European Medicines Agency

London, 30 May 2008
Doc. Ref. EMEA/266786/2008

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

International non-proprietary name (INN): ***beclomethasone dipropionate***

On 22 May 2008, DOR BIOPHARMA UK Ltd officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for orBec, for the treatment of gastrointestinal graft-versus-host disease. orBec was designated as an orphan medicinal product on 13 March 2002.

What is orBec?
orBec is a medicine containing the active substance beclomethasone dipropionate. It was to be available as two separate tablets, to be taken together: one immediate-release tablet (immediate-release means that the tablet has been made to allow the active substance to be released immediately) and one gastro-resistant tablet (gastro-resistant means that the tablet's content passes through the stomach without being broken down until it reaches the intestine).

What was orBec expected to be used for?
orBec was expected to be used for the treatment of gastrointestinal graft-versus-host disease. Graft-versus-host disease can occur in patients following tissue or organ transplantation, when the cells in the transplanted tissue or organ recognise the patient as 'foreign' and attack the body. Patients with gastrointestinal graft-versus-host disease have damage to the stomach and the intestine, which causes severe inflammation of these organs.

How is orBec expected to work?
The active substance of orBec, beclomethasone dipropionate, is a corticosteroid that has been used in inhaled, nasal and skin medicines since the 1970s. It works by dampening down the activity of the immune system (the body's natural defences) by attaching to receptors in various types of immune cell. In orBec, beclomethasone dipropionate was to be taken orally so that it could act within the stomach and intestine. It was expected to block receptors in the stomach and intestine, reducing locally the production of substances that are involved in recognising foreign cells and in the inflammation process. This was expected to lead to a reduction in damage to the stomach and intestine.

What documentation did the company present to support its application to the CHMP?
The applicant presented data on experimental models for beclomethasone dipropionate from the scientific literature.
The effectiveness of orBec was studied in one main study, in which orBec was compared with placebo (a dummy treatment) in 129 patients with gastrointestinal graft-versus-host disease. The main measure of effectiveness was how long it took for treatment to fail during the 50 days of treatment.

How far into the evaluation was the application when it was withdrawn?
The application was at day 180 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.

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.europa.eu http://www.emea.europa.eu

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 question at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that orBec could not have been approved for the treatment of gastrointestinal graft-versus-host disease.

What were the main concerns of the CHMP?
The CHMP was concerned that the single main study did not demonstrate orBec's effectiveness. orBec was not significantly better than placebo in increasing the time until the disease came back during the 50-day treatment period. The CHMP had also concerns that most of the patients who took part in the study came from one study centre, and therefore the results were not representative for the overall population. In addition, the Committee noted that there was a lack of data to demonstrate how the active substance in orBec works in the stomach and intestine, when used for treatment of gastrointestinal graft-versus-host disease.
Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of orBec 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 / compassionate use programmes with orBec?
The company informed the CHMP that there are no consequences for patients currently included in clinical trials or compassionate use programmes with orBec.
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.