17th March 2012

Circular No. P08/2012

Dear Healthcare Professional,

Re: European Medicines Agency gives final recommendations on the medicines manufactured at Ben Venue Laboratories

The Medicines Authority would like to inform you of the European Medicines Agency's recommendations on those medicinal products manufactured at the Ben Venue Laboratories in Ohio, United States.

In November 2011, a good manufacturing practice (GMP) inspection of Ben Venue Laboratories manufacturing plant in Ohio[1] 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 its 14 centrally authorised medicinal products from its site. The European Commission then asked the Committee on Human Medicinal Products (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issue an opinion on whether the marketing authorisation for these medicines should be maintained, varied, suspended or withdrawn across the EU.

The CHMP has now asked the marketing authorisation holders of 12 out of the 14 centrally authorised medicines manufactured at this site (Angiox, Busilvex, Vidaza, Vistide, Velcade, Ecalta diluent, Soliris, Cayston, Luminity, Mepact, Torisel and Vibativ) to remove Ben Venue as a manufacturing site.

[1] 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.

The other two centrally authorised products anticancer medicines Caelyx (doxorubicin hydrochloride) and Ceplene (histamine dihydrochloride) continue to be manufactured at the Ben Venue facility, until the manufacturing processes for Caelyx and Ceplene can be transferred from the Ben Venue Laboratories in Ohio, United States, to alternative facilities.

For Vibativ and Luminity, which are currently not marketed in the EU and for which no alternative manufacturer or formulation is available, the Committee recommends the suspension of the marketing authorisations until a suitable alternative manufacturing site is approved.

While the transfers of the manufacturing process are ongoing, the Agency's Committee for Medicinal Products for Human Use (CHMP) is recommending that the marketing authorisations of the two medicines be maintained because both medicines are considered to be essential for patients and no alternative suppliers 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.

In the meantime, the Agency is recommending that the following measures are maintained:

For **Caelyx**, no new patients should be started on the medicine and Caelyx manufactured at Ben Venue should only be used to complete treatment that has already been initiated. This recommendation remains valid until the sterile filtration and aseptic filling processes have been transferred to a new manufacturing site and supply can be guaranteed from this site. This should be completed by September 2012. Following this, the marketing-authorisation holder, Janssen-Cilag International NV, should transfer the remaining steps in the manufacturing process to a new site by the end of 2014.

Whilst stocks from Ben Venue are still being used in the EU, the marketing authorisation holder of Caelyx is required to promptly inform the CHMP if they become aware of safety concerns, and submit a monthly report detailing reports on effects that could be related to sterilisation problems, such as sepsis. Healthcare professionals should monitor patients closely for such effects and report them immediately to the company or to the Medicines Authority.

Medicines Authority
203 Level 3, Rue D'Argens, Gzira, GZR 1368 – Malta.
Tel. (+356) 23439000 Fax. (+356) 23439161 www.medicinesauthority.gov.mt

For **Ceplene**, the manufacturing process should be transferred by the end of 2013. The marketing-authorisation holder, EpiCept GmbH, should continue to inspect the vials of the medicine visually for signs of contamination with particles.

Despite these concerns, no safety issues have emerged from monitoring of patients receiving Caelyx, Ceplene or any of the 12 other centrally authorised medicines manufactured at the facility.

The **press release** and **question and answer document** issued by the EMA are available. Suspected Adverse Drug Reactions may be reported using the Medicines Authority yellow card scheme or online at **http://www.medicinesauthority.gov.mt/pub/adr.doc** or to the marketing authorisation holder or their local representatives.

Healthcare professionals are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.