European Medicines Agency

London, 2 June 2006
Doc.Ref. EMEA/191862/2006

QUESTIONS AND ANSWERS ON ATRYN

International Non-proprietary Name (INN): ***antithrombin alfa***

On 1 June 2006, the Committee for Medicinal Products for Human Use (CHMP) adopted a final positive opinion, recommending the granting of a marketing authorisation for ATryn 1750 IU powder for solution for infusion, to be used in surgical patients with congenital antithrombin deficiency for the prophylaxis of deep vein thrombosis and thromboembolism in clinical risk situations, i.e., during the peri-surgical period. The company who applied is Genzyme Europe B.V.

On 22 February 2006, the CHMP had adopted a negative opinion for ATryn. At the request of the applicant, the Committee started a re-examination of its opinion. Following the re-examination and the advice of an expert meeting, the CHMP adopted a final positive opinion.

What is ATryn?
ATryn is a white powder to be made up into a solution for infusion (drip into a vein). ATryn contains the active substance antithrombin alfa.

What is ATryn to be used for?
ATryn is to be used in patients who have an inherited reduction of the protein antithrombin who undergo surgery, to prevent problems due to the formation of clots in the vessels of the legs (deep vein thrombosis, DVT) or in other vessels of the body (thromboembolism).

How is ATryn expected to work?
ATryn is an anti-clotting agent. The active substance in ATryn, antithrombin alfa, is a copy of the natural blood protein that is produced by recombinant DNA technology. It is extracted from the milk of goats who have a gene (DNA) inserted, which make them able to produce the human protein in their milk.
In the body, antithrombin blocks thrombin, one of the substances involved in blood coagulation (clotting). Thrombin plays a central role in the process of blood clotting. Patients who have a congenital antithrombin deficiency have blood levels of antithrombin that are lower than normal, which may result in a reduced anti-clotting capacity of the blood. This increases the risk of the formation of clots during high-risk situations. ATryn would be expected to correct the antithrombin deficiency and to give temporary control of the clotting disorder.

What documentation has been presented by the Company to support the application to the CHMP?
The effects of ATryn were first tested in experimental models before being studied in humans. ATryn was studied in 14 patients with congenital antithrombin deficiency at risk of a thromboembolic event (surgery [5 patients] or childbirth [9 patients]). The Company also presented the results of the treatment in 5 patients who received the medicine during surgery in a 'compassionate use programme' (when a Company makes available to doctors a medicine before it is fully licensed to treat a specific patient who needs it).

What were the major concerns, which led to the refusal of the marketing authorisation by the CHMP?
The disease is rare (it is estimated that about one person in 3, 000 to 5,000 have a congenital antithrombin deficiency), and this explains why few patients have been treated during the studies.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 71 29
E-mail: mail@emea.eu.int http://www.emea.eu.int

However, for the proposed indication, only 5 surgical cases were considered. The CHMP considered this number to be too small, and not in line with the EMEA's recommendations (scientific advice) to the Company of 12 patients. The results in patients treated in the compassionate use programme and at childbirth could not be used to support the proposed use in patients undergoing surgery. Also the process for the production of the medicine used in the studies is not exactly the same as that which would have been marketed (addition of a filtration step).
ATryn is a protein-based medicine, and, like all protein-based medicines, it is possible that patients develop antibodies (proteins produced in response to ATryn). The CHMP considered that the Company did not carry out enough studies looking for the development of antibodies.
At that point in time, the CHMP was of the opinion that it was not yet demonstrated that ATryn's benefits were greater than its risks. Hence, the CHMP recommended that ATryn be refused marketing authorisation.

What happened during the re-examination?
During the re-examination, the CHMP looked at information and analyses supplied by the company, and took expert advice. A meeting was held, bringing together leading European experts specialising in the study of blood and blood clotting (haematologists and haemostasis specialists).

What were the conclusions of the CHMP following the re-examination?
The Committee accepted that the data on effectiveness could be based on all the patients who received ATryn in the study, pregnant and non-pregnant, as they present the same high risk of deep-vein thrombosis and thromboembolism.
They concluded that the slight difference in the manufacture between the product used in the studies and the product to be marketed does not preclude clinical use of ATryn. They also concluded that this can be closely monitored by the company once the medicine is on the market, alongside the risk of patients developing antibodies against ATryn.
They also asked the company to look in greater detail into the use of the medicine in pregnant women, so that a suitable dosing schedule can be developed.

Overall, the CHMP concluded that the benefits of ATryn outweigh its risks, and recommended that it be given a marketing authorisation.

