09 October 2014
EMA/667786/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

Iclusig

International non-proprietary name: ponatinib

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

Note

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Background information on the procedure

In October 2013, the EMA was informed that an FDA review of Iclusig concluded 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 (EMEA/H/C/2695/II/002) to update the product information was submitted and assessed in an expedited manner to ensure that the EU product information reflected the most recent data.

After submission of the variation dossier, the MAH informed the EMA that the phase 3 EPIC trial [AP24534-12-301; a phase 3 randomised, open-label study of ponatinib versus imatinib in adult patients with newly diagnosed chronic myeloid leukaemia in chronic phase (CP-CML)] had been discontinued with immediate effect. This decision was made on the grounds of patient safety, because arterial thrombotic events were observed in patients treated with Iclusig.

In the EU, the above mentioned variation was concluded within a 30-day timeframe to put in place additional risk minimisation measures such as updates to the product information and risk management plan, and circulation of a DHPC.

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.

2. Scientific discussion

Ponatinib is a tyrosine kinase inhibitor (TKI), produced by a computational and structure-based approach to the development of a small molecule TKI. Ponatinib was 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.

2.1. Non-clinical aspects

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 with ponatinib use.

BCR-ABL inhibition itself has been suggested to play a role in the development of dyslipidaemia and atherosclerosis due to effects on the insulin receptor pathway[1]. A number of off-target effects including but not limited to platelet-derived growth factor receptor β (PDGFRβ), vascular endothelial growth factor receptor 2 (VEGFR2), and TIE2 may contribute to vascular occlusive events in different ways. The VEGF protein is heavily involved in maintenance and integrity of the vascular endothelium and disruption of its signalling pathway had direct effects on endothelial cells including induction of apoptosis, inhibition of proliferation and impairment of endothelial regeneration[2,3]. Pre-clinically, a worsening of injury, inhibition of endothelial cell proliferation and cell death have been attributed to inhibition of VEGFR2 by another TKI, sunitinib, in a neonatal rodent model of stroke[4]. TIE2, a tyrosine kinase receptor for angiopoietin 1, is almost exclusively expressed in endothelial cells. It was found to have effects on vascular function and survival directly at the TIE2 kinase level and indirectly via ABL kinase based on data from a targeted ABL kinase knockout mouse model in which Chislock et al[5] observed embryonic and perinatal lethality, with mutant mice displaying a focal loss of vasculature and tissue necrosis. PDGF protein is involved in proliferation and migration of vascular smooth muscle cells (VSMC); both events are critical in the pathogenesis of artery obstructive diseases[6,7,8] and PDGF signalling disruption may inhibit vascular injury repair at the level of VSMCs. Some of these ponatinib off-target effects are unique for this TKI relative to other TKIs targeted against BCR-ABL. Further potential mechanisms will be investigated, including effects on proliferation, coagulation and inflammation in a range of in-vitro studies conducted in relevant cell-lines. In addition, in vivo investigations in a mouse model are anticipated to further inform on the liability of ponatinib in context of thrombogenesis.

Whilst ponatinib metabolites are not expected to contribute to vascular occlusive events based on their known physico-chemical properties, the inhibitory potency of selected metabolites in kinase assays will be investigated nevertheless.

The following five non-clinical studies will be conducted with the aim to further characterise the potential mechanisms for vascular occlusive events with ponatinib treatment.

Table 1 Planned non-clinical studies to characterise potential mechanisms for vascular occlusive events with ponatinib treatment

Study description	Proposed reporting timeline
Pro-thrombotic potential of ponatinib in vivo in a murine model of	December 2015

[1] Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009; 16:1103-23.
[2] Lee S, Chen TT, Barcber CL et al. Autocrine VEGF signalling is required for vascular homeostasis. Cell. 2007; 130:691-703.
[3] Elice F, Jacoub J, Rickles FR et al. Hemostatic complications of angiogenesis inhibitors in cancer patients. Am J Hematol 2008; 83:862-870.
[4] Shimotake J, Derugin N, Wendland M, Vexler ZS, Ferriero DM. Vascular endothelial growth factor receptor-2 inhibition promotes cell death and limits endothelial cell proliferation in a neonatal rodent model of stroke. Stroke 2010; 41:343-9.
[5] Chislock E, Ring C, Pendergast AM. Abl kinases are required for vascular function, Tie2 expression and angiopoietin-1-mediated survival. Proc Natl Acad Sci USA 20113; 110:12432-7.
[6] Bailey SR. Coronary restenosis: a review of current insights and therapies. Catheter Cardiovasc Intervent. 2002; 55:265-271.
[7] Sanz-Gonzalez SM, Castro C, Perez P, Andres V. Role of E2F and ERK1/2 in STI571-mediated smooth muscle cell growth arrest and cyclin A transcriptional repression. Biochem Biophys Res Commun 2004; 317:972-9.
[8] Levitzki A. PDGF receptor kinase inhibitors for the treatment of restenosis. Cardiovasc Res 2005: 65:581-6.

Study description	Proposed reporting timeline
thrombosis	
Proliferation and survival of human endothelial cells in vitro	December 2015
Proliferation and survival of human vascular smooth muscle cells in vitro	December 2015
Activation of the pro-coagulation cascade and expression of surface adhesion molecules in human endothelial cells in vitro	December 2015
Initiation of pro-inflammatory events in human endothelial cells in vitro	December 2015

2.2. Clinical aspects

During the assessment, data from the studies listed below was considered, with the most relevant contribution coming from the phase 2 study.

Table 2 Summary of trials contributing to the assessment

	Phase 1: AP24534-07-101	Phase 2: AP24534-10-201	Phase 3: AP24534-12-301
Trial Description Title	A Phase 1 Dose Escalation Trial to Determine the Safety, Tolerability and Maximum Tolerated Dose of Oral AP24534 in Patients with Refractory or Advanced Chronic Myelogenous Leukemia and other Hematologic Malignancies	A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia (**PACE** Trial)	A Phase 3 Randomized, Open-Label Study of Ponatinib versus Imatinib in Adult Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (**EPIC** Trial)
Population	Refractory hematologic malignancies: Ph+ leukemia (CP-CML, AP-CML, BP-CML and Ph+ ALL), AML, and other hematologic malignancies	Adult patients (≥18 years old) with CML in chronic phase (CP), accelerated phase (AP) or blast phase (BP) or with Ph+ acute lymphoblastic leukemia (ALL) who either: • Are resistant or intolerant to either dasatinib or nilotinib • Have the T315I mutation	Patients with newly diagnosed chronic myeloid leukemia in chronic phase (CP-CML)
Dosing	Oral once daily administration (2 mg to 60 mg dose escalation)	Oral 45 mg once daily	Ponatinib: Oral 45 mg dose once daily Imatinib: Oral 400 mg dose once daily
N	81 (65 Ph+ leukemia)	449	307 (155 ponatinib)
Regions/Centers	5 US sites	68 sites in US/Canada, Europe, Australia, Asia	171 sites in US/Canada, Europe, Australia, Asia
Objectives	To determine the MTD or a recommended dose of oral ponatinib in patients with refractory hematologic malignancies	To determine the efficacy of ponatinib in Ph+ leukemia patients who are resistant or intolerant to either dasatinib or nilotinib or who have the T315I mutation	To compare the efficacy of ponatinib with imatinib in adult patients with newly diagnosed chronic myeloid leukemia in chronic phase (CP-CML)

The data previously assessed in the type II variation (EMEA/H/C/2695/II/002) had a cut-off date of September 2013. Updated analyses of the vascular occlusive events occurring in the clinical development program and from other sources (expanded access, commercial use) were conducted using follow-up data available up to 6 January 2014 and 7 April 2014.

A review of non-serious vascular events was also performed and it indicates that a small number could have been classified as serious based on their medical importance. However the reported incidence or character of serious events reported to date is not substantially changed by this.

2.2.1. Clinical safety

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. The limited post marketing experience so far has generally been consistent with the safety profile observed in clinical trials.

In general, the overall safety profile for ponatinib is consistent with known class effects for BCR-ABL TKIs. Risks have not been specifically analysed for patients with/without the T315I mutation.

Vascular Occlusive Events

The number of patients experiencing vascular occlusive events has risen with time. Based on the 6 January 2014 data from the phase 2 trial (N=449), taking into account the re-classification of seriousness performed by the MAH, a total of 81 patients (18%) have experienced serious vascular occlusive events, compared to a total of 62 patients (14%) from the September 2013 data. Overall, a total of 101 patients (23%) have experienced vascular occlusive events (serious and non-serious), compared to a total of 91 patients (20%) from the September 2013 data.

The incidence of arterial thrombotic events (per 100 patient years) remains relatively constant. The number of patients with arterial thrombotic events, and the number of patients with serious arterial thrombotic events, per 100 patient-years are 13.1 and 9.3 respectively based on the January 2014 analysis of the phase 2 trial (compared to 13.3 and 9.1 in the September 2013 analysis).

Patients who have a history of previous myocardial infarction, stroke or revascularisation are considered to be at particular risk of vascular occlusive events. In addition, there is some evidence that patients with 2 or more risk factors for cardiovascular disease (hypertension, hypercholesterolemia, diabetes, obesity) are at greater risk of these events.

The risk of vascular occlusive events is likely to be dose related. An integrated dose intensity analysis concluded that for vascular occlusion, after adjusting for covariates, overall dose intensity is highly statistically significant with an odds ratio of approximately 1.6 for each 15 mg dose increase. As such a dose reduction would be expected to reduce the risk of vascular occlusive events.

Table 3 Vascular Occlusive First Adverse Events in CP-CML Patients who Achieved MCyR at 45 mg or 30mg (data extraction 7 April 2014)

	Most Recent Dose at Onset of First Vascular Occlusive Event		
	45mg	**30mg**	**15mg**
Achieved MCyR at 45mg (N=87)	19	6	0
Achieved MCyR at 30mg (N=45)	1	13	5

Cardiac Failure Events

Based on the January 2014 data analysis of the phase 2 study data (N=449), a total of 23 patients (5.1%) have experienced serious cardiac failure events, and a total of 37 patients (8.0%) have now experienced cardiac failure events (serious and non-serious).

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.

Role of anti-platelet, anti-coagulant or lipid lowering drugs

The possible role of anti-platelet, anti-coagulant or lipid lowering drugs in reducing the risk of vascular occlusive events remains uncertain and has not been studied prospectively. Existing data was analysed but it is confounded by indication as these agents are used in patients at high risk of vascular occlusive events. The potential benefit of these drugs in reducing the risk may be determined by a greater understanding of the mechanisms underlying the risk of vascular occlusive events.

In addition, haemorrhage has been observed in association with the use of ponatinib and therefore the potential risks of haemorrhage with anti-platelet and anti-coagulant agents in this patient population need be considered.

2.2.2. Benefit evaluation

The evidence for the efficacy of ponatinib in the currently authorised patient population has not changed substantially since the marketing authorisation was granted.

The efficacy of ponatinib is likely to be dose related. A starting dose of 45 mg was used in the pivotal trial, based on the maximum tolerated dose, and continues to be recommended in all indications in order to ensure that the efficacy demonstrated in the pivotal trial is achieved.

Efficacy in patients who experienced an arterial thrombotic event was similar to patients who had not experienced such an event, based on the data assessed. Overall survival and progression-free survival appeared similar for patients with or without arterial thrombotic events, across all groups studied, based on currently available follow-up data.

Historical comparison of bosutinib and ponatinib may suggest a better efficacy of ponatinib (major cytogenetic response (MCyR), complete cytogenetic response (CCyR), major molecular response (MMR)) in all populations, however these data are not robust enough to allow any conclusive statement.

Patients with the T315I mutation

Ponatinib is the only TKI which has demonstrated efficacy in patients with the T315I mutation in each of the currently authorised indications.

In the ponatinib phase 2 study, the MCyR in patients with the T315I mutation (70.3%) exceeded the response of those without the mutation (51.7%). Molecular responses including MMR rates (57.8%), MR4 rates (39.1%) and CMR4.5 rates (32.8%) were all higher than in the CP-CML group without the T315I mutation.

The benefit of ponatinib in patients carrying the T315I mutation can be considered overwhelmingly positive, particularly in the absence of any alternative treatment options.

Patients without the T315I mutation

In CP-CML patients who are refractory or intolerant to previous TKIs, ponatinib showed good efficacy in terms of molecular and cytogenetic responses. In the ponatinib phase 2 study the MCyR was 51.7%. The MMR, MR4 and CMR4.5 rates were 23%, 21.2% and 15.8%, respectively.

The overall molecular responses, in all patient populations including CP-, AP-, and BP-CML appeared better in a more heavily treated patient population compared to bosutinib based on literature data. However, it is noted that bosutinib is also licensed for CP-, AP-, and BP-CML.

For Ph+ ALL, bosutinib is not a licensed alternative.

Dose reduction and maintenance of response

Based on the available data, a starting dose of 45mg is recommended in all indications in order to ensure maximal efficacy. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity. Dose modifications (to 30 mg or 15 mg) should be considered for the management of treatment toxicity.

In vitro data indicates that a 40 nM concentration is sufficient to suppress all BCR-ABL mutants. A 30 mg and a 45 mg ponatinib dose led to trough plasma (median C_{min}) levels > 40 nM, sufficient to fully suppress growth of all BCR-ABL mutants. A 15 mg ponatinib dose led to trough plasma concentration < 40 nM, sufficient to suppress all but two clones (E255V and possibly T315I).

The potential for long durations of treatment in responding chronic phase CML patients together with the observed adverse event profile of ponatinib provide a rationale for examining the possibility of reducing dose in patients who have responded to treatment (in the absence of adverse events). A reduced dose would aim at reducing the risk of adverse events (particularly vascular events) while maintaining efficacy.

On October 2013, the investigators of the ongoing phase 2 study were provided with the following instructions regarding CP-CML patients:

- All CP-CML patients currently in the study who have already achieved MCyR should have their dose reduced to 15 mg/day unless, in the judgement of the investigator, the benefit-risk analysis, having into account the patient's CML characteristics, BCR-ABL mutation status, and the patient's cardiovascular risk justifies treatment with a higher dose.
- For all CP-CML patients currently on the study who have not yet achieved MCyR, ponatinib dose reduction to 30 mg/day should be considered unless, in the judgement of the investigator, the benefit-risk analysis, taking into account the patient's CML characteristics, BCR-ABL mutation status, and the patient's cardiovascular risk justifies treatment with a higher dose.

At the time of these recommendations, 143 CP-CML patients were on the study. The subset of patients who underwent dose reduction after these instructions is small. It comprises 21 patients at 30 mg and 41 patients (18 patients who started at 45 mg and 23 patients who started at 30 mg) at 15 mg, for a period of at most 6 months (data from 7 April 2014). Most patients underwent prior dose reduction due to adverse events.

Table 4 Maintenance of response in CP-CML patients who achieved MCyR or MMR at 45 mg dose (data extraction 7 April 2014)

	Achieved MCyR at 45 mg (N=87)		**Achieved MMR at 45mg (N=63)**	
	Number of Patients	Maintained MCyR	Number of Patients	Maintained MMR
No Dose Reduction	**23**	**18 (78%)**	**18**	**11 (61%)**
Dose reduction to 30 mg only	**25**	**24 (96%)**	**13**	**11 (85%)**
≥ 90 day reduction at 30 mg	21	20 (95%)	8	9 (89%)
≥ 180 day reduction at 30 mg	11	10 (89%)	5	4 (80%)
≥ 360 day reduction at 30 mg	5	4 (80%)	2	1 (50%)
Any dose reduction to 15 mg	**39**	**39 (100%)**	**32**	**30 (94%)**
≥ 90 day reduction at 15 mg	32	32 (100%)	27	26 (96%)
≥ 180 day reduction at 15 mg	10	10 (100%)	6	6 (100%)
≥ 360 day reduction at 15 mg	6	6 (100%)	3	3 (100%)

In this limited dataset, the majority of patients who underwent dose reduction maintained response (MCyR and MMR) for the duration of the currently available follow-up. Most patients who ultimately reduced dose to 15 mg initially had their dose reduced to 30 mg for a period.

2.3. Risk minimisation activities

The PRAC requested the submission of an updated Risk Management Plan including a risk minimisation plan.

An additional risk minimisation activity was required by the PRAC. The MAH shall provide relevant healthcare professionals with a brochure highlighting the importance of assessing the risks before starting treatment with ponatinib, available data on the relationship between dose and risk of vascular occlusive events, recommendation to consider discontinuation if a complete haematologic response has not occurred by 3 months, important adverse events for which monitoring and/or dose adjustment are recommended and instructions on management of adverse events based on monitoring and dose modifications or treatment withdrawal. This additional risk minimisation measure has been added to annex II of the Product Information.

The MAH is requested to submit, within 30 days of the CHMP opinion for this procedure, an updated version of the RMP and of the educational materials in order to properly reflect the outcome of this assessment.

2.4. Product Information

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.

Amendments have been introduced to sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Summary of Product Characteristics. The Package Leaflet has been updated accordingly. Annex II has also been amended (see 2.3 risk minimisation activities).

3. Consultation with the Scientific Advisory Group

The PRAC consulted the scientific advisory group for oncology which provided advice on a number of issues.

The SAG proposed that, based on currently existing data, it is not justified to revise the indication and place in treatment of ponatinib. It was highlighted that patients with the T315I mutation or with Ph+ ALL have no alternative treatment approved, and for CML patients without the T315I mutation comparative data with other third line agents is too limited.

The SAG noted that there are very limited prospective data that would identify the shape of the dose efficacy and dose toxicity relationship and there is currently no guidance for dose reduction when MCyR has been reached. The potential risk associated with dose reduction is the reduction in efficacy. The SAG emphasized that appropriate PK/PD information is necessary to provide clinicians with appropriate guidance regarding dose individualisation and possibly therapeutic drug monitoring is of benefit in this patient population in this respect. As such, and on the basis of available data, there is no treatment algorithm allowing dose reduction in patients who achieved MCyR.

When asked to advise on appropriate guidance for monitoring of patients who have undergone dose-reduction following MCyR in the absence of adverse reactions, in order to detect early signs of possible loss of therapeutic response, the SAG considered that data is insufficient that there are neither data providing guidance for dose reduction nor for a dose increase upon loss of a therapeutic response. The nature and the frequency of monitoring in the current European standard of practice is to perform a quantitative RT-PCR and/or cytogenetics in 1-3 months and upon indication on blood sample or bone marrow aspirate.

Finally the SAG considered that there are no data which would support upfront the use of anti-platelet or anticoagulant medications or the use of statins. Data should be generated in order to understand the pathogenesis of VOEs in patients treated with ponatinib and to change the current medical practice. However in the light of the very high risk for thromboembolic complications, anti-coagulant therapy could be considered on a case by case basis taking into account the risk of haemorrhagic complications.

4. Overall discussion and benefit/risk assessment

Within this procedure, the PRAC was asked to address a number of outstanding issues which could not be resolved within the previous 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.

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 the concomitant 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 in Annex II. A phase IV study is also planned to collect more general safety evidence from the clinical use of Iclusig in order to characterise the risks further and potentially identify additional risk minimisation measures.

In addition to clinical studies, non-clinical studies will be performed by the MAH with the aim to further characterise the potential mechanisms for vascular occlusive events with ponatinib treatment. Information from these studies may in the future offer additional opportunities for risk minimisation.

5. Conclusion and 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.