Annex IV

Scientific conclusions

Scientific conclusions

Background information

Ponatinib is a tyrosine kinase inhibitor (TKI), designed with the purpose of inhibiting the kinase activity of native BCR-ABL, and all mutant variants, including 'gatekeeper' T315I.

The Marketing Authorisation was granted by the European Commission on 1 July 2013 for the following indications in adult patients:

- chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation and
- Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

In October 2013, the EMA was informed that the rate of vascular occlusive events was higher than observed in the clinical trials that supported the initial marketing authorisation. A type II variation was submitted and additional risk minimisation measures such as updates to the product information were put in place. However, there were a number of outstanding issues which could not be resolved within the expedited variation procedure and which required a further review of the benefit-risk balance of Iclusig. These included further consideration of the PK-PD profile of ponatinib to determine the optimal dosing in all patient populations and indications (including recommendations for initial dose and dose reductions), further assessment of the nature, severity and frequency of all treatment-emergent vascular occlusive adverse events (and possible sequelae), and heart failure, exploration of the potential mechanisms of action leading to vascular occlusive events and consideration of the possibilities for further risk minimisation measures. Therefore the European Commission triggered a procedure under Article 20 of Regulation (EC) No 726/2004 on 27 November 2013.

Scientific discussion

Non-clinical issues

As part of the assessment of potential causes that may lead to an increased occurrence of vascular occlusive events in ponatinib treated patients, molecular mechanisms based on on-target and off-target effects were discussed. A number of plausible molecular mechanism exists that may contribute to vascular occlusive events. Further non-clinical studies will be conducted with the aim to further characterise the potential mechanisms for vascular occlusive events with ponatinib treatment.

Clinical issues

The overall safety profile for ponatinib is generally consistent with that considered at the time of marketing authorisation, with the notable addition of the risk of vascular occlusive events. A total of 81 (18%) patients on the phase 2 study (n=449) have experienced serious vascular occlusive events and overall, a total of 101 patients (23%) have experienced vascular occlusive events (serious and non-serious). The incidence of arterial thrombotic events (per 100 patient years) remains relatively constant.

In view of the high risk for vascular occlusive events, the PRAC considered that it should be made clear in the product information that ponatinib should be discontinued in patients who do not respond to treatment (no haematologic response by 3 months).

Serious cardiac failure events have occurred in a total of 23 patients (5.1%). The majority of cases of cardiac failure occurred in patients at known risk from underlying disease, cardiovascular risk factors and prior treatment with cardiotoxic medications including other TKIs. There is also an association between vascular occlusive events and a risk of cardiac failure as a secondary event. It is therefore appropriate to reinforce existing recommendations for the cardiovascular status of the patient to be assessed before initiating treatment.

The possible role of anti-platelet, anti-coagulant or lipid lowering drugs in reducing the risk of vascular occlusive events remains uncertain. Therefore no formal recommendation can be issued regarding concomitant the use of these agents and the potential risks of haemorrhage with anti-platelet and anti-coagulant agents in ponatinib treated patients need to be considered.

The risk of vascular occlusive events is likely to be dose related and therefore a dose reduction would be expected to reduce the risk of vascular occlusive events. The PRAC considered whether a recommendation for dose reduction (in the absence of an adverse event) in patients with chronic phase CML who have achieved major cytogenetic response was appropriate. Efficacy data in relation to dose reduction indicates that patients who have been dose reduced maintained response (MCyR and MMR) for the duration of the currently available follow-up. This raises the question of whether similar outcomes in terms of efficacy could be achieved with lower (starting and/or maintenance) doses, which are expected to reduce the risk of vascular occlusive events. However these data include a relatively small number of patients, most of which had been dose reduced due to adverse events, and follow-up time is limited. It is therefore unclear whether the maintenance of response observed in this particular group of patients can be generalised to the CP-CML population. While these data can be useful for physicians considering dose reduction, it is currently considered insufficient to adopt a formal recommendation for dose reduction in patients who have not experienced an adverse event. Conducting further studies aimed at clarifying the dose-efficacy relationship of ponatinib is considered key to allow exploration of dose reduction in the context of risk minimisation, which could ultimately lead to improving the benefit-risk balance of the product. A dose-ranging study will be conducted in patients with CP-CML in order to determine the optimal starting dose of Iclusig and characterise the safety and efficacy of Iclusig following dose reductions after achieving MCyR. This study is considered key to the benefit-risk of ponatinib and has been imposed as a condition to the marketing authorisation.

Risk minimisation measures

The Product Information for Iclusig was revised to include the following:

- Updated recommendations to assess cardiovascular status and consider alternative treatments where appropriate.
- Inclusion of safety and efficacy data following dose reduction in CP-CML patients who have achieved MCyR to inform physicians of the currently available data on dose reduction.
- Discontinuation of treatment if haematologic response has not occurred by 3 months.
- Additional warnings about hypertension, cardiac failure and risk of bleeding with anti-clotting agents.
- Updated information on adverse reactions.

An additional risk minimisation activity was required by the PRAC. The MAH shall provide relevant healthcare professionals with educational material highlighting important medical risks for which

monitoring and/or dose adjustment are recommended, instructions on management of adverse events based on monitoring and dose modifications or treatment withdrawal and available data on the relationship between dose and risk of vascular occlusive events.

Overall conclusion

Based on the totality of the data assessed during the procedure and on the advice from the Scientific Advisory Group for oncology, the PRAC concluded that the benefit-risk balance of Iclusig remains favourable taking into account the product information amendments and subject to the risk minimisation measures and additional pharmacovigilance activities agreed.

Grounds for the recommendation

Whereas

- The PRAC considered Iclusig (ponatinib) in the procedure under Article 20 of Regulation (EC) No 726/2004, initiated by the European Commission.
- The PRAC reviewed all data presented by the MAH on the safety and efficacy of Iclusig, as well as the views expressed by the oncology scientific advisory group.
- The PRAC took note of the serious risk of vascular occlusive events associated with Iclusig, which is likely to be dose-related.
- The PRAC also considered the currently available data on dose-efficacy and dose-toxicity relationship, and concluded that it was too limited to allow for a formal recommendation for dose reduction as a risk minimisation measure in patients who have not experienced toxicity. Nevertheless the Committee agreed that it is important to reflect these data in the product information.
- The PRAC also noted that, although limited, the data in chronic phase CML is indicative of maintenance of response in patients who are dose reduced and therefore it was considered important to generate further data on the dose-efficacy relationship to potentially inform future risk minimisation measures.

The PRAC is therefore of the opinion that the benefit-risk balance of Iclusig remains favourable taking into account the product information amendments and subject to the risk minimisation measures and additional pharmacovigilance activities agreed.

The PRAC has therefore recommended the variation to the terms of the marketing authorisation for Iclusig.

The PRAC also recommended that a dose-ranging study be conducted in patients with CP-CML in order to determine the optimal starting dose of Iclusig and characterise the safety and efficacy of Iclusig following dose reductions after achieving major cytogenetic response.

CHMP opinion

The CHMP, having considered the PRAC recommendation, agrees with the overall scientific conclusions by the PRAC and is of the opinion that the marketing authorisation for Iclusig should be varied.