European Medicines Agency

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

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

On 24 January 2008, Ipsen Ltd officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a new indication for NutropinAq, for the long-term treatment of children with severe idiopathic short stature.

What is NutropinAq?
NutropinAq is a solution for injection in a cartridge, which contains the active substance somatropin. It is given by injection under the skin, using the injection pen specially designed for the cartridge. NutropinAq is already used to treat children in the following situations:

- when they fail to grow because of a lack of growth hormone;
- if they are short because of Turner syndrome (a rare genetic disorder affecting girls). This must be confirmed by chromosome analysis (DNA testing);
- before puberty, when they fail to grow because of longstanding kidney disease (chronic renal insufficiency). NutropinAq is used until the child receives a kidney transplant.

NutropinAq is also used to treat adults with growth hormone deficiency, as replacement therapy. The deficiency can have started in adulthood or childhood, and needs to be confirmed by testing before treatment begins.

What was NutropinAq expected to be used for?
In the new indication, NutropinAq was expected to be used to treat children with 'severe idiopathic short stature' (severe growth impairment with no identifiable cause). It was to be used as long-term treatment in children who were predicted to be short, in comparison with their parents' height, once they had reached adulthood. It was to be used if all possible causes of the child's short height had been excluded, such as low growth hormone levels.

How does NutropinAq work?
Growth hormone is a substance secreted by a gland located at the base of the brain called the pituitary gland. It promotes growth during childhood and adolescence, and also acts on the way the body handles proteins, fat and carbohydrates. The active ingredient in NutropinAq, somatropin, is identical to the human growth hormone. It is produced by a method known as 'recombinant DNA technology': the hormone is made by a bacterium that has received a gene (DNA) that makes it able to produce human growth hormone.

What documentation did the company present to support its application to the CHMP?
The company presented the results of one main study looking at the effectiveness of NutropinAq in 118 children with short stature who did not have growth hormone deficiency or any other identifiable condition that could cause their growth impairment. For the first year, the study compared the effectiveness of NutropinAq given three times a week with that of no treatment. After this, the design of the study was changed so that the patients received NutropinAq given either three times a week or once a day. The main measure of effectiveness was the increase in adult height. This was based on the

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difference between the height that each child was predicted to reach based on their height and bone maturity before they started to receive NutropinAq, and their actual height when they had reached adulthood. In total, the children received the medicine for up to ten years.

How far into the evaluation was the application when it was withdrawn?
The evaluation had finished and the CHMP had given a negative opinion. The company had requested a re-examination of the negative opinion, but this had not yet finished when the company withdrew.

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's list of questions, at the time of the withdrawal, the CHMP had given a negative opinion and did not recommend the approval of NutropinAq for the long-term treatment of children with severe idiopathic short stature.

What were the major concerns of the CHMP?
The CHMP was concerned that only a modest benefit of NutropinAq in severe idiopathic short stature had been demonstrated, with an average gain in final adult height of around 6 to 7 cm in the main study. In addition, a benefit of the medicine in improving the child's psychological or social wellbeing had not been shown. The Committee raised a concern that the use of NutropinAq for the long periods necessary to treat severe idiopathic short stature might increase the risk of the development of tumours or diabetes later in life.
Therefore, at the time of the withdrawal, the CHMP's view was that that the benefits of NutropinAq in the long-term treatment of children with severe idiopathic short stature did not outweigh its possible risks.

What were the reasons given by the company for withdrawing 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 in clinical trials or compassionate use programmes using NutropinAq?
The company informed the CHMP that there are no ongoing clinical trials or compassionate use programmes in Europe with NutropinAq in this indication.

What is happening for NutropinAq for treatment of failure to grow due to growth hormone deficiency, Turner syndrome or chronic renal insufficiency?
There are no consequences on the use of NutropinAq in the authorised indications, for which the balance of benefits and risks remains unchanged.