EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 May 2012
EMA/303404/2012

Assessment report for Cayston

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

INN: aztreonam

Procedure number: EMEA/H/C/996/A-20/0024

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

Cayston was granted a marketing authorisation in the EU on 21 September 2009. It is indicated for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 18 years and older.

Cayston is a powder and solvent for nebuliser solution containing 75 mg aztreonam as the active substance.

Until recently Cayston had three approved manufacturing sites, one of which was BVL phase IV facility. However, no Cayston batches manufactured at BVL were ever supplied to the EU market.

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.

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 Cayston.

On the basis of the above, and taking into account that Cayston has another two alternative manufacturing sites authorised and able to supply the EU market:

- The CHMP recommends the maintenance of the marketing authorisation subject to 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.

- No Cayston batches manufactured at the BVL site can be released to the EU market by the marketing authorisation holder;

3. Conclusion and grounds for 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 Cayston,
- No batches of Cayston manufactured at the BVL site have ever been released to the EU market, and therefore no provisional measures were recommended,
- There are alternative manufacturing sites authorised within the Cayston marketing authorisation,

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