EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for Vistide

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

INN: Cidofovir

Procedure number: EMEA/H/C/121/A-20/0035

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

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Table of contents

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

Vistide was granted a marketing authorisation in the EU on 23 April 1997. It is indicated for the treatment of CMV retinitis in adults with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction. Vistide should be used only when other agents are considered unsuitable.

Vistide is a concentrate for solution for infusion containing 75 mg/ml cidofovir anhydrous as the active substance.

Vistide has two approved manufacturing sites, one of which is BVL North Complex. Since February 2011, Gilead has only released drug product manufactured at the alternative manufacturing site to the European markets.

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.

Medicinal products for intravenous use are required to be sterile by definition, and this is built into the manufacturing process. In case there is contamination, this might not be uniform throughout the batch, so random sampling and testing of the final products will not detect contamination with absolute certainty, and compliance with the tests for sterility cannot certify absolute absence of microbial contamination. Greater assurance of sterility invariably originates from reliable stringent manufacturing procedures which are in strict compliance with GMP.

Vistide is terminally-sterilised and therefore the possibility of lack of sterility in the batches manufactured at BVL North facility was not considered to be a concern for this product. However, the fact that the manufacturing process of Vistide comprises terminal sterilization cannot guarantee the absence of particulate matter in the vial.

Information provided by the MAH indicated that, in December 2011, only 1 batch manufactured at the BVL North facility and within expiry date was in the EU market.

In light of the potential risk of contamination of the batch manufactured at the BVL site with a potential impact on the safety of the product, and taking into account that an alternative site is registered for Vistide and therefore no shortage of supply was foreseen, the CHMP recommended on 9 December 2011 the suspension of marketing of the batches manufactured at the BVL site and the recall of batches manufactured at the BVL site up to pharmacy level.

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 Vistide.

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

- 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 Vistide manufactured in a facility with GMP deficiencies and hence to protect public health,

- 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 authorised manufacturers within the marketing authorisation dossier;

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

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 Vistide,
- The marketing of the batches manufactured at the BVL site has been suspended and all the batches of Vistide manufactured at BVL have been recalled,
- There is an alternative manufacturing site authorised within the Vistide marketing authorisation dossier,

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