European Medicines Agency

London, 21 August 2008
Doc. Ref. EMEA/402553/2008

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

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

On 23 July 2008, IDEA AG officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Diractin, for the treatment of the symptoms of inflammation and pain associated with osteoarthritis.

What is Diractin?
Diractin is a medicine that contains the active substance ketoprofen. It was to be available as a gel containing 22.9 mg of ketoprofen per gram of gel.

What was Diractin expected to be used for?
Diractin was expected to be used to treat the symptoms of inflammation and pain associated with osteoarthritis (a condition that causes swelling and pain in the joints).

How is Diractin expected to work?
The active substance in Diractin, ketoprofen, is a non-steroidal anti-inflammatory drug (NSAID). It is expected to work by blocking an enzyme called cyclo-oxygenase, which produces prostaglandins, substances that are involved in the inflammation process. By reducing the production of prostaglandins, Diractin is expected to reduce the inflammation and pain caused by osteoarthritis.
In Diractin gel, the ketoprofen is contained in special, small, fatty particles (called 'Transfersomes') that are expected to carry the ketoprofen through the skin and release it deep below the skin, where the inflammation in osteoarthritis occurs.

What documentation did the company present to support its application to the CHMP?
The effects of Diractin were first tested in experimental models before being studied in humans.
The effectiveness of Diractin was studied in one main study involving 866 patients with osteoarthritis of the knee. The study compared the effectiveness of three different doses of Diractin (25 mg, 50 mg and 100 mg twice a day) with that of placebo (a dummy treatment). The main measure of effectiveness was the change in the severity of pain after 12 weeks of treatment.

How far into the evaluation was the application when it was withdrawn?
The application was at day 181 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 Diractin

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

could not have been approved for the treatment of the symptoms of inflammation and pain associated with osteoarthritis.

What were the main concerns of the CHMP at that time?
The CHMP was concerned that the effectiveness of Diractin had not been sufficiently demonstrated in the single main study: compared with placebo, Diractin did not reduce pain levels to an extent that would be relevant for patients.
Therefore, at the time of the withdrawal, the CHMP was of the opinion that any benefits of Diractin 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 Diractin?
The company informed the CHMP that there are no consequences for patients currently included in clinical trials. No compassionate use programmes with Diractin are being conducted. If you are in a clinical trial and need more information about your treatment, contact the doctor who is giving it to you.