European Medicines Agency

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

International Non-proprietary Name (INN): **eptacog alfa** (activated)

On 3 April 2006, Novo Nordisk A/S has officially notified the Committee for Medicinal Products for Human Use (CHMP) that they wish to withdraw their application for a new indication for NovoSeven, in the treatment of acute intracerebral haemorrhage (ICH) in adults for limiting haemorrhage growth and improving clinical outcome.

What is NovoSeven?
NovoSeven is a powder and solvent for injection that contains the active substance eptacog alfa (activated human recombinant coagulation factor VII). NovoSeven has been approved in the European Union since 1996.
NovoSeven is currently used for the treatment and prevention of bleeding connected with surgery in patients with haemophilia who have developed 'inhibitors' (antibodies) to factor VIII or IX. It is also used in patients with acquired haemophilia, in patients with congenital factor VII deficiency, and in patients with Glanzmann's thrombasthenia (a rare bleeding disorder) who cannot be treated by a transfusion of platelets.

What was NovoSeven expected to be used for this indication?
NovoSeven was to be used to treat adult patients with intracerebral haemorrhage (bleeding inside the brain). NovoSeven was expected to limit the bleeding, and so reduce the consequences of the intracerebral haemorrhage.

How is NovoSeven expected to work in this indication?
NovoSeven contains eptacog alfa (activated), which is a blood coagulation factor protein. In the body, eptacog alfa acts like one of the substances involved in blood coagulation (clotting), Factor VII. It increases the production of thrombin, another coagulation factor, on the surface of the particles that make up blood clots (the platelets), and this helps producing a stable 'plug' at the site of bleeding. In intracerebral haemorrhage, NovoSeven is expected to slow down the bleeding and the spread of the haemorrhage, thus improving the outcome for the patient.

What documentation has been presented by the Company to support the application to the CHMP?
The Company submitted the results of three studies, involving a total of 486 patients. The main study was carried out in 399 patients (aged 66 on average), and compared the effectiveness of three dosages of NovoSeven to that of a placebo (dummy treatment). The effectiveness of NovoSeven was assessed by looking at its effect on the volume of the haemorrhage inside the brain, measured using a scan (percentage change in the volume after 24 hours of treatment with NovoSeven or placebo).

How far into the evaluation was the application when it was withdrawn?
The application was at Day 157 when the Company withdrew it.
The CHMP normally takes up to 90 days (with the possibility to extend it to another 90 days) to adopt an opinion after it has received an application for a change to a marketing authorisation. Following CHMP opinion, it usually takes around 6 weeks to the European Commission to update the licence.

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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 concerns and was of the provisional opinion that NovoSeven could not be approved for the treatment of acute intracerebral haemorrhage.

What were the main concerns of the CHMP?
The main concern of the CHMP was that the data were too limited to evaluate the benefit and the potential risks of NovoSeven in intracerebral haemorrhage. The data submitted show that NovoSeven has an effect on the volume of the haemorrhage, but it is not clear how this effect translates into a better outcome for the patient, especially at the dose selected for this indication. In addition, there were concerns on the thromboembolic side effects (excessive clotting) for this indication, but the number of patients treated was too small for the CHMP to be able to balance this risk against the potential benefit.
Therefore, at the time of the withdrawal, the CHMP's view was that the benefit 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 NovSeven?
The Company has informed the CHMP that the current clinical trial of NovoSeven in intracerebral haemorrhage will continue.

What is happening for NovoSeven used in other conditions?
There are no consequences for NovoSeven's use in the indications for which it is already authorised, where the known benefit and risk remain unchanged.