European Medicines Agency

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Questions and answers on the withdrawal of the marketing application for Advexin

International non-proprietary name (INN): ***contusugene ladenovec***

On 17 December 2008, Gendux Molecular Limited officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Advexin for the treatment of Li-Fraumeni cancer. Advexin was designated as an orphan medicinal product on 23 October 2006.

What is Advexin?
Advexin is a suspension for injection that contains contusugene ladenovec, a genetically modified virus which carries the p53 gene.

What was Advexin expected to be used for?
Advexin was expected to be used to treat Li-Fraumeni cancer in patients from the age of 18 years. Li-Fraumeni cancer is a type of cancer that occurs in patients with Li-Fraumeni syndrome, a condition where a gene called p53 is defective because of a mutation. People who have this mutation are more likely to develop cancer. Li-Fraumeni cancer can occur in many areas of the body but usually affects the breast, brain, bone or soft tissue (tissue that connects, surrounds and supports other structures in the body).

How is Advexin expected to work?
The active substance in Advexin, contusugene ladenovec, is a 'viral vector'. This is a type of virus that has been altered genetically so that it can carry a gene into the cells of the body. The virus in Advexin is an 'adenovirus' that has been engineered so that it cannot make copies of itself and therefore does not cause infections in humans. The gene carried by the virus in Advexin is the normal (non-defective) p53 gene.
Advexin was expected to be injected directly into the tumours, thus allowing the cancer cells to produce normal p53 protein again. The p53 protein, which is produced from the non-defective p53 gene present in the human body, normally contributes to the repair of damaged DNA and causes cell death when the DNA cannot be repaired. Because cancer cells contain damaged DNA, the p53 protein either helps to repair the DNA or causes the cells to die.
In Li-Fraumeni cancer, where the p53 gene is defective, the p53 protein does not work properly and the cancer cells can continue to grow and divide. Advexin was expected to cure or slow down the disease by restoring the normal protective function of the cells.

What documentation did the company present to support its application to the CHMP?
The effects of Advexin were first tested in experimental models before being studied in humans.
The company presented information from a study on one patient with Li-Fraumeni cancer in the lower abdomen, the bones and the brain. The patient received 12 Advexin injections into some of the tumours over a five-month period. The effectiveness of the medicine was assessed by using scans to look at how the tumours responded to treatment. The company also presented the results of a number of small studies looking at the effects of a range of doses of Advexin on different types of cancer.

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How far into the evaluation was the application when it was withdrawn?
The application was at day 179 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 licence.

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 Advexin could not have been approved for the treatment of Li-Fraumeni cancer.

What were the main concerns of the CHMP?
The CHMP was concerned that there was not enough evidence to show that the injection of Advexin into Li-Fraumeni tumours led to benefits for patients. The Committee also had concerns over what happens to the medicine in the body, how it should be given and how safe it is. In addition, the company had not supplied enough evidence to demonstrate that Advexin could be made in a reliable manner, or that it would not be harmful to the environment or to people in close contact with the patient.

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 Advexin?
The company did not inform the CHMP whether there were any consequences of the withdrawal for patients in clinical trials or compassionate use programmes with Advexin.