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European Medicines Agency recommends further measures to minimise risk of blood vessel blockage with Iclusig

The European Medicines Agency (EMA) has concluded its review of the benefits and risks of Iclusig (ponatinib), a medicine used for the treatment of leukaemia (cancer of the white blood cells), and has recommended strengthened warnings in the product information aimed at minimising the risk of blood clots and blockages in the arteries.

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 review followed a previous assessment of clinical trial data which indicated 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.

The available evidence shows that the risk of blood vessel blockage with Iclusig is likely to be dose-related, however the data are insufficient 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. Therefore, the recommended starting dose of Iclusig should remain 45 mg once a day. The product information will be updated with strengthened warnings about the risks with Iclusig, and to also provide healthcare professionals with the latest evidence in case they wish to consider reducing the dose of Iclusig in patients with 'chronic phase' CML who are responding well to treatment, and who might be at particular risk of blood vessel blockage. Additionally, healthcare professionals should stop Iclusig if a complete response has not occurred within three months of treatment, and should monitor patients for high blood pressure or signs of heart problems.

The company that markets Iclusig will provide healthcare professionals with educational material highlighting important risks for which monitoring and/or dose adjustments are recommended and including available data on the relationship between dose of Iclusig and risk of blood vessel blockage.

A study on the safety and benefits of Iclusig is also planned, to help clarify if lower doses of the medicine would 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 review of Iclusig was first carried out by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). During its review, the PRAC assessed available data on the nature, frequency and severity of

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blood clots or blockage of the arteries or veins and considered the potential mechanism for these side effects. The PRAC also sought the advice of a group of experts in oncology before finalising its recommendations, which have now been endorsed by the Agency's Committee for Medicinal Products for Human Use (CHMP) in its final opinion. The CHMP opinion will be sent to the European Commission, which will issue a legally binding decision valid throughout the EU in due course.

Information to patients

- Iclusig is a medicine used for the treatment of leukaemia, a type of cancer that affects white blood cells. Patients treated with Iclusig may be at increased risk of developing blood clots and blockages in the blood vessels, which can have serious consequences (such as heart attacks or strokes).
- Before starting treatment, your doctor will assess your risk of heart and circulatory problems, and will continue to check your condition at regular intervals during your treatment with Iclusig.
- Treatment with Iclusig will usually be stopped if there is insufficient beneficial response within three months, or if you develop heart or circulatory problems during treatment.
- If you have any questions or concerns, you should consult your doctor or another healthcare professional.

Information to healthcare professionals

Healthcare professionals should follow these recommendations:

- The benefit-risk balance of Iclusig remains positive in all authorised indications, and the starting dose remains 45 mg per day. The cardiovascular status of the patient should be assessed before starting therapy with Iclusig, and regularly monitored during treatment.
- Treatment with Iclusig should be stopped if a complete haematologic response has not occurred by three months. Dose modifications or treatment interruption (temporary or permanent) should be considered to manage treatment toxicity.
- The risk of vascular occlusive events with Iclusig is likely to be dose-related; however, the currently available data on the dose-efficacy and dose-toxicity relationship are not sufficient to make a formal recommendation on dose reduction, and there is a risk that lower doses might have reduced efficacy.
- Safety and efficacy data concerning dose reduction following major cytogenetic response in chronic phase CML patients have been included in the SmPC, to provide information to the prescriber and to facilitate an individual assessment of the benefit-risk balance of Iclusig with regards to dose reduction.
- If a reduced dose of Iclusig is used, doctors should monitor patients for maintenance of therapeutic response.
- Educational material will be provided to healthcare professionals, highlighting important risks for which monitoring and/or dose adjustments are recommended. The material will also provide the available evidence regarding the safety and efficacy of ponatinib when dose is reduced in patients with chronic phase CML who have achieved major cytogenetic response. Any assessment relating to dose reduction should take into account a number of factors, including the patient's cardiovascular risk, side effects of therapy, and time to cytogenetic response.

A dose-ranging study will be conducted in patients with chronic phase CML in order to determine the optimal starting dose of Iclusig and characterise the safety and efficacy of Iclusig following dose

reduction after achieving major cytogenetic response. This study has been imposed as a condition of the marketing authorisation for Iclusig. The EMA will evaluate the results of this study as soon as they are available.

More about the medicine

Iclusig is a medicine used to treat adults with the following types of leukaemia (cancer of the white blood cells):

- 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.

The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were then sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's final opinion.

The CHMP opinion will now be forwarded to the European Commission, which will issue a final decision in due course.

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