EUROPEAN MEDICINES AGENCY
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Questions and answers on the review of MabThera (rituximab)

Outcome of a procedure under Article 20 of Regulation (EC) No 726/2004

On 24 May 2012, the European Medicines Agency completed a review of MabThera following the detection of *Leptospira licerasiae* bacteria in bioreactors used in the manufacture of its active ingredient. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that there are no risks to public health and that the benefits of the MabThera continue to outweigh its risks. The Committee agreed with the corrective measures put in place at the manufacturing site and recommended that the medicine's marketing authorisation be maintained.

What is MabThera?

MabThera is a medicine used to treat non-Hodgkin's lymphoma and chronic lymphocytic leukaemia (types of cancer), and rheumatoid arthritis (a disease that causes inflammation of the joints). It contains the active substance rituximab, a monoclonal antibody designed to target B-lymphocytes, a type of white blood cell.

MabThera has been authorised in the EU since June 1998 and is marketed in all EU Member States. More information about MabThera can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

Why was MabThera reviewed?

In December 2011, the EMA was informed by Roche that *L. licerasiae* bacteria had been detected in some bioreactors used in the manufacture of the active ingredient of MabThera at its site in Vacaville, USA. The bacterial contamination was detected by routine microscopic examination during the early (pre-harvest) stages of production, in May and again in August 2011. The bacteria were not detected in later stages of production, or in the finished product, and all material in which the bacteria had been detected was discarded.

L. licerasiae is a bacterial species that can cause leptospirosis, a water-borne infection transmitted from animals to humans.

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On 15 December 2011, at the request of the European Commission, the CHMP started a review of the medicine and its manufacture with a view to issuing a recommendation on whether its marketing authorisation should be maintained, varied, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The CHMP reviewed the available quality data provided by the company on the detection of *L. licerasiae*. The CHMP also requested an inspection of the Vacaville site to investigate the cause and nature of the contamination. The inspection involved a thorough assessment of laboratories, warehouses as well as manufacturing and utility facilities. The inspectors also evaluated the quality management systems at the site.

What are the conclusions of the CHMP?

The CHMP concluded that *L. licerasiae* was most likely introduced into the cell culture media used in the bioreactors, and that personnel acting as external carriers and/or the media preparation process were possibly to blame.

The Committee noted that batches of active substance produced from cultures which tested positive for the bacteria at pre-harvest are not being further processed. Adequate corrective and preventive measures have also been introduced at the Vacaville site, which should minimise any potential contamination and improve the detection of the bacteria.

The Committee also noted that the findings were not associated with any clinically relevant risk for patients treated with MabThera, as no bacteria were detected in the active substance, or in the finished product. In addition, the manufacturing process is considered robust enough to eliminate any bacteria or proteins released by the bacteria.

Having considered all available data, the Committee concluded that the benefits of the medicine continue to outweigh its risk and recommended the maintenance of its marketing authorisation subject to certain conditions. These conditions include the requirement of the company to develop a more sensitive test for detecting the bacteria and to submit further data on the corrective measures in place at the Vacaville site.

A European Commission decision on this opinion will be issued in due course.