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# Assessment report for Velcade

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

INN: bortezomib

Procedure number: EMEA/H/C/00539/A-20/056

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

Velcade was granted a marketing authorization in the EU on 26 April 2004.

Velcade is indicated as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation. Velcade in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.

Velcade is available as powder for solution for injection in two presentations: 1.0 mg and 3.5 mg. Velcade 1.0 mg is only manufactured at the BVL North Complex site, while Velcade 3.5 mg has

alternative manufacturing sites able to ensure supply the EU market. Switching between the 1.0 mg and the 3.5 mg presentation is considered to have no clinical impact for patients.

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.

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 GMPs.

In light of the potential risk of contamination of the batches manufactured at the BVL site with a potential impact on the safety of the product, taking into account that alternative sites are registered for the manufacturing of Velcade 3.5 mg, and also that switching from the 1.0 mg presentation to the 3.5 mg presentation has no clinical impact for patients, the CHMP recommended on 21 November 2011 the recall of all batches of Velcade 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 Velcade.

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

- The CHMP confirms that the provisional measures adopted in November 2011 were adequate and necessary to address the concerns raised in respect of batches of Velcade manufactured in a facility with GMP deficiencies and hence 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 add a new manufacturer for Velcade 1.0 mg to the list of authorized manufacturers within the marketing authorization dossier, which upon approval shall be followed by a variation application to delete the BVL site from the list of authorized manufacturers within the marketing authorization dossier;

(ii) No Velcade 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 Velcade,
- All the batches of Velcade manufactured at BVL have been recalled,

- There is an authorised alternative manufacturing site for the 3.5 mg presentation within the Velcade marketing authorisation dossier,
- There is no authorised alternative manufacturing site for the 1.0 mg presentation, but switching from the 1.0 mg to the 3.5 mg presentation will have no clinical impact on patients,

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