25 May 2012
EMA/303390/2012

Assessment report for Mepact

Review under Article 20 of **Regulation (EC) No 726/2004**, as amended

INN: mifamurtide

Procedure number: EMEA/H/C/802/A20/0022

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

The European Medicines Agency (EMA) was made aware on 10 November 2011 of the cessation of manufacture at Ben Venue Laboratories as a result of findings by the Supervisory Authorities of United Kingdom (MHRA) and France (AFSSAPS) and by US FDA inspectors during a Good Manufacturing Practice (GMP) inspection of Ben Venue Laboratories, Inc. (BVL) manufacturing site conducted jointly from 6 to 11 November 2011. This cessation included manufacturing operations in the three operational parts of the facility, North Complex, South Complex and Phase IV.

This inspection was a follow-up to a previous inspection conducted in March 2011 that had been triggered by the European Medicines Agency as part of the increased surveillance of this site. During the November 2011 inspection, a critical finding was identified with regard to deficiencies in the quality oversight of manufacturing and quality operations. In particular the inspectors pointed out as critical that since the last inspection there was an elevated risk of lack of sterility in the batches manufactured at BVL. The key issues identified in the North facility concerned recent water leaks in the aseptic core and preparation area, HEPA filter failures, media growth, environmental monitoring and facility maintenance. The inspectors also identified the presence of particulate contamination potentially affecting both the North and South facilities. The investigation performed by BVL did not provide reassurance concerning the root cause and the nature of the particles. Taken together, all the deficiencies observed in the oversight of manufacturing and quality operations raise questions on the overall quality assurance system at BVL, and this is considered to have a potential detrimental impact on the quality and safety of products manufactured and released by the site.

On 10 November 2011, Ben Venue Laboratories announced the cessation of production pending further investigation and resolution of issues related to equipment re-qualification and maintenance identified by the inspection team. This cessation included manufacturing operations in the three operational parts of the facility, North Complex, South Complex and Phase IV, that are listed as manufacturing sites for 14 centrally approved products: Angiox, Busilvex, Caelyx, Cayston, Ceplene, Ecalta, Luminity, Mepact, Soliris, Torisel, Velcade, Vibativ, Vidaza, and Vistide.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 17 November 2011 to assess the above concerns and to give its opinion on measures necessary to ensure the safe and effective use of those products, and on whether the marketing authorisations for these products should be maintained, varied, suspended or withdrawn. Furthermore the Commission asked the CHMP to consider if there was a need to take provisional measures, notably a withdrawal of medicinal products (or certain batches thereof) from the market.

2. Scientific discussion

Mepact was granted a marketing authorization in the EU on 6 March 2009.

Mepact is indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with post-operative multi-agent chemotherapy. Osteosarcoma is invariably fatal in the absence of treatment. The addition of Mepact to conventional treatment regimens increases the number of patients with a long term survival prognosis. Currently, there are no alternative treatments to Mepact available for this patient population in the EU.

Mepact has 2 manufacturing sites authorised, one of which is the BVL South Complex. The alternative authorised site was granted approval in September 2011 and product from this site was first supplied to the market in December 2011.

Deficiencies observed in the oversight of manufacturing and quality operations at BVL raise questions on the overall quality assurance system, which can potentially have a detrimental impact on the quality and safety of products manufactured and released by the site.

Mepact is presented as a powder for suspension for infusion, and reconstitution follows a specific procedure described in detail in the Summary of Product Characteristics, which includes the use of a filter provided with each pack. The main concern identified in the BVL South Complex where Mepact is manufactured was the presence of particulate contamination, which can be minimised by the use of the product filter during reconstitution. The impact of any particulate contamination of Mepact is therefore limited and outweighed by the benefits of a product for osteosarcoma for which there is no therapeutic alternative.

On 13 January 2012, the supervisory authority issued a revised GMP compliance certificate for BVL (UK GMP 6105 Insp GMP/IMP 6105/16949-0018) affecting the North, South and Phase IV facilities. According to this certificate, the BVL site is not meeting the GMP requirements to allow the manufacture of Mepact.

On the basis of the above and taking into account that Mepact now has an alternative manufacturing site authorised and able to supply the EU market:

- The CHMP recommends the maintenance of the marketing authorisation subject to the following conditions:

(i) The submission by the MAH of a variation application to delete the BVL site from the list of authorized manufacturers within the marketing authorization dossier;

(ii) No Mepact batches manufactured at the BVL site can be released to the EU market by the Marketing Authorisation Holder.

In addition the CHMP recommends that, once supply from the new site is sufficient, the MAH replaces any existing stock of Mepact manufactured by BVL in the distribution chain by product manufactured by the newly approved site.

3. Conclusion and grounds for the recommendation

Having considered the overall submitted data provided by the MAH in writing, as well as the documentation provided by the inspectors,

Whereas

- The Ben Venue Laboratories site is not in compliance with EU GMP for the manufacture of Mepact,
- There is an authorised alternative manufacturing site within the Mepact marketing authorisation dossier.

the CHMP recommends the maintenance of the marketing authorisation for Mepact subject to the conditions laid down in Annex II of the opinion.