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# PRAC recommends further measures to minimise risk of blood vessel blockage with Iclusig

## PRAC recommendations to be considered by CHMP for final opinion

The EMA's Pharmacovigilance Risk Assessment committee (PRAC) has completed a review of the benefits and risks of Iclusig (ponatinib), a medicine used for the treatment of leukaemia (cancer of the white blood cells). The aim of this review was to examine the risk of blood clots or blockage of the arteries or veins and to assess whether further measures were needed to minimise this risk.

Iclusig is authorised for use in patients with chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL) who cannot take or tolerate several other medicines of the same class (known as 'tyrosine-kinase inhibitors'). The PRAC considered that the benefits of Iclusig continue to outweigh its risks; however, the Committee recommended that the product information for patients and healthcare professionals should be updated with strengthened warnings, particularly about the risk of blood clots and blockages in the arteries.

The PRAC assessed the available data on the nature, frequency and severity of blood clots or blockage of the arteries or veins. Although the Committee noted that this risk is likely to be dose-related, there are insufficient data to formally recommend the use of lower doses of Iclusig, and there is a risk that lower doses might not be as effective in all patients and in long-term treatment. The PRAC therefore considered that the recommended starting dose of Iclusig should remain 45 mg once a day. However, updates to the product information are recommended to provide healthcare professionals with the latest evidence, in case they wish to consider reducing the dose in patients with 'chronic phase' CML who are responding well to treatment, and who might be at particular risk of blood vessel blockage. In addition, healthcare professionals should stop Iclusig if there has been no response after three months of treatment, and monitor patients for high blood pressure or signs of heart problems.

A new study on the safety and benefits of Iclusig is planned to help clarify if lower doses of the medicine carry a lower risk of blood clots or blockages of the blood vessels while still having a beneficial effect in patients with chronic phase CML.

The PRAC recommendation will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP), which will adopt the EMA's final opinion.

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## More about the medicine

Iclusig is a cancer medicine used to treat adults with the following types of leukaemia:

- chronic myeloid leukaemia (CML);
- acute lymphoblastic leukaemia (ALL) in patients who are 'Philadelphia-chromosome positive' (Ph+).

Iclusig is used in patients who cannot tolerate or do not respond to dasatinib or nilotinib (other medicines for the treatment of leukaemia) and for whom subsequent treatment with imatinib is not considered appropriate. It is also used in patients who have a genetic mutation called 'T315I mutation' which makes them resistant to treatment with imatinib, dasatinib or nilotinib.

The active substance in Iclusig, ponatinib, belongs to a group of medicines called 'tyrosine-kinase inhibitors'. Ponatinib works by blocking a tyrosine kinase (an enzyme) called Bcr-Abl, which is found in some receptors on the surface of the cancer cells where it is involved in stimulating the cells to divide uncontrollably. By blocking Bcr-Abl, Iclusig helps to control the growth and spread of leukaemia cells.

Iclusig was authorised as an orphan medicine (a medicine to treat rare diseases) in the EU in July 2013.

## More about the procedure

The review of Iclusig was initiated on 27 November 2013 at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004.

This follows an initial assessment of clinical trial data with Iclusig, conducted in November 2013, indicating that cases of blood clots and blockages in the arteries or veins were occurring at a higher rate than was observed at the time of the medicine's initial authorisation. At the time, the EMA recommended a number of measures to help minimise this risk, which included additional warnings (e.g. against use in patients who have had a heart attack or stroke in the past). Since a number of issues required further investigation, including a better understanding of the nature, frequency and severity of events obstructing the arteries or veins, the potential mechanism through which the medicine leads to these side effects and whether there was a need to revise the dosing recommendation of Iclusig, the European Commission asked to Agency to perform an in-depth review.

The current review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. As Iclusig is a centrally authorised medicine, the PRAC recommendations will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt a final opinion. This will then be sent to the European Commission, which will issue a final legally binding decision valid throughout the EU in due course.

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