European Medicines Agency

London, 26 June 2008
Doc. Ref. EMEA/309003/2008

QUESTIONS AND ANSWERS ON THE WITHDRAWAL OF THE MARKETING APPLICATION
for
SPANIDIN

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

On 17 June 2008, Euro Nippon Kayaku GmbH officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Spanidin, for the induction of remission in adult patients suffering from clinically refractory Wegener's granulomatosis. Spanidin was designated as an orphan medicine on 29 March 2001.

What is Spanidin?
Spanidin is a powder that is made up into a solution for injection. It contains the active substance gusperimus.

What was Spanidin expected to be used for?
Spanidin was expected to be used to control the symptoms of Wegener's granulomatosis in patients who were not responding to other treatments. Wegener's granulomatosis is a rare, auto-immune disease (a disease which is caused by the body's own defence system attacking normal tissue). In this disease, the immune system attacks neutrophils (a type of white blood cell), causing inflammation of small and medium-sized blood vessels and the formation of granulomas (clumps of white blood cells). This causes a range of symptoms that mainly affect the airways, lungs and kidneys. If left untreated, it can result in organ damage or death.

How is Spanidin expected to work?
The active substance in Spanidin, gusperimus, is an immunosuppressive medicine, which means that it reduces the activity of the immune system (the body's natural defences). It is expected to work in Wegener's granulomatosis by disrupting the growth and activity of white blood cells called lymphocytes, which are involved in the inflammation process. By reducing the number of lymphocytes and interfering with the way they work, Spanidin is expected to reduce the inflammation in the blood vessels that causes the symptoms of the disease.

What documentation did the company present to support its application to the CHMP?
The effects of Spanidin were first tested in experimental models before being studied in humans.
Spanidin has been studied in one main study involving 45 patients with Wegener's granulomatosis who were 'refractory' (not responding) to standard treatment. They received Spanidin for six 'cycles', with each cycle consisting of three weeks 'on' treatment followed by one week 'off'. The main measure of effectiveness was the number of patients who stayed in remission (with no signs of active disease) for at least two months during treatment. Spanidin was not compared with any other treatment in this study, but the patients could take corticosteroids (a group of immunosuppressive medicines) in addition to Spanidin.

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

How far into the evaluation was the application when it was withdrawn?
The application was at day 194 when the company withdrew. After the CHMP had assessed the responses from the company to a list of questions, there were still some unresolved issues outstanding.
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 two months for the European Commission to grant a license.

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 some concerns and was of the provisional opinion that Spanidin could not have been approved for the induction of remission in adult patients suffering from clinically refractory Wegener's granulomatosis.

What were the main concerns of the CHMP at that time?
The CHMP was concerned that the main study was not sufficient to demonstrate the effectiveness of Spanidin, because of the way it was designed and carried out. In particular, the study included some patients who could have taken other treatments for their disease, so could not be considered to be 'refractory'. In addition, Spanidin was not compared with any other treatment, so it was not possible to distinguish the effects of Spanidin and of steroids. The CHMP was also concerned that the study included some patients for whom induction treatment was not necessary, and others who did not have the symptoms of 'classic' Wegener's granulomatosis affecting the airways, lungs or kidneys.
The CHMP noted that an additional study would be necessary to overcome these concerns. This study would need to involve patients who are truly refractory to other treatments, or it would need to compare Spanidin directly with cyclophosphamide (the standard treatment for inducing remission in Wegener's granulomatosis).
Therefore, at the time of the withdrawal, the CHMP was of the opinion that a benefit of Spanidin had not been sufficiently demonstrated and any benefits 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 or compassionate use programmes with Spanidin?
The company informed the CHMP that there are no consequences for patients currently included in clinical trials or compassionate use programmes with Spanidin. 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.