

26th October 2011

Circular No. P17 /2011

Dear Healthcare Professional,

Re: Xigris (drotrecogin alfa (activated)) to be withdrawn due to lack of efficacy.

The Medicines Authority has been informed of Eli Lilly's decision to voluntarily withdraw Xigris from the market worldwide further to the 28-day mortality results from the PROWESS-SHOCK study. Eli Lilly has also decided to discontinue all other ongoing clinical trials.

Xigris, which contains the active substance (drotrecogin alfa (activated)), was authorised in the European Union under exceptional circumstances in 2002 for the treatment of severe sepsis in adult patients with multiple organ failure, in addition to best standard care. An authorisation under exceptional circumstances means that at the time of the marketing authorisation, the applicant was unable to provide evidence on the efficacy and safety of the medicine in the same comprehensive way as with most medicines and the benefit-risk balance of the medicine has to be reviewed annually by the Agency's Committee of Medicinal Products for Human Use (CHMP). The use of Xigris was restricted to the most severe sepsis patients (at least 2 organ failures) and had to be started within 48 h, and preferably 24 h, of the onset of severe sepsis. Xigris was contra-indicated in children below the age of 18 and in patients at increased risk of bleeding.

After the annual reassessment in 2007 the CHMP concluded that the initial efficacy results of the pivotal clinical study (the PROWESS study) had not been reproduced in further studies. The CHMP thus considered that more clarification was needed regarding the benefit-risk balance of Xigris and requested Eli Lilly to conduct a new placebo-controlled clinical study to confirm that the benefits of Xigris outweigh its risks in patients with septic shock, an indication which is very close, although not identical, to severe sepsis with multiple organ failure. Eli Lilly accepted to conduct that new study, named PROWESS-SHOCK.

The results of the POWESS-SHOCK study have now become available and they fail to meet the primary endpoint of a statistically significant reduction in 28-day all-cause mortality in patients treated with Xigris compared with placebo. The study also fails its secondary endpoint of a reduction of mortality in the population of patients with severe protein C deficiency. The small difference in the 28-day mortality of the overall population (26.4% in the Xigris arm versus 24.2% in the placebo arm; n=1680 patients) is not statistically significant. The risk of severe bleeding events, which is the main risk with this product, was 1.2% in the Xigris arm and 1.0% in the placebo arm, suggesting there was no increased harm. These results call into question the overall benefit-risk balance of Xigris for the indicated patient population (severe sepsis). Eli Lilly has thus decided to withdraw the product from the market worldwide.

At this stage physicians should not initiate new patients with Xigris and should stop ongoing treatment. (Xigris is administered once, as a continuous intravenous infusion, for a total duration of 96 hours).

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