EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for Caelyx

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

INN: doxorubicin hydrochloride

Procedure number: EMEA/H/C/00089/A-20/061

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

Caelyx was granted a marketing authorisation in the EU on 21 June 1996.

Caelyx 2 mg/ml concentrate for solution for infusion is a liposomal formulation of doxorubicin hydrochloride, used in the following indications:

- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.

- For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.

- In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.

- For treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (< 200 CD4 lymphocytes/mm3) and extensive mucocutaneous or visceral disease.

Caelyx may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline).

Caelyx finished product is a sterile injection available in vials (10 ml, 25ml) manufactured aseptically at the North facility of Ben Venue Laboratories, its sole manufacturing site.

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.

With no alternative manufacturing site nor therapeutic alternative on the EU market, and given that no complaints or adverse events was received indicating sterility assurance concerns from the product lots manufactured, the CHMP considered that the benefit/risk for Caelyx remained positive for essential use, to meet clinical needs for patients already receiving treatment with Caelyx. Notwithstanding the essentialness of Caelyx, provisional measures were adopted to ensure public health:

1. The circulation of a DHPC to inform healthcare professionals of the recommendations of the CHMP in relation to the use of Caelyx, of the risk associated with the use of Caelyx and to encourage the reporting of any suspected adverse drug reactions that may reflect contamination;

2. That no new patients should be initiated with treatment and existing stock in the market place should only be used to complete treatment courses that have already been initiated;

3. That weekly reports of pharmacovigilance signals potentially indicative of product contamination should be provided by the MAH to the CHMP till otherwise recommended.

The CHMP confirmed at the time that no objection was raised to the release of Caelyx batches by the qualified person, in compliance with the marketing authorisation, provided that those batches were only released to meet the needs of patients who have already started treatment.

The CHMP assessed the weekly reports of pharmacovigilance signals, and concluded that the rate of reporting was not increased, nor was there any concrete signal that could be attributed to product contamination. As a consequence, the CHMP considered that frequency of reporting could be decreased provided that the MAH reported any suspected information on an expedited basis.

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 Caelyx and other essential medicines. According to this certificate, the BVL site is meeting the GMP requirements to allow the manufacture of Caelyx.

The MAH was requested to address the availability of their 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 Caelyx. On the basis of this information, the CHMP is reassured that the MAH is taking

active steps to fully reintroduce supply as soon as possible (possibly Q3 2012) and to ensure long term availability.

Due to the complexities associated to the production of liposomal doxorubicin, transfer of the entire manufacturing operation to a different site is a lengthy process which is expected to take approximately 2 years. However, a stepwise approach which involves prioritizing the transfer of the aseptic operations can be done at an earlier stage and would lower the risk of contamination in the final product.

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

- 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 Caelyx manufactured in a facility with GMP deficiencies and hence to protect public health. Based upon recommendations agreed in November, the CHMP maintains its opinion that no new patients should be initiated with treatment and that reporting of signals by the MAH should be pursued.

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

1. The submission by the MAH, by September 2012, of a variation application to transfer the sterile filtration and aseptic filing steps from BVL to an alternative GMP compliant manufacturing site;

2. The submission by the MAH, by December 2014 of a variation application to add to the marketing authorisation dossier an authorised manufacturing site for Caelyx which fulfils the requirements set out in Article 41 of Directive 2001/83/EC;

3. 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 2014. The MAH shall provide reassurance that the new site can provide adequate supplies.

4. Whilst stocks from Ben Venue are still being used in the EU, the company is required to promptly inform the CHMP if they become aware of safety concerns and the MAH shall provide to the CHMP monthly reports of pharmacovigilance signals potentially indicative of product contamination.

5. No new patients shall be initiated with treatment and the existing stock in the market place shall only be used to complete treatment courses that have already been initiated. The lifting of this condition should be considered at the time of the transfer of the sterile filtration and aseptic filing steps from BVL to a new GMP compliant manufacturing site. The MAH shall provide reassurance that the new site can provide adequate supplies.

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 Caelyx;
- Caelyx is considered essential to meet clinical needs of patients who already initiated therapy;
- To date, no safety issues have emerged from the monitoring of Caelyx lots manufactured at BVL,

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