European Medicines Agency

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QUESTIONS AND ANSWERS ON THE WITHDRAWAL OF THE MARKETING AUTHORISATION APPLICATION
for
INSULIN HUMAN RAPID MARVEL
INSULIN HUMAN LONG MARVEL
INSULIN HUMAN 30/70 MIX MARVEL

International non-proprietary name (INN): ***human insulin***

On 20 December 2007, Marvel LifeSciences Ltd. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its applications for marketing authorisations for Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel, for the treatment of diabetes mellitus.

What are Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel?
These three medicines are all solutions for injection that contain 100 International Units of insulin per millilitre. They were to be available in vials or as cartridges to be used in injection pens.

What were these medicines expected to be used for?
The medicines were expected to be used to treat patients with diabetes who need insulin to maintain their blood levels within normal levels, and to control diabetes in newly diagnosed patients and pregnant women.

How are these medicines expected to work?
Diabetes is a disease in which the body does not produce enough insulin to control the level of blood sugar. Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel are replacement insulins, which contain an active substance that is identical to the insulin made by the pancreas. The active substance, insulin human, is produced by a method known as 'recombinant DNA technology': it is made by a bacterium that has received a gene (DNA), which makes it able to produce insulin.
These medicines would have contained insulin in two different forms: a soluble form, which acts quickly (within 30 minutes of injection), and an 'isophane' form, which is absorbed more slowly and gives a longer duration of action. The three 'Marvel insulins' were to contain one or both types of insulin:

- Insulin Human Rapid Marvel: soluble insulin,
- Insulin Human Long Marvel: isophane insulin,
- Insulin Human 30/70 Mix Marvel: 30% soluble insulin and 70% isophane insulin.

Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel were to be 'biosimilar' medicines. This means that they were to be similar to biological medicines that are already authorised in the European Union (EU) and contain the same active substances (also known as the 'reference medicines'). The reference medicines for these insulins were to be Humulin S, Humulin I and Humulin M3.
For more information on biosimilar medicines, see the question-and-answer document here.

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What documentation did the company present to support its application to the CHMP?
The company presented data from studies designed to show that the Marvel insulins were comparable with the reference medicines in experimental models and in humans. The company presented the results of studies carried out in 24 healthy volunteers looking at the effect of the Marvel insulins on blood sugar levels, compared with the Humulin insulins. It also presented the results of one main study in 526 patients with diabetes, who received either the Marvel insulins or the Humulin insulins for up to 12 months. The main measure of effectiveness was the effect of the medicines on the levels of a substance in the blood called glycosylated haemoglobin (HbA1c), which gives an indication of how well the blood glucose is controlled.

How far into the evaluation was the application when it was withdrawn?
The application was at day 120 when the company withdrew.
The CHMP had formulated a list of questions to be answered by the company, but the company had not yet responded to them.
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, the CHMP had some concerns and was of the provisional opinion that Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel could not have been approved for the treatment of diabetes mellitus.

What were the main concerns of the CHMP?
The main concerns of the CHMP were that the comparability of the Marvel insulins and the Humulin insulins had not been shown.
The studies in healthy volunteers did not show that the Marvel insulins had the same effect in lowering blood sugar levels as the Humulin insulins, and the main study showed a trend in favour of Humulin.
The CHMP was also concerned that the company had not supplied enough information on how the active substance or the finished products are made, and that the processes used to make them had not been validated.
Therefore, at the time of the withdrawal, the CHMP's view was that Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel could not be considered as biosimilar to the reference medicinal products Humulin S, Humulin I and Humulin M3.

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 Insulin Human Rapid Marvel, Insulin Human Long Marvel or Insulin Human 30/70 Mix Marvel?
The company informed the CHMP that there are no clinical trials or compassionate use programmes currently with the Marvel insulins.