cell transplantation
- Ph+ ALL: allogenic stem cell transplantation, or palliative best supportive care

Ponatinib is administered orally at a dose of 45 mg once daily. Dasatinib is administered orally at a daily dose of 100 mg per day. Nilotinib is administered orally at a daily dose of 800 mg per day. Hydroxyurea is administered orally at a daily dose of 2000 mg per day. Interferon-alfa is administered subcutaneously at a daily dose of 9,000,000 IU per day. Allogenic stem cell transplantation is not a drug treatment but a procedure. Palliative best supportive consisted of two palliative chemotherapy regimens.

According to the pCODR Clinical Guidance Panel (CGP), all comparators are potentially appropriate given the intended use of ponatinib as a last alternative for patients with CML or Ph+ ALL who have failed other TKIs. The CGP considered the most appropriate comparators to be stem cell transplantation and hydroxyurea (only applicable for CML). However, not all patients would be considered eligible for all comparators (i.e. stem cell transplantation). The interpretation of the comparisons of ponatinib should be placed in the context of the profile of an individual patient.

Patients considered the following factors important in the review of ponatinib, which are relevant to the economic analysis: a choice in alternative therapy, regain lost response and buy time for a suitable bone marrow donor. Patients were willing to withstand the side effects of ponatinib to ensure a best response. These factors – response, adverse events, and survival – were accounted for in the economic model.

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

Barriers to implementation: severe toxicities to monitor; lack of long-term, head-to-head clinical trials with other available treatments for CML or ALL; and high cost of the drug.

Enablers to implementation: treatment option for patients who are resistant to other treatment; small patient population; and convenient dosing schedule and administration.

The economic model examined the barriers and enablers to the implementation of ponatinib.

Ponatinib costs $141.31 per 15 mg or $330.77 per 45 mg tablet. At the recommended dose of 45 mg per day, the daily cost of ponatinib is $330.77, if using the 45 mg strength tablet. Dasatinib costs $38.00 per 20 mg unit, $76.48 per 50 mg unit, and $84.29 per 70 mg unit. At the recommended dose of 100 mg per day, the daily cost of dasatinib is either $190.00, $152.96, or $168.58, depending on the strength of the tablet used. Nilotinib costs $28.7s per 140 mg or $39.72 per 200 mg unit. At the recommended dose of 800 mg per day, the daily cost of nilotinib is $158.89, if using the 200 mg strength tablet. Imatinib costs $6.82

per 100 mg. At the recommended dose of 400 mg per day, the daily cost of imatinib is $27.27. Hydroxyurea costs $1.02 per 500 mg. At the recommended dose of 2000 mg per day, the daily cost of hydroxyurea is $4.08. Interferon-alfa costs $218.76 per 18,000,000 IU or $364.60 per 30,000,000 IU. At the recommended dose of 9,000,000 IU, the daily cost of interferon-alfa is $218.76 or $364.60, depending on the vial size used.

1.2 Summary of Results

The following table summarizes the results of the submitter, and the reanalysis by the EGP, for each phase and comparator. Details of these analyses follow the table. As the reanalyses by the EGP was completed with the model provided by the submitter, the best estimate range presented does not reflect precision of the estimate.

Comparator	EGP lower bound	EGP upper bound	Submitter's ICUR
CP-CML			
Dasatinib	$95,311	$102,688	$66,351
Nilotinib	$94,743	$101,694	$65,708
SCT	$91,366	$97,533	$64,659
Hydroxyurea	$94,518	$100,065	$68,454
Interferon-alfa	$57,224	$68,635	$39,859
AP-CML			
SCT	dominant		dominant
Hydroxyurea	$49,082	$55,051	$39,455
BP-CML			
SCT	dominant		dominant
Hydroxyurea	$66,399	$77,535	$62,870
Ph+ ALL			
SCT	dominant		dominant
Hydroxyurea	$87,966	$113,069	$62,574

SCT: stem cell transplantation
*dominant refers to ponatinib costing less and being more effective than the comparator

CP-CML

Dasatinib

According to the economic analysis that was submitted by ARIAD Pharmaceuticals, when ponatinib is compared with dasatinib:

- the extra cost of ponatinib is $213,519 (ΔC). Costs considered in the analysis included drug costs, resource use costs and adverse event costs.

- the extra clinical effect of ponatinib is 3.22 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on cytogenic response and overall survival.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $66,351.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $95,311 and $102,688 when ponatinib is compared with dasatinib.

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 ponatinib is between $203,589 and $338,002. Cost was most affected by the unit cost of ponatinib and the complete cytogenic response of ponatinib.
- the extra clinical effect of ponatinib is between 1.98 and 3.55 (ΔE). Clinical effect was most affected by the complete cytogenic response of ponatinib and the time horizon.

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

- The time horizon was shortened to 20 years (from lifetime horizon), the extra cost is $213,519 ($\Delta C_1$) and the extra clinical effect is 2.60 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $76,130 (from $66,351).
- The cost per mg of ponatinib is based on 3 x 15 mg (instead of one tablet of 45 mg), the extra cost is $264,832 ($\Delta C_2$) and the extra clinical effect is 3.22 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $82,297 (from $66,351).
- The lower 95% confidence interval of CCyR for ponatinib is used, the extra cost is $149,275 ($\Delta C_3$) and the extra clinical effect is 2.31 (ΔE_3), which decreases the estimated incremental cost-effectiveness ratio to $64,651 (from $66,351).
- The upper 95% confidence interval of CCyR for ponatinib is used, the extra cost is $276,465 ($\Delta C_4$) and the extra clinical effect is 4.10 (ΔE_4), which increases the estimated incremental cost-effectiveness ratio to $66,781 (from $66,351).
- The proportion of patients treated with stem cell transplantation after progression is 60% (instead of 80%), the extra cost is $233,914 ($\Delta C_5$) and the extra clinical effect is 3.39 (ΔE_5), which increases the estimated incremental cost-effectiveness ratio to $69,079 (from $66,351).

The EGPs estimates differed from the submitted estimates.

Nilotinib

According to the economic analysis that was submitted by ARIAD Pharmaceuticals, Inc., when ponatinib is compared with nilotinib:

- the extra cost of ponatinib is $211,114 (ΔC). Costs considered in the analysis included drug costs, resource use costs and adverse event costs.

- the extra clinical effect of ponatinib is 3.21 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on cytogenic response and overall survival.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $65,708.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $94,743 and $101,694 when ponatinib is compared with nilotinib.

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 ponatinib is between $200,993 and $335,406. Cost was most affected by the unit cost of ponatinib and the complete cytogenic response of ponatinib.
- the extra clinical effect of ponatinib is between 1.98 and 3.54 (ΔE). Clinical effect was most affected by the complete cytogenic response of ponatinib and the time horizon.

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

- The time horizon was shortened to 20 years (from a lifetime horizon), the extra cost is $195,488 ($\Delta C_1$) and the extra clinical effect is 2.59 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $74,342 (from $65,708).
- The cost per mg of ponatinib is based on 3 x 15 mg (instead of one tablet of 45 mg), the extra cost is $262,427 ($\Delta C_2$) and the extra clinical effect is 3.21 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $81,679 (from $65,708).
- The lower 95% confidence interval of CCyR for ponatinib is used, the extra cost is $146,871 ($\Delta C_3$) and the extra clinical effect is 2.30 (ΔE_3), which decreases the estimated incremental cost-effectiveness ratio to $63,750 (from $65,708).
- The upper 95% confidence interval of CCyR for ponatinib is used, the extra cost is $274,060 ($\Delta C_4$) and the extra clinical effect is 4.10 (ΔE_4), which increases the estimated incremental cost-effectiveness ratio to $66,781 (from $65,708).
- The proportion of patients treated with stem cell transplantation after progression is 60% (instead of 80%), the extra cost is $236,513 ($\Delta C_5$) and the extra clinical effect is 3.39 (ΔE_5), which increases the estimated incremental cost-effectiveness ratio to $69,711 (from $65,708).

The EGPs estimates differed from the submitted estimates.

Stem cell transplantation

According to the economic analysis that was submitted by ARIAD Pharmaceuticals, Inc., when ponatinib is compared with stem cell transplantation:

- the extra cost of ponatinib is $185,047 (ΔC). Costs considered in the analysis included drug costs, resource use costs and adverse event costs.

- the extra clinical effect of ponatinib is 2.86 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on cytogenic response and overall survival.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $64,659.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $91,366 and $97,533 when ponatinib is compared with stem cell transplantation.

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 ponatinib is between $133,725 and $268,139. Cost was most affected by the unit cost of ponatinib and the complete cytogenic response of ponatinib.
- the extra clinical effect of ponatinib is between 1.37 and 2.93 (ΔE). Clinical effect was most affected by the complete cytogenic response of ponatinib and the time horizon.

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

- The time horizon was shortened to 20 years (from a lifetime horizon), the extra cost is $177,619 ($\Delta C_1$) and the extra clinical effect is 2.36 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $75,162 (from $64,659).
- The cost per mg of ponatinib is based on 3 x 15 mg (instead of one tablet of 45 mg), the extra cost is $236,360 ($\Delta C_2$) and the extra clinical effect is 2.86 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $82,589 (from $64,659).
- The lower 95% confidence interval of CCyR for ponatinib is used, the extra cost is $120,803 ($\Delta C_3$) and the extra clinical effect is 1.95 (ΔE_3), which decreases the estimated incremental cost-effectiveness ratio to $61,860 (from $64,659).
- The upper 95% confidence interval of CCyR for ponatinib is used, the extra cost is $247,993 ($\Delta C_4$) and the extra clinical effect is 3,75 (ΔE_4), which increases the estimated incremental cost-effectiveness ratio to $66,081 (from $64,659).
- The proportion of patients treated with stem cell transplantation after progression is 60% (instead of 80%), the extra cost is $158,135 ($\Delta C_5$) and the extra clinical effect is 2.66 (ΔE_5), which decreases the estimated incremental cost-effectiveness ratio to $59,508 (from $64,659).

The EGPs estimates differed from the submitted estimates.

Hydroxyurea

According to the economic analysis that was submitted by ARIAD, when ponatinib is compared with hydroxyurea:

- the extra cost of ponatinib is $248,656 (ΔC). Costs considered in the analysis included drug costs, resource use costs and adverse event costs.
- the extra clinical effect of ponatinib is 3.63 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on cytogenic response and overall survival.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $68,454.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $94,518 and $100,065 when ponatinib is compared with hydroxyurea.

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 ponatinib is between $241,446 and $375,860. Cost was most affected by the unit cost of ponatinib, the proportion of patients treated with stem cell transplantation and the complete cytogenic response of ponatinib.
- the extra clinical effect of ponatinib is between 2.41 and 3.98 (ΔE). Clinical effect was most affected by the complete cytogenic response of ponatinib and the time horizon.

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

- The time horizon was shortened to 20 years (from a lifetime horizon), the extra cost is $233,012 ($\Delta C_1$) and the extra clinical effect is 3.01 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $77,439 (from $68,454).
- The cost per mg of ponatinib is based on 3 x 15 mg (instead of one tablet of 45 mg), the extra cost is $299,972 ($\Delta C_2$) and the extra clinical effect is 3.63 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $82,581 (from $68,454).
- The lower 95% confidence interval of CCyR for ponatinib is used, the extra cost is $184,412 ($\Delta C_3$) and the extra clinical effect is 2.72 (ΔE_3), which decreases the estimated incremental cost-effectiveness ratio to $67,714 (from $68,454).
- The upper 95% confidence interval of CCyR for ponatinib is used, the extra cost is $311,601 ($\Delta C_4$) and the extra clinical effect is 4.52 (ΔE_4), which increases the estimated incremental cost-effectiveness ratio to $68,886 (from $68,454).
- The proportion of patients treated with stem cell transplantation after progression is 60% (instead of 80%), the extra cost is $274,401 ($\Delta C_5$) and the extra clinical effect is 3.83 (ΔE_5), which increases the estimated incremental cost-effectiveness ratio to $71,680 (from $68,454).

The EGPs estimates differed from the submitted estimates.

Interferon-alfa

According to the economic analysis that was submitted by ARIAD Pharmaceuticals, Inc., when ponatinib is compared with interferon-alfa:

- the extra cost of ponatinib is $143,310(ΔC). Costs considered in the analysis included drug costs, resource use costs and adverse event costs.
- the extra clinical effect of ponatinib is 3.60 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on cytogenic response and overall survival.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $39,859.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $57,224 and $68,635 when ponatinib is compared with interferon-alfa.

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 ponatinib is between $135,840 and $270,254. Cost was most affected by the unit cost of ponatinib and the complete cytogenic response of ponatinib.
- the extra clinical effect of ponatinib is between 2.37 and 3.94 (ΔE). Clinical effect was most affected by the complete cytogenic response of ponatinib and the time horizon.

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

- The time horizon was shortened to 20 years (from a lifetime horizon), the extra cost is $127,659 ($\Delta C_1$) and the extra clinical effect is 2.97 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $42,956 (from $39,859).
- The cost per mg of ponatinib is based on 3 x 15 mg (instead of one tablet of 45 mg), the extra cost is $194,626 ($\Delta C_2$) and the extra clinical effect is 3.60 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $54,132 (from $39,859).
- The lower 95% confidence interval of CCyR for ponatinib is used, the extra cost is $79,066 ($\Delta C_3$) and the extra clinical effect is 2.69 (ΔE_3), which decreases the estimated incremental cost-effectiveness ratio to $29,432 (from $39,859).
- The upper 95% confidence interval of CCyR for ponatinib is used, the extra cost is $206,256($\Delta C_4$) and the extra clinical effect is 4.49 (ΔE_4), which increases the estimated incremental cost-effectiveness ratio to $45,974 (from $39,859).
- The proportion of patients treated with stem cell transplantation after progression is 60% (instead of 80%), the extra cost is $168,801 ($\Delta C_5$) and the extra clinical effect is 3.79 (ΔE_5), which increases the estimated incremental cost-effectiveness ratio to $44,548 (from $39,859).

The EGPs estimates differed from the submitted estimates.

AP-CML

Stem cell transplantation

According to the economic analysis that was submitted by ARIAD Pharmaceuticals, Inc., when ponatinib is compared with stem cell transplantation, ponatinib was less costly and more effective.

The EGP examined several scenario analyses of ponatinib versus stem cell transplantation. Under all of the scenarios examined, ponatinib was less costly and more effective, due to incremental QALY gains in the SCT phase following ponatinib.

The EGP's best estimate of the incremental cost of ponatinib when compared with stem cell transplantation in the AP-CML phase is that there are potential cost savings ranging from $74,395 to $104,226 (ΔC) associated with ponatinib and that the difference in the incremental effect (ΔE) could be between 0.24 and 1.05 QALYs. These estimates are based on a time horizon of 10 years, a cost of ponatinib based on 3 tablets of 15 mg (instead of one tablet of 45 mg) and an exploration around the 95% CI of the MaHR of ponatinib.

The EGPs estimates were similar to the submitted estimates.

Hydroxyurea

According to the economic analysis that was submitted by ARIAD Pharmaceuticals, Inc., when ponatinib is compared with hydroxyurea:

- the extra cost of ponatinib is $110,683 (ΔC). Costs considered in the analysis included drug costs, resource use costs and adverse event costs.
- the extra clinical effect of ponatinib is 2.81 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on cytogenic response and overall survival.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $39,455.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $49,082 and $55,051 when ponatinib is compared with hydroxyurea.

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 ponatinib is between $91,720 and $121,551. Cost was most affected by the unit cost of ponatinib and the major cytogenic response of ponatinib.
- the extra clinical effect of ponatinib is between 1.67 and 2.48 (ΔE). Clinical effect was most affected by the major cytogenic response of ponatinib and the time horizon.

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

- The time horizon was shortened to 10 years (from a lifetime horizon), the extra cost is $103,934 ($\Delta C_1$) and the extra clinical effect is 2.07 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $50,170 (from $39,455).
- The cost per mg of ponatinib is based on 3 x 15 mg (instead of one tablet of 45 mg), the extra cost is $113,385 ($\Delta C_2$) and the extra clinical effect is 2.81 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $40,418 (from $39,455).
- The lower 95% confidence interval of MaHR for ponatinib is used, the extra cost is $89,237 ($\Delta C_3$) and the extra clinical effect is 2.06 (ΔE_3), which increases the estimated incremental cost-effectiveness ratio to $43,237 (from $39,455).
- The upper 95% confidence interval of MaHR for ponatinib is used, the extra cost is $132,129 ($\Delta C_4$) and the extra clinical effect is 3.55 (ΔE_4), which decreases the estimated incremental cost-effectiveness ratio to $43,237 (from $39,455).

The EGPs estimates differed from the submitted estimates.

BP-CML

Stem cell transplantation

According to the economic analysis that was submitted by ARIAD Pharmaceuticals Inc., when ponatinib is compared with stem cell transplantation, ponatinib was less costly and more effective.

The EGP examined several scenario analyses of ponatinib versus stem cell transplantation. Under all of the scenarios examined, ponatinib was less costly and more effective, due to incremental QALY gains in the SCT phase following ponatinib.

The EGP's best estimate of the incremental cost of ponatinib when compared with stem cell transplantation is that there are potential cost savings ranging from $70,666 to $87,395 (ΔC) associated with ponatinib and that the difference in the incremental effect (ΔE) could be between 0.57 and 1.02 QALYs. These estimates are based on a time horizon of 10 years, a cost of ponatinib based on 3 tablets of 15 mg (instead of one tablet of 45 mg) and an exploration around the 95% CI of the MaHR of ponatinib.

The EGPs estimates were similar to the submitted estimates.

Hydroxyurea

According to the economic analysis that was submitted by ARIAD, when ponatinib is compared with hydroxyurea:

- the extra cost of ponatinib is $102,924 (ΔC). Costs considered in the analysis included drug costs, resource use costs and adverse event costs.
- the extra clinical effect of ponatinib is 1.64 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on cytogenic response and overall survival.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $62,870.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $66,399 and $77,535 when ponatinib is compared with hydroxyurea.

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 ponatinib is between $91,025 and $108,362. Cost was most affected by the unit cost of ponatinib and the major cytogenic response of ponatinib.
- the extra clinical effect of ponatinib is between 1.18 and 1.63 (ΔE). Clinical effect was most affected by the major cytogenic response of ponatinib and the time horizon.

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

- The time horizon was shortened to 10 years (from a lifetime horizon), the extra cost is $96,968 ($\Delta C_1$) and the extra clinical effect is 1.41 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $68,918 (from $62,870).
- The cost per mg of ponatinib is based on 3 x 15 mg (instead of one tablet of 45 mg), the extra cost is $105,953 ($\Delta C_2$) and the extra clinical effect is 1.64 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $64,721 (from $62,870).
- The lower 95% confidence interval of MaHR for ponatinib is used, the extra cost is $94,025 ($\Delta C_3$) and the extra clinical effect is 1.37(ΔE_3), which increases the estimated incremental cost-effectiveness ratio to $68,567 (from $62,870).
- The upper 95% confidence interval of MaHR for ponatinib is used, the extra cost is $111,823 ($\Delta C_4$) and the extra clinical effect is 1.90 (ΔE_4), which decreases the estimated incremental cost-effectiveness ratio to $58,772 (from $62,870).

The EGPs estimates differed from the submitted estimates.

Ph+ ALL

Stem cell transplantation

According to the economic analysis that was submitted by ARIAD, when ponatinib is compared with stem cell transplantation, ponatinib was less costly and more effective.

The EGP examined several scenario analyses of ponatinib versus stem cell transplantation. Under all of the scenarios examined, ponatinib was less costly and more effective, due to incremental QALY gains in the SCT phase following ponatinib.

The EGP's best estimate of the incremental cost of ponatinib when compared with stem cell transplantation is that there are potential cost savings ranging from $11,733 to $20,579 ($\Delta C$) associated with ponatinib and that the difference in the incremental effect (ΔE) could be between 0.38 and 0.76 QALYs. These estimates are based on a time horizon of 10 years, a cost of ponatinib based on 3 tablets of 15 mg (instead of one tablet of 45 mg) and an exploration around the 95% CI of the MaHR of ponatinib.

The EGPs estimates were similar to the submitted estimates.

Hydroxyurea

According to the economic analysis that was submitted by ARIAD, when ponatinib is compared with hydroxyurea:

- the extra cost of ponatinib is $115,732 ($\Delta C$). Costs considered in the analysis included drug costs, resource use costs and adverse event costs.
- the extra clinical effect of ponatinib is 1.85 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on cytogenic response and overall survival.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $62,574.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $87,966 and $113,069 when ponatinib is compared with hydroxyurea.

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 ponatinib is between $110,296 and $119,142. Cost was most affected by the unit cost of ponatinib and the major cytogenic response of ponatinib.
- the extra clinical effect of ponatinib is between 0.98 and 1.35 (ΔE). Clinical effect was most affected by the major cytogenic response of ponatinib and the time horizon.

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

- The time horizon was shortened to 10 years (from a lifetime horizon), the extra cost is $111,251 ($\Delta C_1$) and the extra clinical effect is 1.16 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $95,496 (from $62,574).
- The cost per mg of ponatinib is based on 3 x 15 mg (instead of one tablet of 45 mg), the extra cost is $119,200 ($\Delta C_2$) and the extra clinical effect is 1.85 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $64,449 (from $62,574).
- The lower 95% confidence interval of MaHR for ponatinib is used, the extra cost is $110,587 ($\Delta C_3$) and the extra clinical effect is 1.52 (ΔE_3), which increases the estimated incremental cost-effectiveness ratio to $72,531 (from $62,574).
- The upper 95% confidence interval of MaHR for ponatinib is used, the extra cost is $120,878 ($\Delta C_4$) and the extra clinical effect is 2.17 (ΔE_4), which decreases the estimated incremental cost-effectiveness ratio to $55,594 (from $62,574).

The EGPs estimates differed from the submitted estimates.

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?

The EGP estimates of ΔC & ΔE differed for the following reasons: a time horizon of 10 years (instead of a lifetime horizon), a cost per mg of ponatinib based on 3 x 15 mg tablets, and the 95% confidence intervals around the cytogenic responses. The CGP felt that these estimates best reflected patients with CML/ALL, what is observed in clinical practice and the uncertainty in the data due to lack of head-to-head clinical trials against the various comparators. Though the EGPs best estimates provide a range that is somewhat narrow, this does not reflect precision; re-analyses were done with the model provided.

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

Factors relevant to patients, which included response, survival, and regain lost response for a suitable bone marrow donor, were addressed and were incorporated into the economic model through survival estimates taken from the clinical trial. Patients also noted that here were side effects with ponatinib, which was addressed through the inclusion of adverse events in the model. These estimates were taking from the clinical trial.

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

Yes, the structure was adequate. The model was transparent and the ability to modify inputs was provided. The one modification that could be manipulated was the consideration of controlling the disease prior to a direct stem cell transplantation, however, this would favour the comparator by increasing costs in the comparator arm. However, a limitation with partitioned survival models is the inability to control directly for post-progression survival.

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?

Cytogenic response had an important effect on the results. As the cytogenic response was not measured in a head-to-head clinical trial, the EGP explored the 95% confidence intervals around these responses for ponatinib. Time horizon, when shortened to 20 or 10 years (depending on the phase and disease), also had an important effect on the results. Although there are clinical concerns of extrapolating data to 20 or 10 years, the parametric extrapolation to 20 or 10 years appeared plausible. Finally, whether ponatinib is costed based on 3x15 mg tablets or 1 x 45 mg tablet impacted the incremental cost results.

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?

Cost inputs were adequate. Appropriate resource use was included and costed in an adequate way.

Clinical inputs ideally would have been taken from a head-to-head clinical trial. Single arm comparisons introduces the risk of bias as populations included and study designs may have underlying differences. The CGP also identified that the patient population that was modeled/included in the clinical trial may not reflect that of clinical practice. The population modeled may be healthier, and therefore may limit the generalizability of the results included in this cost-effectiveness analysis. Finally, survival may be overestimated; the predicted overall survival in the first three years of the model does not fit the trial data well and there is an overestimation of survival. The EGP was not able to modify this in the provided model.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The budget impact is most sensitive to an increase in the number of patients with CML and ALL, market shares of ponatinib and cost of ponatinib. PAG has indicated that indication creep is a concern, which would increase the number of patients treated if moved into first line.

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

The number of patients with disease was estimated. As the number of patients treated is a cost driver, this is a key limitation.

1.5 Future Research

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

Using survival data that does not need to be fitted, nor curves that are digitized, would increase the generalizability of the results.

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

A trial where patients have needed to fail both dasatinib and nilotinib would better reflect real life and provide further evidence on the effectiveness of ponatinib. Further, patient populations included in the clinical trial should reflect what is seen in clinical practice.

2 DETAILED TECHNICAL REPORT – Economic analysis of ponatinib for the treatment of chronic phase chronic myeloid leukemia

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 of ponatinib for the treatment of accelerated or blast phase chronic myeloid leukemia

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 DETAILED TECHNICAL REPORT – Economic analysis of ponatinib for the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia

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

5 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Hematology 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 Ponatinib (Iclusig) for Chronic Myeloid Leukemia/ Acute Lymphoblastic Leukemia. A full assessment of the clinical evidence of Ponatinib (Iclusig) for Chronic Myeloid Leukemia/ Acute Lymphoblastic 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.cadth.ca/pcodr).

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*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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.

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.cadth.ca/pcodr). 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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