European Medicines Agency

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QUESTIONS AND ANSWERS ON THE WITHDRAWAL OF THE APPLICATION FOR MARKETING AUTHORISATION
for
AQUILDA

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

On 23 May 2008, Sanofi-Aventis officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Aquilda, for the treatment of euvolaemic and hypervolaemic dilutional hyponatraemia.

What is Aquilda?
Aquilda is a medicine containing the active substance satavaptan. It was to be available as tablets containing 5 or 25 mg satavaptan.

What was Aquilda expected to be used for?
Aquilda was expected to be used in patients with hyponatraemia (abnormally low levels of sodium in the blood). Hyponatraemia can lead to symptoms such as headache, confusion and reduced levels of consciousness. Aquilda was to be used in two groups of patients:

- patients who are 'euvolaemic' (when the amount of water in the body is normal);
- patients who are 'hypervolaemic' (when the amount of water in the body is higher than normal). These patients normally have water retention, such as oedema (swelling) or ascites (a build-up of fluid in the abdomen).

How is Aquilda expected to work?
The active substance in Aquilda, satavaptan, is a vasopressin-2 receptor antagonist. This means that it blocks one type of receptors to which the hormone vasopressin normally attaches itself. Vasopressin, which is also known as anti-diuretic hormone (ADH), stimulates the kidneys to excrete salts including sodium, and to reduce the production of urine.
By blocking the vasopressin-2 receptor, Aquilda was expected to prevent vasopressin having its effect on water retention. This would have led to an increase in the levels of sodium in the body and to a reduction in the amount of water in the body by increasing urine production. This was expected to help reduce the symptoms of hyponatraemia.

What documentation did the company present to support its application to the CHMP?
The effects of Aquilda were first tested in experimental models before being studied in humans.
The company presented the results of two main studies involving a total of 112 euvolaemic patients with 'syndrome of inappropriate ADH secretion' (SIADH). It also presented the results of three studies in hypervolaemic patients:

- two studies in patients whose hyponatraemia was linked to cirrhosis (a type of liver disease); this included a total of 250 patients, with 73 of these participating in both studies
- one study was carried out in 118 patients whose hyponatraemia was linked to congestive heart failure (a type of heart disease).

All three studies compared the effectiveness of Aquilda with that of placebo (a dummy treatment). In all of the studies, the main measure of effectiveness was the effect of Aquilda on blood sodium levels. One of the studies in hypervolaemic patients also looked at changes in body weight.

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

How far into the evaluation was the application when it was withdrawn?
The application was at day 174 when the company withdrew. The CHMP was assessing the responses given by the company to a list of questions.
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 Aquilda could not have been approved for the treatment of euvolaemic and hypervolaemic dilutional hyponatraemia.

What were the main concerns of the CHMP?
The main concern of the CHMP was related to the effectiveness of the medicine. The CHMP noted that all of the studies looked at the effect of Aquilda on blood sodium levels, and did not look at its effect on measures that are more relevant to patients, such as the improvement in symptoms. The CHMP also noted that correcting sodium levels in patients with hypervolaemic hyponatraemia is of limited benefit unless it helps to treat the underlying liver or heart disease. The Committee also had a concern that there was not enough data to support the effectiveness and the safety of the medicine, since there were too few patients treated and they were not treated for long enough.
In addition, the Committee had concerns over the possible action of satavaptan on the heart, and on the potential activity of some of its metabolites (its breakdown products in the body).
Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of Aquilda 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 or compassionate use programmes with Aquilda?
The company informed the CHMP that there are no consequences for patients currently included in clinical trials with Aquilda.
If you are in a clinical trial and need more information about your treatment, contact the doctor who is giving it to you.