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Questions and answers

Withdrawal of the marketing authorisation application for Combimarv (human insulin)

On 15 November 2012, Marvel LifeSciences Ltd officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Combimarv, intended for the treatment of patients with diabetes who require insulin to control their blood glucose.

What is Combimarv?

Combimarv is a medicine that contains the active substance human insulin. It was to be available as a suspension for injection.

Combimarv was developed as a biosimilar medicine. This means that it was intended to be similar to a biological medicine (the 'reference medicine') that is already authorised in the European Union (EU). The reference medicine for Combimarv in this application was Humulin M3.

For more information on biosimilar medicines, see the questions-and-answers document here.

What was Combimarv expected to be used for?

Combimarv was expected to be used to treat patients with diabetes who require insulin to control their blood glucose (sugar).

How is Combimarv expected to work?

Diabetes is a disease in which the body does not produce enough insulin to control the level of blood sugar or when the body is unable to use insulin effectively. Combimarv was intended as a replacement insulin that is similar to the insulin made by the body.

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The insulin in Combimarv is produced by a method known as 'recombinant DNA technology': it is made by bacteria that have received a gene (DNA) which makes the bacteria able to produce the insulin.

What did the company present to support its application?

The application was a joint application from Marvel LifeSciences for Combimarv and two other medicines (Solumarv and Isomarv medium, also developed as biosimilar medicines).

The company presented the results of studies designed to show that Combimarv is similar to its reference medicine Humulin M3 in terms of its structure, biological activity and clinical performance. Among these were results from studies that looked at how the body handles Combimarv compared with Humulin M3 and how these insulins affect blood sugar levels.

In addition, the company presented the results from a main study in 432 patients with diabetes comparing the safety and effectiveness of the three medicines from Marvel LifeSciences with their respective reference medicines.

How far into the evaluation was the application when it was withdrawn?

The application was withdrawn after the CHMP had evaluated the initial documentation provided by the company and formulated a list of questions. While the CHMP was awaiting the company's response to the questions, it requested an inspection of the site where studies with the medicine had taken place.

What was the recommendation of the CHMP at that time?

After its initial assessment, the CHMP had significant concerns and was of the provisional opinion that Combimarv could not have been approved. The initial concerns related mainly to the manufacture of the medicine and whether Combimarv was sufficiently similar to its reference medicine.

The CHMP also noted problems with the study data provided by the company, including statistical errors and missing information. The concerns over the data led the CHMP to request an inspection of Bombay Bioresearch Centre (BBRC) in India, where studies were carried out for Marvel LifeSciences (the sponsor of the studies), and also of Marvel LifeSciences's UK site. The inspection, carried out by the German, Swedish and UK medicines agencies, identified a number of critical and major findings which revealed a failure to conduct the studies in compliance with Good Clinical Practice (GCP) and seriously questioned the reliability of the study data. The failures identified were such that the data provided by the company could not be used to evaluate the marketing authorisation application.

What were the reasons given by the company for withdrawing the application?

In its letter notifying the Agency of the withdrawal of application, the company stated that they decided to withdraw the applications in order to repeat the studies at a validated contract research organisation and to submit additional data.

The withdrawal letter is available here.

What consequences does this withdrawal have for patients in clinical trials?

The company informed the CHMP that at the time of the withdrawal no patients were receiving Combimarv in clinical trials.