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

Outcome of a procedure under Article 31 of Directive 2001/83/EC as amended

The European Medicines Agency has completed an investigation into the production processes at Baxter's manufacturing plant in Castlebar, Ireland. The investigation follows the detection in December 2010 of endotoxins in dialysis solutions produced at the plant. The Agency's Committee for Medicinal Products for Human Use (CHMP) has finalised recommendations to ensure the adequate supply of these dialysis solutions in the EU while measures are being put in place at Castlebar to enable the production of endotoxin-free solutions.

Which products are affected by the review?

The products affected by this review are some of the dialysis solutions produced at Baxter's Castlebar plant. These include: Dianeal, Extraneal and Nutrineal solutions for peritoneal dialysis; Monosol and a sodium chloride solution for haemodialysis.

Dialysis solutions are used in patients with kidney problems to help clear waste substances (such as urea) from the blood.

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 may affect 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.

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What is the background to the current investigation?

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

Despite these measures, endotoxins were still detected in new batches of solutions produced at the plant, causing the manufacture of these solutions to be shut down at the plant. It was believed that the endotoxins were being produced by 'biofilms' (layers of bacteria that adhere to each other), which are very resistant to cleaning processes.

Due to the lack of sufficient alternative sources for dialysis solutions, the CHMP could not recall all affected products from the Castlebar plant at that time. However the Committee aimed to reduce reliance on the plant and made recommendations in January 2011 for the use of products imported from four production sites outside the EU (in Canada, USA, Singapore and Turkey). All affected products from Castlebar were eventually recalled in stages across the EU.

The CHMP started the current review to investigate fully the issues related to the endotoxin contamination and to make recommendations to help protect public health and to prevent future supply shortages.

What are the conclusions of the CHMP?

The CHMP concluded that the root cause of the presence of endotoxins in the affected production lines was a combination of factors: undetected cracks in equipment may have allowed the growth of bacteria, while the design of the plant and the cleaning methods used may have allowed the contamination to spread.

The CHMP noted that improvements are being made to Castlebar plant to ensure future production of endotoxin-free dialysis solutions. These include changes to the design of the plant, new cleaning regimens and the introduction of improved testing methods. The Irish medicines agency will inspect the plant again in October 2011 after which it will go through a 12-month 'requalification period' where the plant will be carefully monitored and the products will undergo rigorous testing. The corrective measures being made at Castlebar will also be applied to Baxter's other manufacturing sites.

As part of the future risk management plan the Committee adopted proposals for a period of intense monitoring of any reports of aseptic peritonitis during the initial months of marketing new products from CastleBar.

The Committee also adopted a strategy to ensure adequate supply of products in the EU should problems reoccur in the future. In order to facilitate this, the CHMP had earlier during the investigation made recommendations to formally include the production sites in Canada, USA, Turkey and Poland in the products' marketing authorisations in Europe.

What are the recommendations for patients and prescribers?

- Healthcare professionals should continue to monitor dialysis patients for any adverse events including aseptic peritonitis and report any suspected cases to the company using the reporting forms that will be provided by Baxter.

- Patients who suspect they have aseptic peritonitis or notice any relevant symptoms (cloudy effluent in drain bag at the end of dialysis, abdominal pain, nausea, vomiting and fever) should contact their doctor.
- Patients who have any questions should contact their doctors to discuss their treatment.

The European Commission issued a decision on 16 December 2011.