European Medicines Agency

London, 24 January 2008
Doc. Ref. EMEA/599866/2007

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

Active substance: ***Superparamagnetic iron oxide nanoparticles stabilised with dextran and sodium citrate***

On 13 December 2007, Guerbet officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Sinerem, intended for diagnostic use for the characterisation of lymph nodes visualised by MRI (magnetic resonance imaging) in the evaluation of primary tumour spread in pelvic cancers.

What is Sinerem?
Sinerem is a powder to be made up into a solution for infusion (drip into a vein). It contains extremely small particles of iron oxide (nanoparticles).

What was Sinerem expected to be used for?
Sinerem was to be used as a diagnostic agent in patients undergoing an MRI scan. It was to be used as a 'contrast agent' to help make internal body structure more visible on the scan.
Sinerem was to be used in patients with pelvic cancers. Pelvic cancers are cancers affecting organs in the lower abdomen, such as the prostate gland, the bladder, the womb or the cervix. Sinerem was to be used to see if the cancer was spreading, by helping visualise the patients' lymph nodes. These are part of the lymphatic system, a network of structures in the body involved in body defence (immune system). When a cancer is in the process of spreading, the cancer cells travel within the lymphatic system, and can be detected in the lymph nodes.

How is Sinerem expected to work?
The active substance in Sinerem is iron oxide in the form of nanoparticles in a clear, colloidal (jelly-like) solution of dextran, a type of sugar. The very small size of the particles allows them to be carried in the body, and to enter the lymphatic system. Once in the lymphatic system, the nanoparticles are taken up by a certain type of immune system cell called 'macrophages' within the lymph nodes. When exposed to the action of an external magnet as during an MRI scan, the particles become magnetic, and they can be seen more easily on the scan image. This should help making a difference between normal lymph nodes that contain macrophages and therefore magnetic particles, and lymph nodes that are invaded with cancer cells and contain fewer macrophages and fewer magnetic particles.

What documentation did the company present to support its application to the CHMP?
The effects of Sinerem were first tested in experimental models before being studied in humans.
There was one main study of the effectiveness of Sinerem, involving a total of 271 patients with pelvic cancers. The patients underwent two MRI scans to detect any cancer cells in their lymph nodes, one with Sinerem and one without. The patients then had an operation to remove the lymph nodes, and the results of the scans were compared by three different specialist readers to the results obtained when looking at the lymph nodes under a microscope to see if they contained any cancer cells.

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How far into the evaluation was the application when it was withdrawn?
The application was at day 175 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 2 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 Sinerem could not have been approved for diagnostic use for the characterisation of lymph nodes visualised by MRI (magnetic resonance imaging) in the evaluation of primary tumour spread in pelvic cancers.

What were the main concerns of the CHMP?
The main concern of the CHMP was that the effectiveness of Sinerem in enhancing the images seen in the MRI scan had not been shown. There were inconsistencies between readers regarding any improvement Sinerem may have brought in detecting cancer spread in lymph nodes during an MRI scan, and Sinerem could not therefore be considered as useful in the management of patients with such conditions.
Therefore, at the time of the withdrawal, the CHMP's view was that the benefits of Sinerem as a diagnostic agent in the characterisation of lymph nodes in patients with pelvic cancer 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 Sinerem?
The company informed the CHMP that compassionate use programmes using Sinerem are ongoing and will be reconsidered accordingly.
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.