EMA/418308/2018
EMEA/H/C/002695

Iclusig (*ponatinib*)

An overview of Iclusig and why it is authorised in the EU

What is Iclusig and what is it used for?

Iclusig is a cancer 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) in its different stages known as chronic, accelerated and blast phases;
- acute lymphoblastic leukaemia (ALL) in patients who are 'Philadelphia-chromosome positive' (Ph+). Ph+ means that some of the patient's genes have rearranged themselves to form a special chromosome called the Philadelphia chromosome that leads to the development of leukaemia. The Philadelphia-chromosome is found in some ALL patients and is present in most patients with CML.

Iclusig is used in patients who cannot tolerate or do not respond to dasatinib (patients with CML or ALL) or nilotinib (patients with CML), which are other cancer medicines of the same class, 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.

These diseases are rare, and Iclusig was designated an 'orphan medicine' (a medicine used in rare diseases) on 2 February 2010. Further information on the orphan designations can be found here: ema.europa.eu/Find medicine/Human medicines/Rare disease designation (CML; ALL).

How is Iclusig used?

Iclusig can only be obtained with a prescription and treatment should be started by a doctor who is experienced in the diagnosis and treatment of leukaemia.

Iclusig is available as tablets (15 mg, 30 mg and 45 mg). The recommended starting dose is 45 mg once per day. Treatment is continued for as long as the patient benefits. If a patient develops certain severe side effects, the doctor may decide to reduce subsequent doses or delay or stop treatment. The doctor should consider stopping treatment if the level of white cells in the blood does not return to normal within three months.

Iclusig can lead to clots or blockages in arteries and veins and patients should have the condition of their heart and circulation considered before starting and during treatment, and be treated

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appropriately for any problems. The dose may need to be reduced or interrupted if the patient experiences certain side effects; it should be interrupted immediately if a blockage develops in an artery or vein.

For more information about using Iclusig, see the package leaflet or contact your doctor or pharmacist.

How does Iclusig work?

The active substance in Iclusig, ponatinib, belongs to a group of medicines called 'tyrosine kinase inhibitors'. These compounds act by blocking enzymes known as tyrosine kinases. Ponatinib acts by blocking a tyrosine kinase called Bcr-Abl. This enzyme is found on the surface of leukaemia 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.

What benefits of Iclusig have been shown in studies?

Iclusig has been investigated in one main study involving 449 patients with CML or Ph+ ALL and who were intolerant or resistant to treatment with dasatinib or nilotinib, or had the T315I mutation. In the study, Iclusig was not compared with another treatment. The response to treatment was assessed by measuring the proportion of patients who had a 'major haematological response' (when the number of white blood cells returns to normal or there is no evidence of leukaemia) or a 'major cytogenetic response' (when the proportion of white blood cells containing the Philadelphia chromosome falls to below 35%).

The results of the study showed that treatment with Iclusig led to clinically relevant responses in all groups of patients:

- among the patients with CML in the chronic phase, around 54% (144 out of 267) had a major cytogenetic response;
- among the patients with CML in the accelerated phase, around 58% (48 out of 83) had a major haematological response;
- among the patients with CML in the blast phase, around 31% (19 out of 62) had a major haematological response;
- among the patients with Ph+ ALL, around 41% (13 out of 32) had a major haematological response.

What are the risks associated with Iclusig?

The most common serious side effects with Iclusig (which may affect more than 2 in 100 people) are pneumonia (infection of the lungs), pancreatitis (inflammation of the pancreas), pyrexia (fever), abdominal pain (stomach ache), myocardial infarction (heart attack), atrial fibrillation (irregular rapid contractions of the upper chambers of the heart), peripheral arterial occlusive disease (problem with blood flow in the arteries), anaemia (low red blood cell counts), angina pectoris (pains to the chest, jaw and back due to problems with blood flow to the heart), decreased blood levels of platelets (components that help the blood to clot), febrile neutropenia (low white blood cell counts with fever), hypertension (high blood pressure), coronary artery disease (heart disease caused by the obstruction of the blood vessels that supply the heart muscle), cardiac failure (when the heart does not work as well as it should), cerebrovascular accident (stroke), sepsis (blood poisoning), cellulitis (inflammation

of the deep skin tissue), acute kidney injury (kidney damage), urinary tract infection (infection of the structures that carry urine) and increased levels of lipase (an enzyme).

Arterial occlusive adverse events (clots or blockages in the arteries) occurred in 25% of patients, with serious adverse events occurring in 20% of patients. Serious venous occlusive adverse events (clots or blockages in the veins) occurred in 5% of patients. Venous thromboembolic reactions (problems due to blood clots in the veins) occurred in 6% of patients.

For the full list of side effects and restrictions with Iclusig, see the package leaflet.

Why is Iclusig authorised in the EU?

The European Medicines Agency decided that Iclusig's benefits are greater than its risks and it can be authorised for use in the EU. Iclusig was shown to be an effective treatment for those patients with CML or Ph+ ALL who have limited treatment options. Regarding its safety, the side effects with Iclusig were largely similar to those of other tyrosine kinase inhibitors and mostly manageable with dose reduction or dose delay. The risk of problems (including heart attacks and strokes) resulting from blood clots or blockages in arteries or veins could be reduced by checking for and treating contributory conditions such as high blood pressure and raised cholesterol both before and during treatment.

What measures are being taken to ensure the safe and effective use of Iclusig?

The company that markets Iclusig will provide educational material for all doctors who are expected to prescribe this medicine highlighting important risks for which monitoring and dose adjustments are recommended. Also, the company will conduct a study in order to determine the best starting dose of Iclusig and to assess the safety and effectiveness of Iclusig following dose reduction in patients with chronic phase CML who achieve major cytogenetic response.

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Iclusig have also been included in the summary of product characteristics and the package leaflet.

As for all medicines, data on the use of Iclusig are continuously monitored. Side effects reported with Iclusig are carefully evaluated and any necessary action taken to protect patients.

Other information about Iclusig

Iclusig received a marketing authorisation valid throughout the EU on 1 July 2013.

Further information on Iclusig can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

This overview was last updated in 07-2018.