European Medicines Agency

London, 20 September 2007
Doc. Ref. EMEA/423515/2007

**QUESTIONS AND ANSWERS ON RECOMMENDATION FOR THE REFUSAL OF A CHANGE TO THE MARKETING AUTHORISATION**
**for**
**NUTROPINAQ**

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

On 20 September 2007, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of a change to the marketing authorisation for the medicinal product NutropinAq 10 mg/2 ml (30 IU) solution for injection. The change concerned an extension of indication to add the long-term treatment of children with severe idiopathic short stature. The company that applied for authorisation is IPSEN Ltd. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

**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:

- who fail to grow because of a lack of growth hormone,
- who are short because of Turner syndrome (a rare genetic disorder affecting girls), confirmed by chromosome analysis (DNA testing),
- before puberty, when they fail to grow because of longstanding kidney disease (chronic renal insufficiency) up to the time when they receive 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.

**What was NutropinAq expected to be used for?**
NutropinAq was also 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, if all possible causes of their short height had been excluded.

**How does NutropinAq work?**
Growth hormone is a substance secreted by a gland located at the base of the brain (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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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.

**What were the major concerns that led the CHMP to recommend the refusal of the change to the marketing authorisation?**

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 short stature might lead to problems later in life, including the potential development of tumours or diabetes.

Therefore, at that point in time, the CHMP was of the opinion that the benefits of NutropinAq in the long-term treatment of children with severe idiopathic short stature did not outweigh its possible risks. Hence, the CHMP recommended that the change to the marketing authorisation be refused.

**What are the consequences of the refusal for patients in clinical trials or compassionate use programmes using NutropinAq?**

The company informed the CHMP that there are no ongoing clinical trials 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.