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European Medicines Agency recommends changes in use of leukaemia medicine Iclusig (ponatinib) in order to minimise risk of blood clots

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has made a number of recommendations to help minimise the risk of blood clots obstructing arteries or veins in patients taking the leukaemia medicine Iclusig.

The CHMP recommends that Iclusig should not be used in patients who have had a heart attack or stroke in the past, unless the potential benefits to them outweigh the risks. In addition, the cardiovascular risks of all patients should be assessed and measures should be taken to reduce risks before starting and during treatment with Iclusig. Patients who have high blood pressure should have their blood pressure controlled, and treatment with Iclusig should be stopped immediately in any patient with signs of blood clots obstructing arteries or veins. Further details on these recommendations can be found below.

The CHMP's recommendations follow a review of updated clinical trial data indicating that blood clots were occurring at a higher rate than was observed at the time of the medicine's initial authorisation. Conditions related to blood clots, such as heart attacks and strokes, were already considered to be possible side effects of Iclusig and were listed in the EU product information.

Since the medicine's initial approval in July 2013, its use has been limited to patients who could not be treated with other medicines of the same class, for example, because patients were intolerant to the other medicines or their disease was resistant to them.

The CHMP recommendations are broadly in line with previous advice of the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) and an opinion will be sent to the European Commission for an update of the EU product information.

The Agency now plans to conduct a further in-depth review of relevant data on the benefits and risks of Iclusig and will make recommendations on whether there should be further changes to how the medicine is used.

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Information to patients

- Iclusig remains available as a treatment for leukaemia. However, new measures are to be taken to help reduce the risk of conditions associated with blood clots (such as heart attacks, strokes and deep vein thrombosis).
- Your doctor will assess your risk of heart or circulatory problems and will take measures to reduce these risks before and during treatment with Iclusig.
- If you have high blood pressure, your doctor will advise on how to reduce your blood pressure and may consider interrupting your treatment if your blood pressure remains too high.
- If you have had a heart attack or stroke in the past, your doctor will carefully consider whether treatment with Iclusig is appropriate for you.
- If you have been prescribed Iclusig, you should be alert for the signs and symptoms of blood clots, which may include severe pain or swelling in the legs, sudden unexplained breathlessness, rapid breathing or cough, chest pain, and face, arm or leg weakness or numbness. In case you notice any of these signs and symptoms you should seek medical advice immediately.
- Please speak to your doctor or pharmacist should you have any questions about your treatment.

Information to healthcare professionals

Following a review of the data on the risk of occlusive vascular events with Iclusig, the European Medicines Agency has concluded that healthcare professionals may continue to use ponatinib in its authorised indication with increased caution. The Agency has made the following recommendations:

- Iclusig should not be used in patients with a history of heart attack or stroke, unless the potential benefits of treatment outweigh the risks.
- The cardiovascular status of patients should be assessed and cardiovascular risk factors actively managed before starting treatment with Iclusig. Cardiovascular status should continue to be monitored and optimised during treatment.
- Hypertension should be controlled during treatment with Iclusig and healthcare professionals should consider interrupting treatment if hypertension is not controlled.
- Patients should be monitored for evidence of vascular occlusion or thromboembolism, and treatment should be interrupted immediately if this occurs.

The recommendations are based on a review of data from clinical studies, including two ongoing studies (a phase I dose-finding study and a pivotal phase II study), which showed a higher incidence of arterial and venous thrombotic events in patients treated with Iclusig than was observed at the time of marketing authorisation. In the phase I study, preliminary analysis of follow-up data from September 2013 showed a rate of serious occlusive vascular events of 22% (18 out of 81 patients) while in a preliminary analysis of data from the phase II study the rate was 13.8% (62 out of 449 patients). Median treatment duration was 2.7 years in the phase I study and 1.3 years in the phase II study.

In addition, in a recently discontinued phase III study that compared Iclusig with imatinib with a median treatment duration of 3 months, there was a higher number of occlusive vascular events reported in the Iclusig arm, although the data from this study are still preliminary.

The reported events from the studies include cardiovascular, cerebrovascular, peripheral vascular and venous thrombotic events. These events were seen in patients with and without risk factors but were

seen more frequently in older patients and patients with a history of ischaemia (such as heart attacks) and strokes, high blood pressure, diabetes or blood fat disorders.

More about the medicine

Iclusig is an anticancer medicine that contains the active substance ponatinib. It is 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 do not respond to dasatinib or nilotinib (other medicines of the same class); or who cannot tolerate dasatinib or nilotinib and for whom subsequent treatment with imatinib (a third such medicine) 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.

Iclusig was authorised centrally in the EU in July 2013.

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