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Questions and answers on shortcomings in quality assurance at Ben Venue Laboratories

Interim recommendations for centrally authorised medicines

The European Medicines Agency is currently reviewing shortcomings in quality assurance identified during an inspection at Ben Venue Laboratories, Ohio, USA, where a number of centrally and non-centrally authorised medicines are manufactured. The Agency's Committee for Medicinal Products for Human Use (CHMP) is assessing the impact on the quality of centrally authorised medicines manufactured at the site.[2] While the assessment is ongoing, the CHMP has recommended, as a precaution, the recall of all batches of Busilvex, Ecalta[3], Luminity, Velcade, Vidaza and Vistide manufactured at Ben Venue, and specific measures for Caelyx, Ceplene and Torisel[3] which are not being recalled.

Which medicines are affected by the Agency's review?

The Agency's review covers the following centrally authorised medicines manufactured at Ben Venue Laboratories: Angiox, Busilvex, Caelyx, Cayston, Ceplene, Ecalta, Luminity, Mepact, Soliris, Torisel, Velcade, Vibativ, Vidaza and Vistide. They are sterile medicines delivered by injection, used to treat certain types of cancer, infections, a rare genetic disease and to detect and treat certain heart problems.[4]

A number of non-centrally authorised medicines are also manufactured at this site and are being assessed by EU Member States taking a similar approach to the Agency's review. If they are marketed in several EU countries, this is being coordinated by the Co-ordination Group for Mutual Recognition and Decentralised Procedures for human medicines (CMDh).

[1] Procedure numbers: EMEA/H/C/562/A20/0042, EMEA/H/C/654/A20/0013, EMEA/H/C/796/A20/0011, EMEA/H/C/1240/A20/0001, EMEA/H/C/799/A20/0045, EMEA/H/C/791/A20/0036, EMEA/H/C/788/A20/0019, EMEA/H/C/996/A20/0024, EMEA/H/C/802/A20/0022, EMEA/H/C/539/A20/0056, EMEA/H/C/978/A20/0017, EMEA/H/C/472/A20/0013, EMEA/H/C/089/A20/0061, EMEA/H/C/121/A20/0035

[2] The CHMP assessment is being conducted in the context of a formal review under Article 20 of Regulation (EC) No 726/2004, initiated at the request of the European Commission on 17 November 2011.

[3] Made of two components: a powder or concentrate and a diluent. Only the diluent is manufactured at Ben Venue.

[4] 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.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Why are these medicines being reviewed?

A Good Manufacturing Practice (GMP) inspection of Ben Venue in November 2011 highlighted several shortcomings in the quality-management system in place at Ben Venue, particularly in relation to the sterile filling process and possible particle contamination during the manufacturing process.[5] During the inspection, Ben Venue decided to cease all manufacture and distribution of medicines from its site.

The causes and impact of the possible particle contamination and the sterility assurance problem are currently being assessed.

How is the CHMP assessing the impact on centrally authorised medicines produced at this site?

The CHMP is conducting an assessment on the benefits and risks for each medicine concerned. For each product the CHMP has considered whether supply from Ben Venue is essential to meet patients' clinical needs, taking into account the availability of alternative treatments, the quantity of the medicine currently in stock in the EU, and the possibility of sourcing the product from alternative manufacturers.

What are the interim recommendations of the CHMP?

Given the potential risks identified, as a precautionary measure, the CHMP is recommending that only products that are absolutely essential for patients and for which no alternative supplier is available should continue to be used. On the basis of the currently available information, the CHMP is making the following interim recommendations in order to protect public health while the inspection and review are being finalised:

Caelyx, Ceplene and Torisel

The CHMP considers supplies of Caelyx, Ceplene and Torisel from Ben Venue to be essential for patients and that existing stocks in the EU should remain available to them, as Ben Venue is the only manufacturing site for these medicines. The Committee is issuing the following recommendations for these products:

- For Ceplene and Torisel, healthcare professionals are advised to visually inspect any vials for particles prior to administration. For Torisel, only the diluent and not the concentrate for infusion is manufactured at Ben Venue. Therefore the diluent vial should be inspected. No supply shortage is foreseen, but the marketing authorisation holders must identify alternative manufacturing sites to guarantee future supply.
- For Caelyx, there is an ongoing supply shortage, and the CHMP has issued detailed recommendations which have been sent in writing to healthcare professionals.[6] Patients already receiving Caelyx may continue their treatment for as long as supplies last but no new patients should be started on Caelyx.

[5] The November 2011 inspection of the Ben Venue Laboratories manufacturing site was 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) as 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.

[6] More information can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.

Busilvex, Ecalta, Luminity, Velcade, Vidaza and Vistide

The CHMP recommends, as a precaution, that all batches of Busilvex, Ecalta, Luminity, Velcade, Vidaza and Vistide manufactured at Ben Venue be recalled from the EU market. Recalling batches of these medicines supplied by Ben Venue will not impact on patients since alternative manufacturers are supplying the EU market with these products. Luminity, which is for diagnostic use, has been produced but not yet distributed in the EU (stock is currently quarantined by the marketing authorisation holder).

Angiox and Mepact

The CHMP is not currently recommending any urgent measures. Mepact is unlikely to be affected because it is filtered before use and Angiox is manufactured at a site for which no problems have been identified to date.

Cayston, Soliris and Vibativ

The CHMP is not recommending any urgent measures for these medicines while the review is ongoing because supplies from Ben Venue are not currently available on the EU market.

What are the recommendations for healthcare professionals?

- Angiox, Ceplene, Mepact and Torisel can continue to be used. For Ceplene and Torisel however, healthcare professionals are advised to visually inspect the vials for Ceplene and Torisel diluent for particles before giving them to patients.
- No new patients should be started on Caelyx. Existing Caelyx stocks, while they last, should only be used to complete treatment that has already been initiated. 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.[6]
- Pharmacists have been notified of the recall of Busilvex, Ecalta, Luminity, Velcade, Vistide and Vidaza in writing. Affected batches should be identified and returned to the supplier.

What are the recommendations for patients?

- Patients should report any adverse reactions to their doctor or pharmacist.
- Patients who have any questions or concerns about their treatment should speak to their doctor or pharmacist.

What will happen next?

These are interim measures issued in order to protect public health while the inspection and the review are being finalised. The European Medicines Agency will provide updates as soon as new information becomes available.