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Questions and answers on final recommendations on Caelyx and Ceplene manufactured at Ben Venue Laboratories

Outcome of procedures under Article 20 of Regulation (EC) No 726/2004

On 15 March 2012, the European Medicines Agency completed a review of Caelyx (doxorubicin hydrochloride) and Ceplene (histamine dihydrochloride)[1], two centrally authorised anticancer medicines manufactured at Ben Venue Laboratories, Ohio, USA. The review was initiated following shortcomings in quality assurance identified at this site, and follows the finalisation on 22 February 2012 of the review of the other 12 centrally authorised medicines manufactured at the same site (Angiox, Busilvex, Vidaza, Vistide, Velcade, Ecalta diluent, Soliris, Cayston, Luminity, Mepact, Torisel and Vibativ)[2]. The Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended maintaining the marketing authorisations for Caelyx and Ceplene until new manufacturing sites are approved as these medicines are considered essential for patients and no alternative suppliers or alternative formulations are currently available.

Why were these medicines reviewed?

A good manufacturing practice (GMP) inspection of Ben Venue in November 2011[3] highlighted several shortcomings in the quality management system in place at the site, particularly in relation to the sterile filling process and possible particle contamination during the manufacturing process. During the inspection, Ben Venue decided to cease all manufacture and distribution of medicines from its site.

Consequently, on 18 November 2011 the European Commission asked the CHMP to assess the impact of these shortcomings on the quality and safety of medicines produced at Ben Venue, and to issue an opinion on whether the marketing authorisation for these medicines should be maintained, varied, suspended or withdrawn across the EU.

[1] More information on these medicines can be found in the relevant European public assessment reports (EPARs) for each medicine: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.
[2] For more information see: 'European Medicines Agency gives final recommendations for 12 centrally authorised medicines manufactured at Ben Venue Laboratories'.
[3] The November 2011 inspection of the Ben Venue Laboratories manufacturing site conducted by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) jointly with the Food and Drug Administration (FDA) was a follow-up to a previous inspection conducted in March 2011 that had been triggered by the European Medicines Agency as part of a re-inspection program. This inspection had already led to the restriction in the importation of some medicines to the EU from the Ben Venue site.

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What actions have been taken so far?

The CHMP assessed the causes and impact of the possible particle contamination and the sterility assurance problem. Given the potential risks identified, the CHMP issued interim recommendations in November[4] and December[5] 2011 recommending that only medicines that are absolutely essential for patients' needs and for which no alternative supplier or formulation is available, such as Caelyx and Ceplene, should continue to be used.

In addition, on 13 January 2012, the UK's medicines regulatory agency (MHRA) on behalf of the European regulatory network issued a restricted GMP certificate to Ben Venue in order to stop the EU supply of non-essential medicines from Ben Venue, while allowing the continued supply of essential medicines such as Caelyx and Ceplene.

What are the final recommendations of the CHMP?

The CHMP has now finalised the assessment for Caelyx and Ceplene and is recommending the maintenance of their marketing authorisations as these medicines are considered essential for patients and no alternative manufacturers supplying the EU market or alternative formulations are currently available. The Committee also considered the fact that no concerns have been raised from the safety monitoring of these medicines. The medicines can therefore continue to be manufactured at Ben Venue until an alternative manufacturer is approved and supply can be guaranteed. The transfers to alternative manufacturing sites will be completed by December 2013 for Ceplene and by December 2014 for Caelyx. In the case of Caelyx, which is manufactured under sterile conditions the transfer of the entire manufacturing operation to a different site is complex and will be done in a stepwise approach. As part of this stepwise approach, the transfer of the sterile operations will be done by September 2012.

The interim recommendations made in November[4] and December 2011[5] continue to apply:

For Caelyx:

- No new patients should be started on Caelyx. Caelyx manufactured at Ben Venue should only be used to complete treatments that have already been initiated. This recommendation remains valid until the sterile operations have been transferred to a new manufacturing site and supply can be guaranteed from this site. In addition, healthcare professionals should monitor treated patients intensively and report immediately any relevant safety concerns (including sepsis or suspected sepsis) that could be evidence of a quality assurance problem with the sterilisation process. The marketing authorisation holder is required to provide monthly safety monitoring reports and inform the Agency promptly in the event that any concerns are detected.

For Ceplene:

- The marketing authorisation holder will continue to visually inspect the vials for particles before releasing them.

For the other 12 centrally authorised medicines produced at Ben Venue, for which the review was finalised on 22 February 2012, the CHMP had recommended the following[2]:

[4] Press release - European Medicines Agency gives interim recommendations to deal with shortcomings in quality assurance at Ben Venue Laboratories
[5] Press release - European Medicines Agency gives further interim recommendations on dealing with shortcomings in quality assurance at Ben Venue Laboratories
Q&A - European Medicines Agency recommends precautionary recall of remaining batch of Vistide manufactured at Ben Venue Laboratories

- The suspension of the marketing authorisations for Vibativ and Luminity, which are currently not marketed in the EU and for which no alternative manufacturer or formulation is available. The suspension will remain in place until the company obtains approval for a GMP compliant alternative manufacturing site.
- The maintenance of the marketing authorisations with conditions for Busilvex, Vidaza, Vistide, Velcade, Ecalta diluent, Soliris, Cayston, Mepact, Torisel and Angiox, for which alternative manufacturers are supplying the EU market or alternative formulations[6] are available. All companies involved are required to submit an application to remove Ben Venue as a manufacturing site for these medicines.

A European Commission decision on this opinion will be issued in due course.

[6] Alternative formulations for Velcade 1 mg and Ecalta diluent are Velcade 3.5 mg and Ecalta without solvent, respectively.