EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for Art 5(3) procedure: Presence of endotoxins in Baxter peritoneal dialysis solutions

Procedure number: EMEA/H/A-5(3)/1289

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

On 10 December 2010 the European Medicines Agency (EMA) was made aware of a rapid notification class I for peritoneal dialysis (PD) solutions manufactured by the marketing authorisation holder (MAH) Baxter in its Castlebar plant in Ireland potentially affecting batches of Dianeal, Extraneal and Nutrineal solutions distributed in Europe. The presence of endotoxins was identified in some units of the above mentioned PD solutions.

An investigation into the raw materials used in the preparation of these PD solutions and its manufacturing process identified the presence of endotoxins in the final product. The use of solutions containing endotoxins increases the risk of inflammation, and in particular aseptic peritonitis.

On 13 December 2010 the matter was discussed at the Pharmacovigilance working party (PhVWP) and an European wide management of this issue was considered appropriate and necessary to ensure consistency in the supply and distribution of the message to healthcare professionals and patients. European coordination would facilitate appropriate pharmacovigilance and quality follow-up of this issue.

On 14 December 2010, the United Kingdom requested the Committee for Medicinal Products for Human Use (CHMP), in accordance with Article 5(3) of Regulation (EC) No 726/2004, to draw up an opinion on issues related to the detection of endotoxins in a limited number of bags of PD solutions from batches available across Europe and potential measures to be taken. The Committee was asked to give its opinion on the following:

1. Has the root cause of the endotoxin contamination been identified and appropriately managed?

2. What is the risk associated with the use of Baxter peritoneal dialysis solutions contaminated with endotoxin?

3. How should ongoing supply of Baxter peritoneal dialysis solutions be managed, and prioritised in the European market?

4. What messages should be communicated to healthcare professionals and patients in order to manage the risk?

5. What additional pharmacovigilance activities should Baxter implement while contaminated product is available on the market?

Steps taken for the assessment of this procedure:

During the December 2010 CHMP meeting the following was agreed:

Dr. Rafe Suvarna (UK) was appointed Rapporteur for this review procedure under Article 5(3).
Dr. Philippe Lechat (FR) was appointed Co-Rapporteur for this review procedure under Article 5(3).
The procedure started on 14 December 2010.

A list of questions to be addressed at an oral explanation was adopted and circulated to the MAH on 14 December 2010.

An oral explanation was held on 15 December 2010.

On 16 December 2010 the CHMP adopted an opinion.

2. Scientific discussion

2.1. Introduction

On 14 December 2010 the United Kingdom asked the CHMP, in accordance with Article 5(3) of Regulation (EC) No 726/2004, to give an opinion on questions related to the potential presence of endotoxins in PD solutions manufactured by Baxter, in particular the risk to patients and supply situation on the European market for this life-sustaining therapy.
The CHMP views, including recommendations on the strategies to prioritise supply, options for use of alternative products, clinical management of aseptic peritonitis and monitoring of adverse drug reactions (ADRs) in the reported situation are discussed below.

2.2. Discussion

2.1.1 Question 1

Has the root cause of the endotoxin contamination been identified and appropriately managed?

On 9 November 2010 the MAH identified an out of specification (OOS) result for endotoxins in 4 Nutrineal batches. The batches were not released and the MAH opened an investigation to identify the root cause. Raw materials, all microbiological parameters for critical systems and the manufacturing process were investigated.

Using a dye penetration technique to examine the integrity of the vessels, small stress cracks were identified in two tanks which share a unique design and are used for bulk solution in the manufacture of Dianeal, Extraneal and Nutrineal solutions. Further to the discovery, the two tanks were removed from service and all other tanks used in manufacture were tested and confirmed to be unaffected.

It is understood that the stress cracks allowed solution to leak into a sealed cavity leading to the formation of a biofilm which then released bioburden back into the tank at random intervals during manufacture, resulting in increased endotoxin in some filled units.
Swabs taken from the cavities identified the presence of two Gram negative organisms *Stenotrophomonas maltophilia* and *Sphingomonas paucimobilis*. These organisms are non-spore forming and would be eliminated by the terminal sterilisation process but are potential contributors of endotoxin.
The lack of homogeneity in the release of bioburden is considered to have led to bag to bag variation with respect to endotoxin levels with most of the units being within specification.

As a timeline as to when the stress cracks first formed could not be established, a worst case scenario was considered and all in-date batches manufactured on the line were to be suspected to have some units in which the presence of endotoxin might be detected. Batches manufactured in the affected production lines which had not been released were no longer used or released to the market.

The CHMP acknowledged the current data which indicate that the presence of stress cracks was considered to be the root cause. The MAH immediate action upon identification, including the suspension of use of the tanks and the conservative approach regarding batches affected was considered appropriate.

2.1.2 Question 2

What is the risk associated with the use of Baxter peritoneal dialysis solutions contaminated with endotoxin?

It is noted that kidney transplantation is the preferred renal replacement therapy option. However since there are limitations to the transplant donor supply or patient contraindications to transplantation, dialysis is important for patient survival. Peritoneal dialysis, used to remove kidney failure related toxins, restore electrolyte balance and normalise fluid balance, is thus a life sustaining therapy.

The event of most concern associated with the presence of endotoxins in some units of Baxter's PD solutions is aseptic peritonitis.

Peritonitis is a recognised complication of PD therapy with rates varying within clinics and hospitals. There is an increased risk of developing aseptic peritonitis with the use of PD solutions where endotoxins have been detected. Sterile or aseptic peritonitis, unlike bacterial peritonitis, is a time limited inflammatory response, typically with milder clinical symptoms and resolving on removal of the stimulating factors. Symptoms of aseptic peritonitis include, cloudy effluent, abdominal pain, nausea, vomiting and possibly fever. Although the majority of cases of aseptic peritonitis appear to recover after withdrawal of the PD fluid, more serious and long term sequelae (such as damage to the peritoneum and inability to continue with peritoneal dialysis) could occur in some patients. Other consequences may include needless antibiotic use, potential hospitalisation with risk of nosocomial infections and removal of catheter.

The presence of solution in the mixing tanks led to the creation of a biofilm that entered the solution inconsistently through the micro cracks. This lack of homogeneity is likely to have led to bag to bag variation with respect to endotoxin levels with most of the units (bags) being within specification. Therefore, although the risk of aseptic peritonitis exists, the proportion of affected units may be small. Furthermore, switching the patient to alternative PD solutions or therapies is not without risks which need to be carefully considered. Availability of alternative suppliers and its equivalence to current Baxter PD solutions, the type of connectors patients are using and their potential change, the time for staff and patient training, the potential for volume overload (in particular for Extraneal long dwells) and difficulties in diabetic management are some of the issues which need consideration.

2.1.3 Question 3

How should ongoing supply of Baxter peritoneal dialysis solutions be managed, and prioritised in the European market?

Current MAH solutions in Europe include Dianeal, Extraneal, Nutrineal and Physioneal. The MAH PD solutions potentially affected are the Dianeal, Extraneal and Nutrineal solutions. No tanks or lines involved in the production of Physioneal are impacted by the current issue.

Dianeal and Physioneal are base solutions for the short dwells and are the foundation for PD prescription. They both use glucose as the osmotic agent. Other solutions (Extraneal and Nutrineal) are non glucose based osmotic solutions and are prescribed for unique patient needs in combination with the base solutions.

There are risks, including potential shortage of supply with an abrupt switching of Dianeal to Physioneal for all exchanges. In addition, there is no equivalent solution to Extraneal, therefore prioritisation measures need to be implemented.
The MAH is advised to monitor this situation and appropriate patient management should be introduced, with prioritisation of new supplies to vulnerable patients exclusively dependent on affected PD solutions including Extraneal patients with otherwise uncontrollable fluid overload.

Renal units in all member states need to be informed as soon as possible and a communication channel introduced in order to continuously discuss the criteria for prioritisation and adapt it as necessary. The MAH is committed to identify critical patients for whom Extraneal is essential in order to ensure adequate expedite distribution to these patients. In addition, Extraneal manufacturing will be prioritised and the current target is for stock of Extraneal to be fully replaced by the end of January 2011.
Close monitoring of the conversion to Physioneal will also be introduced in order to ensure adequate supply. The MAH is committed and has introduced measures to increase its manufacturing capacity in order to accelerate availability of all PD solutions. Replacement of Dianeal and Nutrineal is expected by March 2010. The MAH is committed to provide the national competent authorities with weekly updates of the supply of all PD solutions in all EU Member States.

2.1.4 Question 4

What messages should be communicated to healthcare professionals and patients in order to manage the risk?

It is important that healthcare professionals and patients are made aware of the potential presence of endotoxins in some units of Dianeal, Extraneal and Nutrineal PD solutions, the potential increased risk of inflammation, in particular aseptic peritonitis, and the potential for shortage of these life-sustaining solutions. Communication of key messages would allow them to weigh the risks and benefits of continuing the use of PD solutions that are potentially affected by this issue, appropriate prioritisation of supplies, including management of vulnerable patients, whilst increasing awareness, monitoring and reporting of suspected cases of aseptic peritonitis.

The CHMP therefore recommended that a healthcare professional letter be issued in Europe. In addition the European Medicines Agency would also communicate on the matter through its website.

In particular, healthcare professionals and patients should be made aware of current options for use of PD solutions. Supplies of new, unaffected PD solutions should be prioritised for vulnerable populations exclusively dependent on affected PD solutions, including Extraneal patients which may include those with otherwise uncontrollable fluid overload ((patients with tendency to fluid overload related to low urine output and/or low peritoneal ultrafiltration).

For other PD patients, healthcare professionals should determine if alternative PD therapies, solutions or dialysis methods should be pursued based on risk of exposure of patients to endotoxin. Consideration could be given to the following:

(1) In Continuous Ambulatory PD (CAPD) patients, replace Dianeal or Nutrineal with Physioneal for the short dwell since Physioneal is not affected by this problem.
(2) In Automated PD (APD) patients using Dianeal, ensure that only 5L bags are used for the short dwell
(3) For patients using Extraneal for the long dwell in CAPD or APD, assess fluid balance and continue Extraneal specifically in patients with low urine output/fluid balance challenges in whom a different PD therapy prescription change will not be sufficient
(4) Switch CAPD patients to APD using Physioneal or Dianeal (5L bags only) if this is feasible
(5) Use PD solutions from alternative manufacturers

When evaluating potential mitigations or PD therapy changes, healthcare professionals should weigh the risk of exposure to endotoxin and the long term consequences of aseptic peritonitis and its management (primarily peritoneal damages and overexposure to antibiotic therapy) and the clinical needs of patients (e.g. uncontrolled fluid balance, diabetes) with other risks such as a heightened risk of bacterial peritonitis related to changes in type of connector for different PD solutions and patient training and use of alternative PD systems.

New PD patients commencing PD therapy should preferably receive product known to be unaffected[1].

Healthcare professionals and patients should be aware of signs and symptoms suggestive of peritonitis, which is a known risk in patients undergoing peritoneal dialysis. Since the risk is increased in the presence of endotoxin, patients using affected PD solutions could present with cloudy effluent suggesting peritonitis with or without signs and symptoms such as abdominal pain, nausea, vomiting or fever. Increased peritoneal fluid white cell count (with a majority of monocytes) and a negative microbiological culture would strongly suggest a sterile aseptic peritonitis.

Healthcare professionals should take microbiological cultures and white cell count and then commence empirical intraperitoneal antibiotic therapy for Gram positive and Gram negative organisms according to their standard protocol. If other possible reasons for cloudy fluid especially bacterial peritonitis have been excluded, the suspected PD fluid should be stopped and the result of this action evaluated.

[1] To identify new unaffected batches each user should check the first three digits/letter combination in the product batch number, where the first two numbers correspond to the year of manufacture (i.e., 10 for 2010, 11 for 2011) and the subsequent letter corresponds to the month (i.e., A for January, B for February, C for March… and so on). If the digits/letter combination starts with **10L** (product produced in December 2010) the product is unaffected. All subsequent unaffected batches will be produced in subsequent order starting with **11A**, e.g. 11B, 11C… 11F,…11L.

2.1.5 Question 5

What additional pharmacovigilance activities should Baxter implement while contaminated product is available on the market?

In addition to communication, which will increase awareness of healthcare professionals and patients on the monitoring of potential adverse reactions relating to aseptic peritonitis, the CHMP considered it appropriate to heighten pharmacovigilance. This would include solicited ADR reporting and their prompt analysis for identification of potential signals, including causality assessment. Reporting forms should be made available to all renal centres in Europe , and the MAH should facilitate mechanisms for rapid return including fax and possibly web-based reporting options.

It is crucial that signal detection activities and case assessment criteria are harmonised and coordinated by the MAH. Peritonitis is a known event in patients undergoing peritoneal dialysis and current background rates are based on spontaneous ADR reporting (which can lead to underestimation). It is therefore critical to consider the signal threshold that will result in a batch being removed from the market (recall), and the MAH should consider quantitative and/or qualitative criteria to categorise causality and determine a recall. The criteria may need to be revised on an ongoing basis, therefore close liaison with national regulatory authorities is vital.
Weekly reports of aseptic peritonitis, including batch specific ADR reports and their analysis are recommended with more frequent ad hoc reports provided if urgent need arises. For any safety signal identified, a risk assessment should be provided. In case a safety signal is identified with a particular batch, it is recommended that measures are undertaken to remove it from the market if needed following a co-ordinated risk assessment and consultation and agreement with national competent authorities.
In addition, national nephrology professional associations may play a role in monitoring of trends in the incidence of aseptic peritonitis at the national level and the MAH should contact these associations to request their involvement.
Potential consequences of the actions taken during this period should be analysed, including needless antibiotic use and potential hospitalisation with risk of nosocomial infections, among others. The possibility of serious and long term sequelae cannot be excluded, therefore it is important that reported cases are followed up by the MAH for severity and clinical outcome.
Batch recall, manufacturing and supply status reports should be provided weekly to national competent authorities so that a co-ordinated overview can be maintained.

3. Conclusion

The CHMP considered data provided by the MAH regarding the quality, supply, clinical management, pharmacovigilance and communication issues relating to the presence of endotoxin in peritoneal dialysis products produced by Baxter.

Quality issues and root cause analysis
On the basis of the data provided the CHMP considered the root cause for increased endotoxin concentrations in batches of Dianeal, Extraneal and Nutrineal to be related to the formation of micro cracks in two mixing tanks involved in the production of these products at the Castlebar manufacturing plant, in Ireland. The CHMP noted that appropriate action in suspending use of the mixing tanks had been taken. The CHMP also noted that the endotoxin was heterogeneously distributed throughout the batches and while only a small proportion of released product was likely to be affected, the MAH's conservative assumption that all batches within expiry date on the market could potentially be affected was appropriate.

Supply issues
The CHMP noted that because Baxter holds a substantial amount of the market share of peritoneal dialysis fluids across the European Union, it would not be possible to remove immediately from the market all potentially affected batches, without incurring drastic consequences for vulnerable patients. However, the MAH is recommended to make all efforts to increase capacity of production of endotoxin free product and replace affected batched of Dianeal, Extraneal and Nutrineal as soon as possible.
The CHMP further considered that the MAH should provide weekly batch recall and current supply reports for all national competent authorities in the EU, as well as weekly reports on manufacturing of new batches (in order to ensure that this remains on target).

In addition, the MAH should provide ad hoc reports detailing changes to manufacturing that could impact on either production capacity or the risk of contamination.

Clinical issues
The CHMP noted that the established clinical effect of endotoxin in peritoneal dialysis fluid appears to be aseptic peritonitis, and that the current presence of endotoxins has not resulted in serious clinical consequences in reported cases. However, the possibility of serious and long term sequelae cannot be excluded. Therefore, it is important that reported cases are followed up for severity and clinical outcome.

The CHMP noted the MAH proposed strategy to increase production of new (unaffected) batches, and to prioritise the production of Extraneal to meet clinical needs as there is no equivalent product and a proportion of patients receiving this product have a critical need for continued supply. In addition, the CHMP considered it important that particularly vulnerable populations (Extraneal patients with fluid overload) should be prioritised to receive unaffected product. The MAH should propose a mechanism to identify these groups and ensure supply.
While priority is given to Extraneal, it is also very important to reinstate new supply of Dianeal and Nutrineal as soon as possible. In addition, the MAH should monitor potential switching to Physioneal, which is not affected by this issue, and which may lead to shortages. Action to prioritise production of Physioneal should be taken if needed.

Heightened pharmacovigilance
Considering the lack of sufficient alternative supply, and the vital clinical need for these products, the CHMP agreed that an immediate removal of all potentially affected batches would not be appropriate. However, it would be important for the MAH to implement heightened pharmacovigilance measures (solicited ADR reporting) and to withdraw any batches associated with a significant increased signals of aseptic peritonitis.
To facilitate this, the MAH should send reporting forms to renal centres and consider web-based reporting tools, as well as fax reporting. The MAH should submit weekly ADR/signal reports to all national competent auhorities, and more frequent ad hoc reports should be provided, if urgent need arises. As there is a background rate of aseptic peritonitis in patients undergoing dialysis, and as current reporting rates are based on spontaneous ADR reporting (c.f. solicited reports), it will be critically important to consider the signal threshold that will result in a batch being taken off the market, and the MAH should consider quantitative and/or qualitative criteria relating to this.

Further national monitoring of aseptic peritonitis
The CHMP considered that national nephrology networks should be contacted in order that they may monitor temporal trends in the incidence of aseptic peritonitis in Member States; the MAH should facilitate this.

Communications
The CHMP advised that the MAH should circulate a direct healthcare professional communication (DHPC) letter in all Member States to address the points above, in particular to provide advice on: prioritisation of supply; options for use of alternative products; clinical management of aseptic peritonitis; and to encourage ADR reporting.

4. Overall conclusions

The Committee considered the procedure under Article 5(3) of Regulation (EC) No 726/2004 on the presence of endotoxins in Baxter's peritoneal dialysis solutions initiated at the request of the United Kingdom.

The following actions are recommended to be carried out by the MAH by March or until the stock situation is normalised.

The CHMP recommended:

- To communicate on the issues identified through a DHPC letter.
- To expedite manufacturing in order to replace batches of Dianeal, Extraneal and Nutrineal that potentially contain endotoxins as soon as possible. Shortages (including alternative MAH products such as Physioneal) should be avoided and vulnerable patients should be prioritised.
- To heighten pharmacovigilance, including collection and assessment of ADR reports and information regarding aseptic peritonitis. Heightened signal detection activities and determination of causality triggers for removal of product from the market to be continuously monitored. Weekly ADR/batch signal data to be provided to all national competent authorities for a co-ordinated risk assessment.
- To collect and monitor information regarding batch recall and supply status. Weekly reports to be provided to all national competent authorities.
- To collect and assess information on manufacturing status, including changes which may affect production. Ad hoc and weekly reports to be provided to all national competent authorities.
- To facilitate national nephrology networks to gather information on trends in aseptic peritonitis rates.