PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

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

October 1, 2015

Feedback on pERC Initial Recommendation for Ponatinib

Name of the Drug and Indication(s):	Ponatinib (ICLUSIG). For the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance.
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	ARIAD Pharmaceuticals, Inc.

Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees _x___ agrees in part ____ disagree

ARIAD Pharmaceuticals, Inc (ARIAD) agrees with the recommended clinical population described in the initial recommendation. However, ARIAD believes that several statements elsewhere in the preliminary recommendation document incompletely characterize the data in both the submission and pCODR's own guidance reports. The concerned statements are identified below and ARIAD believes that slight modifications would better reflect the available evidence.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

_x___ Support conversion to final recommendation.	____ Do not support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.	Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number		Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
1 4		pERC Recommendation Summary of pERC Deliberations	Paragraph 3, line 9 Paragraph 3, line 15	ARIAD requests the inclusion of more context around the statement "…no information compared to bosutinib" and "the Committee expressed concerns as the economic analyses provided did not compare ponatinib to bosutinib". The pERC recommendation should clarify that, at the time that ponatinib was submitted for review (March 2015), bosutinib was also under review (completed April 2015) and the funding status, price, and availability of bosutinib in Canada was not known. A cost-effectiveness analysis comparing ponatinib vs bosutinib would have, therefore, not been possible. Moreover, at no time during the review of ponatinib did pCODR request that bosutinib be included as a comparator. Had this issue been raised, ARIAD could have conducted such an analysis and submitted it alongside responses to other pCODR questions. We understand from you that submission of further economic evidence to address this would not be allowed at this stage in the process. Therefore, the current wording on this issue in the preliminary pERC recommendation does not fully reflect this important timing.
1		pERC Recommendation	Paragraph 3, line 8-9	ARIAD is confused about the statement that "there is insufficient evidence to inform whether ponatinib is cost-effective compared to interferon-alpha" when, in fact, interferon-alpha was a direct comparator in the CP CML economic analysis submitted. Moreover, as noted in pCODR's own EGR, the ICUR range for this comparison was relatively close to the submitted ICURs and differed only when the ERG assumed unnecessary use of 3x15mg tablets or arbitrary changes in the time horizon. Finally, in more advanced phases of CML, interferon-alpha would not likely be used in practice; as noted in the economic report submitted by ARIAD (Sections 4.1.3, 5.1.3), there are virtually no data on the efficacy of interferon-alpha in this population of late line CML patients and interferon-alpha has never been studied in registration trials nor is it specifically licensed for use in this population. Also, the CGR section 1.2.3 does not reference interferon-alpha as a relevant treatment. Nevertheless, for the sake of completeness and transparency, ARIAD included interferon-alpha in the CP CML analysis using a conservative modelling approach (i.e. to the disadvantage of ponatinib). The pERC statement should be corrected.
1		pERC Recommendation	Paragraph 3, line 4-6	ARIAD requests inclusion of more context around the statement that "the Committee noted for advanced (accelerated and blast) phases of CML and Ph+ ALL, there was a wide range in the incremental cost-effectiveness ratios and pERC could not conclude that ponatinib was cost-effective in these subgroups". The EGP's own sensitivity analyses reported estimates <u>equal</u> to those submitted by ARIAD (e.g. ponatinib vs SCT in AP, BP and Ph+ALL). This is clearly noted in the EGR. Additionally, the EGP estimates only differed with those submitted by ARIAD when hydroxurea was the chosen comparator in AP, BP, and

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				Ph+ALL. Yet as detailed in the submission, and as noted in pCODR's own CGR, hydroxyurea offers only palliative/supportive care and is not recommended in clinical guidelines for advanced phases of disease (see section 2.3 of the submitted Clinical Summary) whereas SCT is recommended. Therefore, the relevance of hydroxyurea as a comparator is questionable; it was included in the submission for completeness and transparency. Therefore, the current statement in the preliminary pERC recommendation mischaracterizes the submitted evidence and ERP conclusions.
8		Economic Evaluation	Paragraph 3, line 3	ARIAD requests that further context be included regarding the cost per course according to the recommended and approved dose. The drug cost reported in the preliminary recommendation reflects the cost of ponatinib assuming constant use of 45mg dose in 100% of patients. This is incorrect. As described in the submission, the vast majority of time on treatment in the PACE pivotal trial was spent at lower doses. Dose reductions occurred in 55% of the patients and 67% of the patients had at least one dose interruption (Cortes JE et al NEJM 2013). Indeed, the Health Canada product monograph itself notes that dose should be reduced below 45mg once response is achieved. Therefore, the current sentence in the pERC recommendation ignores the costs at lower doses, yet these doses are critical to the safe and effective use of ponatinib as outlined in the submission, pCODR's own CGR (pages 3, 4, 13) and the Health Canada monograph.

Comments Related to Submitter or Manufacturer-Provided Information

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4	Summary of pERC Deliberations	Paragraph 3, line 19	ARIAD requests removal of the statement "unlikely to be cost-effective…no demonstrated clinical advantage….potentially increased toxicity". This statement is subjective, especially when there was no possibility for ARIAD to submit cost-effectiveness data versus bosutinib (see comments above). Moreover, the available data does indicate superior efficacy and response durability with ponatinib as compared to bosutinib in third-line therapy for CP-CML patients, as shown on Page 58-59 of the submitted Clinical Summary, where the efficacy of ponatinib was approximately double that of all other TKIs analyzed in the published indirect comparison conducted by Dr. Jeffrey Lipton (Department of Hematology/Oncology, Princess Margaret Hospital) that was included in the submission. The superior efficacy based on this

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			analysis could demonstrate ponatinib's cost-effectiveness. Therefore, the current statement in the pERC recommendation does not reflect evidence included in the submission and ignores the context around the availability of cost-effectiveness data versus bosutinib.
4 8	Summary of pERC Deliberations Economic Evaluation	Paragraph 4, line 3 Paragraph 3, line 3	ARIAD requests removal of statements related to the use of 3 x 15mg such as "pERC felt that clinicians would likely use the 15mg tablets in order to make dose adjustments". Ponatinib is an oral tablet available in 15mg and 45mg strengths. With the availability of the 45mg tablet allowing for 1 pill per day dosing, it would never be necessary for patients prescribed 45mg per day to be dispensed a 3-pill (3x15mg) regimen. It is also economically detrimental to do so, as the price of the 45mg strength is not 3x the price of the 15mg. Moreover, as noted in treatment guidelines that were detailed in the submission, monitoring of patients' response to treatment should begin after 3 months, and the median time to response in the PACE trial was approximately 2.8 months. The Health Canada monograph clearly recommends reducing the dose from 45mg after achievement of response, which would not be known until approximately 3 months of treatment have passed. Therefore, there would be no advantage to burdening patients with a multi-pill regimen to reach the licensed 45mg starting dose. The current sentence in the preliminary pERC recommendation is suggestive that use of a 3x15mg approach to enable dose reductions prior to response could be safe and effective, yet this is not supported by the available evidence and is potentially harmful to patients. We also note that the ERP assessed the impact on costs when using 3x15mg, but did not apparently make a similar modification for the comparators. For example, 5x20mg of dasatinib should be used in any sensitivity analysis that assumes 3x15mg of ponatinib. Otherwise, such a sensitivity analysis would be one-sided and arbitrary.
4	Summary of pERC Deliberations	Paragraph 1, line 3	Reference to the OPUS study should be removed. OPUS is not a ponatinib trial and in fact a trial of cetuximab in solid tumors. ARIAD believes that the author may have been referring to the OPTIC trial.
3	Summary of pERC Deliberations	Paragraph 3, line 7	The suggestion that a randomized trial of ponatinib versus other TKIs could have been conducted should be removed. As noted in our submission, and as described in pCODR's own clinical guidance reports, the PACE trial of ponatinib focused exclusively on severe, resistant patients that had failed prior therapies. The vast majority (93%) of patients were in third or later lines of treatment where no other TKI has ever been studied in registration trials of safety or efficacy. Randomizing patients to other TKIs that were either not licensed, or that lacked evidence of safety and efficacy would have been unethical. Indeed, this is why the FDA, EMA and Health Canada have approved the

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			use of ponatinib in the absence of RCT data. The current statement in the preliminiary pERC recommendation is misleading and inaccurate. Moreover, it conflicts with prior pERC conclusions, including that for bosutinib, for which pERC concluded (page 3, pCODR/pERC bosutinib recommendation) that a randomized trial would not have been possible in third line patients. It is not consistent for pERC to conclude that for bosutinib an RCT would not have been possible in third or later lines, while concluding that it would have been possible in the ponatinib trial.