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Questions and answers on the presence of endotoxins in Baxter peritoneal dialysis solutions

Outcome of a procedure under Article 5(3) of Regulation (EC) 726/2004[1]

The European Medicines Agency has completed a review of the impact of the presence of endotoxins in peritoneal dialysis solutions made by Baxter. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that stocks should be replaced, but that this needs to be coordinated to ensure that peritoneal dialysis patients for whom these solutions are essential are not affected by shortages.

What are solutions for peritoneal dialysis?

Peritoneal dialysis is a technique used to clear waste substances (such as urea) from the blood of patients whose kidneys have stopped working. This technique uses the peritoneum, the membrane lining the abdominal cavity, to filter out the waste from the blood. A solution is first pumped into the abdomen. Waste substances from nearby blood vessels then diffuse across the peritoneum into the solution in the abdomen. After a few hours, the solution containing the waste is pumped out and replaced with a fresh solution.

Solutions for peritoneal dialysis are sterile solutions containing a mixture of substances such as glucose, salt and amino acids or icodextrin. Solutions for peritoneal dialysis made by Baxter include those with the trade names Dianeal, Extraneal and Nutrineal.

What are endotoxins?

Endotoxins are harmful substances (toxins) released from bacteria after they have died. Medicines may contain endotoxins when bacterial cell debris are accidentally introduced into the product during manufacture. Tests for endotoxins are systematically carried out during the manufacture of sterile medicines.

[1] Article 5(3) of Regulation (EC) 726/2004, opinion on any scientific matter concerning the evaluation of medicinal products for human use.

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What are the risks of exposure to endotoxins?

If a patient receives a medicine that contains endotoxins, there is a risk that the immune system, the body defence mechanism, will react against the endotoxins and cause inflammation. In particular, endotoxins in peritoneal dialysis solutions can cause 'aseptic peritonitis', an inflammation of the peritoneum that affects the way the peritoneum can filter the blood and can force the patient to stop dialysis until it is resolved. The symptoms of aseptic peritonitis include cloudy effluent (the solution in the drainage bag), abdominal pain, nausea (feeling sick), vomiting and sometimes fever.

Why are there endotoxins in Dianeal, Extraneal and Nutrineal?

During routine testing at the Castlebar plant in Ireland where Baxter makes Dianeal, Extraneal and Nutrineal, a number of batches were found to contain unexpected levels of endotoxins. While these batches were not released onto the market, the findings triggered a review of the processes in the manufacturing plant to identify the root cause of the problem. The company found that two of the tanks that were used in the production of the batches had microscopic cracks where endotoxin-producing bacteria such as *Stenotrophamonas maltophilia* and *Sphingomonas paucimobilis* had settled. The tanks were taken out of the production line, but it is unclear when these cracks first formed, and batches of Extraneal, Dianeal and Nutrineal currently on the market that were produced using these two tanks could contain endotoxins.

Consequently, on 14 December 2010, the UK medicines regulatory agency asked the CHMP to give its opinion on the issue, in particular on the management of the risk to patients and of the supply situation for the European market.

What are the conclusions of the CHMP?

The CHMP invited the company to present the issue and answer a number of questions at an oral explanation at the December 2010 meeting.

The Committee noted that the root cause of the problem has been identified. By removing the affected tanks from the production line and reviewing its procedures, the company has ensured that the risk of the problem recurring is minimised.

The Committee also noted the way the endotoxins had been introduced during the manufacture of the solutions. Because the release of endotoxins into the tanks happened intermittently, it is difficult to identify which batches were affected. However the proportion of bags of solution actually affected is likely to be low.

The dialysis solutions that may be affected are available throughout the European Union (EU) and many patients rely on these life-sustaining medicines. The Committee also had concerns that in some Members States, these Baxter products are the only solutions available to patients. The Committee therefore concluded that measures should be taken to ensure that the impact on patients is kept to a minimum.

The recommendations of the CHMP are that:

- The company replaces batches of Dianeal, Extraneal and Nutrineal that potentially contain endotoxins as soon as possible. The change over should be handled in such a way that shortages are avoided and vulnerable patients who rely on a particular type of solution are not put at risk. This applies especially to patients with fluid overload using Extraneal.

- The company steps up its monitoring systems to ensure that any impact of the exposure to endotoxins of existing users of the solutions is identified as quickly as possible. In particular, the company should report on a weekly basis to national regulatory agencies all suspected cases of aseptic peritonitis with Dianeal, Extraneal and Nutrineal that could be linked to endotoxins. These reports should be analysed by the company and the regulatory agencies to assess if there is sufficient evidence that a particular batch is associated with aseptic peritonitis, and take appropriate measures to remove it from the market if needed.
- The company monitors the stocks and supply of these solutions throughout the EU, and takes all possible measures to increase production to replace the potentially affected products. This monitoring should also include Physioneal, another Baxter peritoneal dialysis solution. Physioneal is not affected by the endotoxin problem, but its supply could be affected as it can be a suitable alternative in some patients.
- The company communicates with healthcare professionals involved in the care of peritoneal dialysis patients to ensure that they are aware of the ongoing issue and its potential consequences, and know how best to handle patients that are potentially affected.

What are the recommendations for patients and prescribers?

- Patients currently on peritoneal dialysis who are using Dianeal, Extraneal and Nutrineal should contact their doctor to discuss the need to adjust their treatment (through a switch to another dialysis solution or an adjustment of their dialysis method).
- If these patients notice any symptoms that suggest that they are developing aseptic peritonitis, they should contact their doctor. Symptoms of aseptic peritonitis include cloudy effluent in the drainage bag, abdominal pain, nausea (feeling sick), vomiting and sometimes fever.
- Prescribers should review their peritoneal dialysis patients to assess the benefit of continuing dialysis as normal while weighing the risk of aseptic peritonitis caused by endotoxins. Various options are available, depending on the dialysis solution and the type of peritoneal dialysis that the patient is using.
- Prescribers should report any suspected cases of aseptic peritonitis to the company using reporting forms that will be provided by Baxter.

The situation with Baxter peritoneal dialysis solutions will be monitored in each Member State. All stocks are expected to be replaced by March 2011.