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Withdrawal of application to change the marketing authorisation for Iclusig (ponatinib)

On 11 August 2023 Incyte Biosciences Distribution B.V. withdrew its application for the use of Iclusig in the treatment of adults newly diagnosed with Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL).

What is Iclusig and what is it used for?

Iclusig is a cancer medicine approved for the treatment of 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 approved for the treatment of 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 approved for the use in patients who have a genetic mutation known as T315I, which makes them resistant to treatment with imatinib, dasatinib or nilotinib.

Iclusig has been authorised in the EU since July 2013. It contains the active substance ponatinib and is available as tablets.

Further information on Iclusig's current uses can be found on the Agency's website: ema.europa.eu/en/medicines/human/EPAR/iclusig

What change had the company applied for?

The company applied to extend the approved use of Iclusig to treat adult patients newly diagnosed with Ph+ ALL, either in combination with chemotherapy or together with corticosteroids in patients who cannot receive chemotherapy and a stem cell transplant.

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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 in 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 did the company present to support its application?

The company presented the results of two studies involving a total of 131 patients newly diagnosed with Ph+ ALL.

One study involving 87 patients looked at the effect of Iclusig in combination with chemotherapy; Iclusig was not compared with any other medicine. The study looked at how long patients lived without the disease becoming resistant to treatment or relapsing (coming back) or until death occurred.

The second study involved 44 patients and looked at the effect of Iclusig when used with corticosteroids in patients who were not fit enough to receive chemotherapy and a stem cell transplant. In this study, Iclusig also was not compared with any other medicine. The study looked at the proportion of patients who had a response after 24 weeks of treatment.

How far into the evaluation was the application when it was withdrawn?

The application was withdrawn after the European Medicines Agency had evaluated the information from the company and had prepared questions for the company. After the Agency had assessed the company's responses to the questions, there were still some unresolved issues and the company was asked to respond to additional questions.

What did the Agency recommend at that time?

Based on the review of the information and the company's response to the Agency's questions, at the time of the withdrawal, the Agency's provisional opinion was that Iclusig could not have been authorised for the proposed use based on the data submitted.

In particular, the Agency considered that although Iclusig was shown to have activity against the cancer in the study investigating its use in combination with chemotherapy, it was not possible to quantify the medicine's benefits and risks. The lack of a comparator, together with the small size of the study, meant it was not possible to establish the relevance of the study results for the target patient population. In addition, the CHMP considered that more information was needed to establish the benefits of Iclusig when used with either high-intensity or reduced-intensity chemotherapy.

The Agency also had concerns about the second study investigating the use of Iclusig with corticosteroids in patients who could not receive chemotherapy and a stem cell transplant, which was of even smaller size and also lacked a comparator.

Furthermore, the numerous changes made to the study protocols and some incorrect information included in the dossier submitted to EMA required requesting an inspection to verify adherence of the studies to good clinical practice guidelines.

Therefore, at the time of the withdrawal, the Agency's opinion was that the company had not fully addressed its concerns and the benefit and risks of Iclusig in the treatment of patients newly diagnosed with Ph+ ALL, in combination with chemotherapy or corticosteroids, could not be established.

What were the reasons given by the company for withdrawing the application?

In its letter notifying the Agency of the withdrawal of application, the company stated that it was not in a position to satisfactorily address the second round of questions raised by EMA's human medicines committee, the CHMP.

Does this withdrawal affect patients in clinical trials?

The company informed the Agency that there are currently no ongoing clinical trials that are affected by this withdrawal.

What is happening with Iclusig for the treatment of other types of leukaemia?

There are no consequences on the use of Iclusig in its authorised uses.