EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 December 2013
EMA/PRAC/746091/2013

List of questions to be addressed by the marketing authorisation holder in writing

Review under Article 20 of Regulation (EC) No 726/2004

Invented name: Iclusig

INN: ponatinib

Procedure number: EMEA/H/C/002695/A-20/0003

Marketing authorisation holder: ARIAD Pharma Ltd

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
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The MAH is requested to provide the following in writing:

Note: where a question refers to 'each of the currently authorised indications', the MAH should provide separate responses for CP-CML, AP-CML, BP-CML and Ph+-ALL.

1. Please provide a detailed analysis of all treatment-emergent vascular occlusive adverse events (and possible sequelae) from clinical trials, spontaneous reporting data and any other available data. Please provide an updated list of all preferred terms (PTs) included in this analysis, which should capture all relevant arterial and venous events. This should include a full assessment of the nature, severity and frequency of these events, and appropriate classification (with justification) of these events by seriousness (ie. serious or non-serious) in line with ICH definitions. In order to further assess the nature of these events, a special effort should be made to collect information from pathology reports, when available.

2. Please provide a detailed analysis of all treatment-emergent events of heart failure from clinical trials, spontaneous reporting data and any other available data. This should include a full assessment of the nature, severity and frequency of these events, and appropriate classification (with justification) of these events by seriousness (ie. serious vs non-serious) in line with ICH definitions. This should also include an assessment of causality and consideration of the extent to which the events of heart failure are associated with vascular occlusive events.

3. Please provide a full analysis of the potential mechanisms which may lead to vascular occlusive events occurring in association with ponatinib treatment based on all available clinical and preclinical data, including pathology reports where available. Please also provide a discussion of any possible differences in the pathophysiology of arterial and venous events. This should also include consideration of the possible effect of any metabolites. In addition, please provide a proposal for any additional clinical or preclinical mechanistic studies needed to further characterise this risk.

4. Please provide a full analysis of the pharmacokinetic-pharmacodynamic (PK-PD) relationship for ponatinib in terms of (a) efficacy and (b) safety for each of the currently authorised indications, based on all available clinical data from the phase 1, 2 and 3 trials and relevant preclinical data. In addition, please provide a proposal for any additional clinical or preclinical studies needed to further characterise the PK-PD profile of ponatinib in each of the authorised indications, including consideration of prolonged use.

5. Based on the PK-PD analysis requested in question 4, please provide a full justification for (a) the current and/or proposed initial dose and (b) any proposed dose modifications for each of the authorised indications.

6. Please provide a full benefit-risk assessment of ponatinib in each of the currently authorised indications in the context of all other authorised treatment options for each indication. Please also specifically discuss the benefit-risk balance of ponatinib treatment in patients with and without the T315I mutation for each of the currently authorised indications.

7. Please provide a detailed proposal for any additional pharmacovigilance and/or risk minimisation measures, and methods to evaluate the effectiveness of existing and proposed measures. An updated RMP and product information proposals should be submitted.