European Medicines Agency

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QUESTIONS AND ANSWERS ON THE WITHDRAWAL OF THE APPLICATION FOR A CHANGE TO THE MARKETING AUTHORISATION
for
GLIVEC

International non-proprietary name (INN): ***imatinib***

On 18 October 2006, Novartis Europharm Limited officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a new indication for Glivec, in the treatment of systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown.

What is Glivec?
Glivec is an anticancer medicine that contains the active substance imatinib. It is available as capsules (yellow: 50 mg; orange: 100 mg) and dark yellow/orange tablets (round: 100 mg; oval: 400 mg).

Glivec is used to treat specific types of the following diseases:

- Chronic myeloid leukaemia (CML), a cancer of the white blood cells in which granulocytes (a type of white blood cell) start growing out of control.
- Acute lymphoblastic leukaemia (ALL), a type of cancer in which lymphocytes (another type of white blood cell) multiply too quickly.
- Myelodysplastic or myeloproliferative diseases (MD/MPD), a group of diseases in which the body produces large numbers of one or more types of abnormal blood cells.
- Advanced hypereosinophilic syndrome (HES) or chronic eosinophilic leukaemia (CEL), diseases in which eosinophils (another type of white blood cell) start growing out of control.
- Gastrointestinal stromal tumours (GIST), a type of cancer (sarcoma) of the stomach and bowel, when there is uncontrolled growth of cells in the supporting tissues of these organs.
- Dermatofibrosarcoma protuberans (DFSP), a type of cancer (sarcoma) in which cells in the tissue beneath the skin divide uncontrollably.

For more information on how Glivec is used to treat these diseases, see the European Public Assessment Report (EPAR) here.

What was Glivec expected to be used for?
Glivec was to be used for the treatment of aggressive systemic mastocytosis in adults. Systemic mastocytosis is a disease in which mast cells accumulate excessively in the bone marrow and in other organs, such as the liver, spleen and intestine. This disease can lead to organ failure and has a poor long-term outcome when it is aggressive.

Mast cells originate in the bone marrow and normally play a key role in the inflammation process and the immune response. Glivec was expected to reduce the abnormal accumulation of mast cells in patients with systemic mastocytosis. Since patients who have a mutation called D816V in the receptor protein c-Kit were expected to be insensitive to Glivec, the medicine was only to be used in patients who did not have this genetic mutation, or whose mutation status was unknown.

Because the number of patients with systemic mastocytosis is low, the disease is rare, and Glivec was designated an orphan medicine (a medicine used in rare diseases) on 26 August 2005.

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How was Glivec expected to work in systematic Mastocytosis?
The active substance in Glivec, imatinib, is a protein-tyrosine kinase inhibitor. This means that it blocks some specific enzymes known as tyrosine kinases. These enzymes can be found in some receptors on the surface of cells, including the c-Kit receptor that is involved in stimulating mast cells to divide uncontrollably in patients with systemic mastocytosis. By blocking these receptors, Glivec is expected to help control cell division.

What documentation did the company present to support its application to the CHMP?
The company presented data from one study including 5 patients with systemic mastocytosis, as well as information on a further 30 patients from other studies, who were all treated with Glivec. Only 3 of these patients were known to have the D816V mutation in c-Kit. The main measure of effectiveness was whether mast cell counts in the blood returned to normal levels after treatment with Glivec. Glivec's effects were not compared to those of any other medicine.

How far into the evaluation was the application when it was withdrawn?
The application was at day 90 when the company withdrew. After the CHMP had assessed the responses from the company to a list of questions, there were still some unresolved issues outstanding.

What was the recommendation of the CHMP at that time?
Based on the review of the data and the company's response to the CHMP list of questions at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Glivec could not have been approved for the treatment of systemic mastocytosis.

What were the main concerns of the CHMP?
The main concerns of the CHMP were the low number of patients with systemic mastocytosis included in the documentation presented by the company, and the low response rate to Glivec treatment in these patients. Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of Glivec had not been sufficiently demonstrated and any benefits did not outweigh the identified risks.

What were the reasons given by the company to withdraw the application?
The letter from the company notifying the EMEA of the withdrawal of the application is available here.

What are the consequences of the withdrawal for patients undergoing clinical trials or compassionate use programmes with Glivec?
The company informed the CHMP that there are no consequences for patients currently included in clinical trials or compassionate use programmes with Glivec. If you are in a clinical trial or compassionate use programme involving Glivec and need more information about your treatment, please contact the doctor who is giving such treatment to you.

What is happening with Glivec used for the treatment of other diseases?
There are no consequences for the use of Glivec in the indications for which it is already authorised, where the known benefit and risk remain unchanged.