



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Questions and answers on endotoxins in dialysis solutions produced at Baxter manufacturing plant

In December 2010 healthcare professionals in the EU were advised that a small proportion of certain Baxter peritoneal dialysis solutions (Dianeal, Extraneal and Nutrineal) could potentially contain endotoxins which may lead to adverse reactions in some patients. A recall of the affected products was not possible as replacements were not available; therefore the Agency's Committee for Medicinal Products for Human Use (CHMP) issued advice to healthcare professionals on how to manage patients using these products.

Baxter has now informed the Agency that the problem is wider than previously thought and that it cannot guarantee the production of endotoxin-free products from a production line at its Castlebar plant in Ireland. In order to avoid shortages of these products in the EU, the CHMP is working with Baxter on their plans to import equivalent products from other production sites outside the EU (USA, Canada, Singapore and Turkey). The Committee is updating the recommendations it gave in December 2010¹ and, at the request of the European Commission, has started an in-depth review² of the manufacturing processes at the affected plant.

What products are affected?

Baxter's Castlebar plant produces dialysis solutions, which are used in patients with kidney problems. The products affected include Dianeal, Extraneal and Nutrineal solutions for peritoneal dialysis and Monosol and a sodium chloride solution for haemodialysis.

What are the risks of exposure to endotoxins?

Endotoxins are harmful substances (toxins) released from bacteria after they have died. If a patient receives a medicine that contains endotoxins, there is a risk that the immune system, the body's defence mechanism, will react against the endotoxins and cause inflammation. In particular, endotoxins in solutions used in peritoneal dialysis can cause 'aseptic peritonitis', an inflammation of the peritoneum that affects the way it filters the blood. Symptoms of aseptic peritonitis include cloudy effluent (the solution in the drainage bag), abdominal pain, nausea (feeling sick), vomiting and sometimes fever. Aseptic peritonitis can force the patient to stop dialysis until it is resolved.

¹ The questions and answers document published in December 2010 can be found [here](#).

² Procedure under Article 31 Directive 2001/83/EC as amended.



What is the background to the current investigation?

In December 2010, the Agency was made aware of the presence of endotoxins in batches of Dianeal, Extraneal and Nutrineal made in the Castlebar plant in Ireland. At the time, the company identified endotoxin-producing bacteria in two tanks as the root cause of the problem and removed them from the production process. It also cleaned the other tanks and pipework involved in the production.

The Agency has since been informed that, despite these measures, endotoxins were detected in new batches of solutions produced at the plant. At the CHMP's January 2011 meeting, the company informed the Committee that it believed that the endotoxins were being produced by 'biofilms' (layers of bacteria that adhere to each other), which are very resistant to cleaning processes.

While the CHMP is carrying out its in-depth investigation and until production of new unaffected peritoneal dialysis solutions can be restarted, the CHMP is giving recommendations to help ensure that patients continue to receive appropriate treatments.

What are the recommendations of the CHMP?

The CHMP underlined its recommendations made in December 2010 that the company should continue its increased monitoring for reports of aseptic peritonitis for batches that are already on the market. The CHMP also noted that the root cause of the presence of endotoxins needs to be identified and urgent action taken to rectify the problem.

The Committee considered that peritoneal dialysis solutions can be imported into the EU while there is a shortfall in the supply of unaffected solutions from the Castlebar plant. The company will make available comparable products from outside the EU (USA, Canada, Singapore and Turkey). These alternative solutions have the same characteristics as the EU products with minor differences. The Committee also recommended that use of the solutions manufactured at the production line at Castlebar should be minimised as far as possible and that further safeguards be introduced into the procedures used for testing batches.

The Committee recommended that the company communicate with healthcare professionals to inform them of the products that will be available and to provide guidance on use of existing products on the market and all the necessary information and training they need to switch their patients to the new products.

What is being done to solve the problem at the Castlebar site?

Baxter is replacing the majority of components of the manufacturing process at the Castlebar plant to ensure that unaffected solutions can be produced as soon as possible. This process will take place over the coming months. The company will also implement other measures according to the outcome of the CHMP review and the ongoing inspection by authorities in Ireland.

What are the recommendations for patients and prescribers?

- Healthcare professionals are informed that, over the next few weeks, patients may need to be switched to imported products manufactured outside the EU. Healthcare professionals and patients will receive information on the new products, explaining any differences with their usual products and how to prioritise and use them.
- Healthcare professionals are reminded to continue to look out for any signs and symptoms of aseptic peritonitis in their patients and provide appropriate treatment.

- Healthcare professionals should report any suspected cases of aseptic peritonitis to the company using reporting forms that will be provided by Baxter.
- Patients who suspect they have aseptic peritonitis or notice any symptoms that suggest that they are developing peritonitis should contact their doctor.
- Patients who have any questions should contact their doctors to discuss their treatment.

What will happen next?

Once finalised, the Agency will communicate on the outcome of the CHMP's full review of the Baxter manufacturing plant. Should there be a need for further interim recommendations while the assessment is ongoing these will be made public by the Agency. The EU regulatory system is intensively monitoring this issue on a continuous basis.