European Medicines Agency

London, 26 April 2007
Doc. Ref. EMEA/111199/2007

QUESTIONS AND ANSWERS ON THE WITHDRAWAL OF THE MARKETING AUTHORISATION APPLICATION
for
IPLEX

International non-proprietary name (INN): ***mecasermin rinfabate***

On 26 March 2007, Insmed Europe Ltd officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for IPLEX, for the treatment of patients with primary growth hormone insensitivity and of patients with growth hormone gene deletion who have developed neutralising antibodies to growth hormone.

What is IPLEX?
IPLEX is a solution for injection containing 60 mg/ml mecasermin rinfabate as the active substance.

What was IPLEX expected to be used for?
IPLEX was to be used in children with short stature whose bodies have problems handling growth hormone because:

- they have primary insensitivity to the hormone, so that injected growth hormone has no effect. 'Primary' means that there is no known reason for the insensitivity.
- they are not able to make growth hormone and have received growth hormone in the past, but have developed neutralising antibodies, special proteins than can prevent injected growth hormone from having an effect.

Because the number of patients with these diseases is low, they are considered 'rare', and mecasermin rinfabate was designated an 'orphan medicine' (a medicine used in rare diseases) on 20 June 2006.

How is IPLEX expected to work?
The active substance in IPLEX, mecasermin rinfabate, is a binary protein made up of two proteins that are normally produced by the body: insulin-like growth factor I (IGF-I) and insulin-like growth factor binding protein 3 (IGFBP-3). Mecasermin rinfabate is produced by a method known as 'recombinant DNA technology': it is made by bacteria that have received a gene (DNA), which makes them able to produce it.

In the body, natural growth hormone promotes growth in children by stimulating the body to produce IGF-I. IGF-I then stimulates the bones to grow. IPLEX provides IGF-I directly, as part of the binary protein, and this allows bone growth while bypassing the need for growth hormone itself. In IPLEX, IGF-I is bound to IGFBP-3 because this mimics the way in which IGF-1 is carried in the body. This may allow IGF-I to circulate in the body at higher levels and for longer periods than unbound IGF-I.

What documentation did the company present to support its application to the CHMP?
The effects of IPLEX were first tested in experimental models before being studied in humans. Its effectiveness has been studied in one clinical trial, which is still ongoing. In the study, 27 children (aged 3 to 15 years) have been receiving IPLEX for up to one year. The main measure of effectiveness was based on the speed of growth during the study, compared to that in the year before the study began.

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How far into the evaluation was the application when it was withdrawn?
The application was at day 120 when the company withdrew. The CHMP had formulated a list of questions to be answered by the company, but the company had not yet responded to them.

The CHMP normally takes up to 210 days to evaluate a new application. Based on the review of the initial documentation, the CHMP prepares a list of questions at day 120, which is sent to the company. Once the company has supplied responses to the questions, the CHMP reviews them and may, before giving an opinion, ask any remaining questions at day 180. Following the CHMP's opinion, it usually takes around 2 months for the European Commission to grant a licence.

What was the recommendation of the CHMP at that time?
Based on the review of the data at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that IPLEX could not have been approved for the treatment of patients with primary growth hormone insensitivity and of patients with growth hormone gene deletion who have developed neutralising antibodies to growth hormone.

What were the main concerns of the CHMP?
The CHMP had major concerns regarding the way the medicine is manufactured, and they were unsure that the medicine that would have been marketed would have been comparable to the one used in the clinical trial. They also had major concerns regarding the way in which the medicine's effectiveness had been assessed, especially regarding the type of patients that have been included in the clinical trial. Patients had also not been treated for long enough to show that the medicine's effect continues when used for longer than one year.

Therefore, at the time of the withdrawal, the CHMP's view was that the benefit of IPLEX had not been sufficiently demonstrated and 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 / compassionate use programmes with IPLEX?
The company informed the CHMP that the withdrawal will have no impact on the ongoing clinical study of the safety and efficacy of IPLEX in the treatment of Growth Hormone Insensitivity Syndrome.

If you are in a clinical trial or compassionate use programme and need more information about your treatment, contact the doctor who is giving it to you.