29th January 2011

Circular No. P01/2011

Dear Healthcare Professional,

Re: European Medicines Agency's review of the manufacture of Baxter's peritoneal dialysis solutions initiated over potential presence of endotoxins in some batches

In December 2010 healthcare professionals in the EU were advised that a small proportion of certain Baxter PD solutions (Dianeal, Extraneal and Nutrineal) manufactured at the company's Castlebar plant in Ireland could contain endotoxins, which may lead to adverse reactions in some patients undergoing peritoneal dialysis because of kidney failure. There is a risk that patients who receive PD solutions that contain endotoxins may develop aseptic peritonitis. However the number of PD bags affected is very small and the overall risk to patients remains low. Patients and healthcare professionals should continue to look out for any symptoms that suggest the development of aseptic peritonitis (e.g. cloudy effluent seen in drain bag at the end of dialysis, abdominal pain, nausea, vomiting and possibly fever) and report any cases as soon as possible.

The European Medicines Agency has now been informed by Baxter that the problem of presence of endotoxins in peritoneal dialysis (PD) solutions has not been solved and that it cannot guarantee the production of endotoxin-free solutions from a production line at its Castlebar plant in Ireland in the short-term. As a consequence, the Agency's Committee for Medicinal Products for Human Use (CHMP), at the request of the European Commission, started a full review of the manufacture of Baxter's dialysis solutions at the affected plant. Batches of Dianeal, Extraneal and Nutrineal considered potentially affected by presence of endotoxin remain on the market as there is currently not enough supply of unaffected products to meet patient needs.

New unaffected Dianeal, Extraneal and Nutrineal PD solutions will be temporarily imported into the EU from alternative Baxter manufacturing sites outside the EU (Canada, US, Singapore and Turkey) in order to promptly replace supply from Ireland. This temporary change over will be needed for several months while the manufacturing problem at Castlebar is fully addressed. During the next few weeks, the supply situation will remain critical. In the meantime, batches of PD solutions manufactured in Castlebar are still being released to meet patients' needs. The CHMP has therefore recommended that further safeguards be introduced into the procedures used for testing of PD solutions to minimise the risks for patients. Use of PD solutions manufactured outside the EU, when available, should be prioritised over the solutions produced in EU, especially to vulnerable patient populations, including Extraneal patients with otherwise uncontrollable fluid overload.

In Malta Dianeal, Extraneal and Nutrineal have an active marketing authorisation and are currently being used. A recall of all potentially affected products was not possible because there were no replacements for these life-saving treatments. To date, the Medicines Authority has received no reports of Adverse Reactions to peritoneal dialysis solutions. However, in line with risk minimisation plans the local stock will be imported from Canada or USA whenever possible.

The CHMP also noted that the root cause of the presence of endotoxins needs to be fully identified and urgent action taken to rectify the problem. Baxter has informed the Committee that it will temporarily shut the manufacturing area in order to replace the majority of components of the manufacturing process to remove endotoxins from the production line at the Castlebar plant. This is expected to ensure the supply of new unaffected PD solutions for patients as soon as possible.

Healthcare professionals will be sent updated advice, including information on new supplies from outside the EU as it becomes available. The EU regulatory system is intensively monitoring this issue on a continuous basis.

The Medicines Authority is participating in the discussions held at the EMA and is in agreement with the full **press release** issued by the EMA, attached here for your perusal. A **question-and-answer** document with more information about the outcome of this assessment is also available.

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