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Assessment report for Luminity

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

INN: Perflutren

Procedure number: EMEA/H/C/654/A-20/0013

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

Luminity was granted a marketing authorisation in the EU on 20 September 2006. The product is an ultrasound contrast-enhancing agent for diagnostic use in adult patients with suspected or established coronary artery disease.

Luminity is presented as glass vials containing 1.5 ml of a solution for intravenous injection or infusion. The product is subjected to a non-pharmacopoeial sterilisation cycle (128 ºC ± 1.0 ºC for 6 minutes).

Luminity has only one approved manufacturing site, the BVL South Complex.

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 GMP.

There is only one batch of Luminity manufactured at the BVL site and released by the Qualified Person within expiry date. However, this batch was placed in quarantine at the initiative of the MAH prior to November 2011, and is not currently available for patients in the EU.

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 account of the fact that Luminity was not available to patients in the EU, the CHMP recommended on 5 December 2011 that the batch manufactured at the BVL site be formally recalled.

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 Luminity.

On the basis of the above, and taking into account that Luminity has no alternative manufacturing site authorised:

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

- The CHMP considers that the particulars and documents provided for in Article 8(3) of Directive 2001/83/EC which need to be submitted in accordance with Annex I of the said Directive are incorrect,

- In addition the CHMP considers that the requirements laid down in article 41 b) of Directive 2001/83/EC are no longer met.

As a consequence, the CHMP recommends the suspension of the marketing authorisation for Luminity in accordance with articles 116, second paragraph and 118 of the said Directive.

In order to lift the suspension of the marketing authorisation, the MAH shall present evidence to confirm that there is, within the marketing authorisation dossier for Luminity, an authorised manufacturing site which fulfils the requirements set out in Article 41 of Directive 2001/83/EC.

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 Luminity,

- All the batches of Luminity manufactured at BVL have been recalled,
- There is no alternative manufacturing site authorised within the Luminity marketing authorisation dossier,

the CHMP considers that the particulars and documents provided for in Article 8(3) of Directive 2001/83/EC which need to be submitted in accordance with Annex I of the said Directive are incorrect and that the requirements laid down in article 41b) of Directive 2001/83/EC are no longer met. The Committee therefore recommends the suspension of the marketing authorisation for Luminity in accordance with Articles 116, second paragraph and 118 of Directive 2001/83/EC.

The conditions for lifting of the suspension are laid down in the Annex.

Annex

CONDITIONS FOR LIFTING THE SUSPENSION

For the suspension to be lifted, the Marketing Authorisation Holder for Luminity shall provide the CHMP with the following:

Evidence to confirm that there is, within the marketing authorisation dossier for Luminity, an authorised manufacturing site which fulfils the requirements set out in Article 41 of Directive 2001/83/EC