European Medicines Agency

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QUESTIONS AND ANSWERS ON WITHDRAWAL OF MARKETING APPLICATION
for
Orathecin

International Non-proprietary Name (INN): **Rubitecan**

On 19 January 2006, EuroGen Pharmaceuticals Ltd officially notified the Agency's Committee for Medicinal Products for Human Use (CHMP) of its decision to withdraw its application for marketing authorisation for the medicinal product orathecin (rubitecan). The indication applied for was the treatment of patients with advanced or metastatic pancretic cancer.
Orathecin was designated as an orphan medicinal product on 10 June 2003.
Link to withdrawal EMEA press release.

What is Orathecin?
Orathecin is a capsule to be taken orally. Orathecin contains 0.5 or 1.25 of the active substance rubitecan.

What was Orathecin expected to be used for?
Orathecin was to be used to treat patients with advanced cancer of the pancreas, who cannot be operated or who have metastasis (cancer cells that spread from the original site to other parts of the body), and who do not respond to the other anticancer drugs used for the treatment of their disease.

How is Orathecin expected to work?
Orathecin belongs to a group of alkaloids called camptothecins. Alkaloids are substances that are naturally found in plants. Certain camptothecins are used in medicine as anti-cancer agents. When cells are growing, as in the case for cancer cells, the genetic material (DNA) inside the cell may become twisted. Cells have several proteins, which help to remove any twists in the DNA. This avoids that the DNA breaks, which would damage the cells. Camptothecins are able to block one of the proteins that can remove twists in the DNA. This protein is called topoisomerase I. By blocking this protein, Orathecin is expected to damage the cancer cells.

What documentation has been presented by the Company to support the application to the CHMP?
The effects of orathecin were first tested in experimental models before being studied in humans.
Orathecin has been investigated in two main clinical studies. The studies included approximately 800 patients with advanced or metastatic cancer of the pancreas. The studies looked at how long the patients survived after receiving orathecin, compared to those receiving the standard medicines used to treat pancreatic cancer, including 5-fluorouracil (5-FU) or gemcitabine. Orathecin was given to the patients until their cancer progressed or they could not tolerate the treatment anymore.

How far into the evaluation was the application when it was withdrawn?
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 give an opinion, ask any remaining questions (at day 180) to the Company. Following CHMP opinion, it usually takes around 2 months to the European Commission to give a licence.

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The application was at Day 172 days, when the Company withdrew it.
The CHMP was assessing the responses given by the Company to a list of questions.

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 the withdrawal, the CHMP had concerns and was of the provisional opinion that Orathecin could not be approved for treatment of patients with advanced or metastatic pancretic cancer.

What were the main concerns of the CHMP?
In the studies presented by the Company, it could not be shown that Orathecin extends the life of patients nor improves their quality of life. Moreover, patients treated with Orathecin experienced many side effects, including serious ones. 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?
Link to the withdrawal letter.

What are the consequences of the withdrawal for patients undergoing clinical trials / compassionate use programmes with Orathecin?
The Company informed the Agency that at the time of the withdrawal, all clinical trials in the European Union are closed to enrolment and there is no ongoing compassionate use programmes.
However, if you are in a clinical trial or compassionate use programme and need more information about your treatment, contact the doctor who is giving you the treatment.
No information has been given by the Company on the future development of the product.