INITIATION OF THE PROCEDURE LAID DOWN IN ARTICLE 20 OF REGULATION (EC) No 726/2004

This is an initiation by the European Commission of a procedure under Article 20 of Regulation (EC) No 726/2004

Common name(s):	**ponatinib**
Product Name(s):	**Iclusig**

Iclusig is indicated in adult patients with:

- 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

- 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.

Treatment is to be initiated with a starting dose of 45 mg once daily, and should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity. It is recommended that dose modifications be considered for the management of treatment toxicity.

Iclusig was authorised in the EU in July 2013. At the time of authorisation, some conditions related to thrombosis were known side effects of Iclusig and the EU product information mentions the risk of myocardial infarction, cerebral infarction (stroke), and related disorders.

In October 2013, the EMA was informed that an FDA review concluded that the rate of vascular occlusive events was higher than initially observed. A type II variation (EMEA/H/C/2695/II/002) was submitted by the marketing authorisation holder (MAH) in order to address the new data on vascular occlusive events and consequently, update the product information in the EU to reflect the most recent data.

During the assessment of the variation dossier, the MAH also informed the EMA that the phase 3 EPIC trial (AP24534-12-301; a phase 3 randomized, open-label study of ponatinb versus imatinib in adult patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML CP)) had been discontinued with immediate effect.

On 31 October 2013, the FDA announced that the MAH had agreed to their request to voluntarily suspend marketing and sales of Iclusig because of the risk of life-threatening blood clots and severe narrowing of blood vessels. This suspension includes a provision for the medicine to continue to be used in certain situations where no suitable alternatives are available. In the EU, since the initial approval, the medicine's use had been limited to patients who had no other available treatment options with medicines in this class, for example because they were intolerant to other medicines of this class or their disease was resistant to such treatment.

The CHMP assessed the above mentioned variation to address the new data on vascular occlusive events during its November 2013 meeting and recommended additional risk minimisation measures such as updates to the Product Information and Risk Management Plan, and circulation of a DHPC. However, there are a number of outstanding issues which could not be resolved within the variation procedure and which require a further review of the benefit-risk balance of Iclusig. These would more specifically include further consideration of the pharmakinetic-pharmadynamic profile of Iclusig to determine whether there is a need to revise the optimal dosing , further assessment of the nature, severity and frequency of all treatment-emergent vascular occlusive adverse events (and possible sequelae), and heart failure and exploration of the potential mechanisms of action leading to vascular occlusive events.

Therefore, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit-risk balance for the centrally authorised medicinal product Iclusig. The EC requests the Agency to give its opinion on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn. As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

Having regard to the potential serious consequences for public health, the Agency is asked to consider by the end of 2013, if there is a need to take provisional measures, notably a suspension of use of the medicinal products.

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