EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2012
EMA/303396/2012

Assessment report for Ceplene

Procedure under Article 20 of **Regulation (EC) No 726/2004**

INN: histamine dihydrochloride

Procedure number: EMEA/H/C/796/A-20/0011

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

Ceplene maintenance therapy is indicated for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Ceplene has not been fully demonstrated in patients older than age 60.

In 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. 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. In

particular, the BVL north facility was found by the supervisory authorities to have GMP deficiencies leading to a potential risk of lack of sterility and the presence of particulate matter in the products.

Ceplene is terminally sterilised, so the CHMP considered that lack of sterility during the manufacturing process would not be a major concern with the product. However the BVL south facility, the sole authorised manufacturing site for Ceplene, was also found to have an elevated risk of presence of particulate matter in the final product.

With no alternative manufacturing site nor therapeutic alternative on the EU market, the CHMP considered in December 2011 that no recall of batches manufactured at BVL was necessary. Notwithstanding, the following provisional measures were adopted to ensure public health:

1. The circulation of a DHPC to reinforce to healthcare professionals the need for visual inspection of the product prior to administration, and encourage the reporting of quality complaints and/or suspected adverse drug reactions that might reflect contamination;

2. The visual inspection, by the MAH, of every unit of Ceplene in stock whilst product manufactured at BVL remains on the market;

To date, there have been no reports of unsatisfactory visual inspection indicative of concerns from the product lots manufactured at BVL.

On 13 January 2012, the supervisory authority issued a restricted GMP compliance certificate for BVL (UK GMP 6105 Insp GMP/IMP 6105/16949-0018) affecting the North facility, South and Phase IV plants to cover essential medicines. According to this certificate, the BVL site is meeting the GMP requirements to allow the manufacture of Ceplene.

The MAH was requested to address the availability of stock and its supply strategy. The MAH has provided detailed information about its on-going strategy (short and long term plans) regarding the availability of Ceplene. On the basis of this information, the CHMP is reassured that the MAH is taking active steps to ensure long term availability.

Due to the complexities associated to the production of Ceplene, transfer of the entire manufacturing operation to a different site is a lengthy process which is expected to take approximately one year.

On the basis of the above, and taking into account that BVL is currently authorised for the manufacture of Ceplene:

- The CHMP confirms that the provisional measures adopted in December 2011 were adequate and necessary to address the concerns raised in respect of batches of Ceplene manufactured in a facility with GMP deficiencies and hence to protect public health.

- The CHMP recommends that the marketing authorisation for Ceplene is maintained, subject to the following conditions:

1. The submission by the MAH, by December 2013 of a variation application to add to the marketing authorisation dossier an authorised manufacturing site for Ceplene which fulfils the requirements set out in Article 41 of Directive 2001/83/EC;

2. The submission by the MAH of a variation application, within 1 month of approval of a GMP compliant site, to delete BVL from the list of authorised manufacturing sites in the marketing authorisation dossier if GMP concerns still exist at BVL in December 2013. The MAH shall provide reassurance that the new site can provide adequate supplies;

3. The MAH is also requested by the CHMP to perform a visual inspection of every unit of Ceplene in stock whilst product manufactured at BVL remains on the market.

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 BVL site is in compliance with EU GMP for the manufacture of Ceplene;
- Ceplene is considered essential to meet clinical needs of patients;
- To date, there have been no reports of unsatisfactory visual inspection indicative of concerns from the product lots manufactured at BVL.

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