EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for Dialysis solutions from Baxter group of companies and associated companies produced at Castlebar

Procedure number: EMEA/H/A-31/1290

Referral under Article 31 of Directive 2001/83/EC

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature redacted (under the format of a black box: [redacted]).

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 17 January 2011[1] the European Commission triggered a referral under Article 31 of Directive 2001/83/EC. The Committee for Medicinal Products for Human Use (CHMP) was requested to give its opinion on whether measures are necessary to ensure the safe and effective use of dialysis solutions from Baxter group of companies and associated companies produced at Castlebar[2].

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

2. Scientific discussion

2.1. Introduction

In December 2010 the CHMP was informed that a small proportion of certain Baxter peritoneal dialysis (PD) solutions (DIANEAL, EXTRANEAL and NUTRINEAL) produced at Castlebar (Baxter's manufacturing plant in Ireland) could potentially contain endotoxins. The root cause was traced to small stress cracks in two mixing tanks (Tanks F and G) used at the Castlebar manufacturing plant. The cracks caused solution to leak into a cavity leading to the formation of a biofilm which then released bioburden back into the solution tank at random intervals, resulting in increased levels of endotoxin in some units. Based on testing of recalled samples only a small minority of units in a batch were considered by Baxter to be affected but as these could not be identified all batches of EXTRANEAL, DIANEAL and NUTRINEAL produced using this manufacturing line and within expiry date were considered to be affected. Tanks F and G were removed from use and the manufacturing line subject to extensive cleaning. Exposure to endotoxin was found to be associated with an increased risk of aseptic peritonitis. At the request of the United Kingdom (UK), the CHMP started a procedure under Article 5(3) of Regulation (EC) No 726/2004 to provide recommendations to the Member States on the management of this situation. A full recall of the potentially affected products was not considered possible as there were insufficient alternatives available. Based on the information provided by Baxter, the CHMP was satisfied that the root cause had been identified and that measures had been taken to eliminate the endotoxin from the Castlebar plant. The CHMP issued recommendations to manage the problem of the presence of endotoxins and supply on 16 December 2010[3].

Further out-of-specification endotoxin results were observed in new batches manufactured as of 17 December 2010 and the Castlebar manufacturing plant was shut down and subjected to further extensive cleaning [redacted] considered effective at targeting biofilm. The production facility was cleaned and subjected to a total disinfection using a fog dispersal system. A good manufacturing practice (GMP) inspection by the Irish Medicines Board (IMB) of the Castlebar site in January 2011 raised concerns that the biofilm had spread due to the routine recirculation of sanitising agents through various tanks in a particular manufacturing area and the infrequent transfer of bulk solution from Tank F to Tank M, (and a subsequent Health Hazard Assessment from the MAH also implicated Tank H). Concern was also raised that contaminating organisms developed resistance to routine cleaning measures. This suggested that additional batches of DIANEAL, EXTRANEAL and NUTRINEAL and sodium chloride 0.9% solution for haemodialysis and the additional product Monosol solution for haemodialysis could also potentially be affected.

Following the receipt of further information from Baxter, indicating that their manufacturing problem was not resolved and the root cause not identified, an Article 31 referral procedure of Directive 2001/83/EC was initiated by the European Commission (EC). An extensive list of questions was addressed to Baxter in the framework of the Article 31 procedure to allow a thorough review of the matter.

[1] On 18 January 2011, the EC circulated an updated notification, superseding and replacing the previous one received. A correction was introduced in the list of products affected.
[2] The products involved in this referral procedure are those concerned by the Castlebar manufacturing endotoxin issue, i.e., produced at the affected lines, as defined in annex I of the Opinion. These include the peritoneal dialysis solutions DIANEAL, EXTRANEAL and NUTRINEAL; and Monosol and sodium chloride 0.9% solution for haemodialysis.
[3] For further information on the recommendations adopted, see the published Assessment report for Art 5(3) procedure: Presence of endotoxins in Baxter peritoneal dialysis solutions

Recommendations were given to minimise the use of affected product from Castlebar[4]. Taking into account the crucial nature of these medicinal products, and the means by which unaffected batches of PD solutions could be made available to patients across the EU in the shortest possible timeframe, alternatives were sought. In view of severe supply limitations for DIANEAL, EXTRANEAL and NUTRINEAL and the risk of switching patients to alternative PD solutions or therapies, the CHMP considered that the use of comparable products produced by Baxter at alternative manufacturing sites outside the EEA (European Economic Area) should be prioritised. Dialysis solutions[5] were thus imported from Canada, Singapore, Turkey and USA. All products were tested in accordance to currently approved EU specifications, as applicable. Whilst awaiting full availability of these products in the EU, a limited selected number of batches produced at Castlebar which had passed all approved specifications and an additional intensive testing for endotoxins, needed to be used to avoid interruptions of patients treatment. To meet supply demands importation of PD solutions from other sites (Canada, Turkey and USA) increased. The MAH chose to import only once from Singapore, and this manufacturing plant was no longer used as an alternative. Once sufficient quantities of the unaffected batches of PD solutions were available, a stepwise recall of Castlebar PD solutions was initiated. The CHMP agreed that until an adequate root cause and corrective measures have been identified it would not be acceptable to release new PD solutions from the Castlebar plant.

Considering the likelihood of prolonged use of large quantities of unlicensed (imported) PD solutions on the EU market, and in order to ensure continued supply of licensed medicinal products to the EU, the necessary data packages to support the inclusion of additional manufacturing sites were expedited within the article 31 referral procedure.
The available data to support inclusion of sites from which products are currently being imported (Canada, Turkey and USA) into the existing PD solutions marketing authorisations were submitted. The necessary data packages to support the inclusion of one more additional manufacturing site located in Europe (Poland) which was expected to become fully operational soon, was also expedited. In light of the uncertainty over the root cause and the future re-instatement of supply from Castlebar, the addition of manufacturing sites to the marketing authorisations aimed at mitigating future supply problems arising for PD solutions in Europe, ensuring that sufficient PD solutions are available.

A total of 12 data packages were submitted by Baxter including Alliston, Canada; Lublin, Poland; Istanbul, Turkey and North Cove, USA, and information was provided per site and per product. Modules 2 and 3 of the common technical document (CTD) were affected. Only CTD sections which were different to the approved CTD sections were included in the submissions, and this was considered acceptable.
A combined assessment for all PD solutions was presented, including product specific differences highlighted when appropriate. DIANEAL contains Glucose, EXTRANEAL contains Icodextrin and NUTRINEAL contains [redacted] (an amino acid mix), however, the products share many similarities for instance, they contain the same ingredients, are made in the same way, are packed similarly and sterilised by the same method.

A tabular overview of which products can be produced at each manufacturing site is provided below:

Manufacturing Site	**Product Manufactured**			
	EXTRANEAL	**NUTRINEAL**	**DIANEAL PD1**	**DIANEAL PD4**
Alliston, Canada	X	X		X
Istanbul, Turkey	X	X	X	X
Lublin, Poland			X	X
North Cove, USA	X			X

The CHMP reviewed all the data available for each of the four sites concerned. The timeframe necessary to address the issues identified at Castlebar, with the interruption of supply from this site, led to the need to authorise these additional manufacturing sites to ensure supply of PD solutions in Europe. Whilst all data to finalise the article 31 was not available, a stepwise approach was followed for the assessment, resulting in subsequent opinions being adopted by the CHMP.

In April sufficient data was available to recommend the inclusion of the sites located in Canada, Poland and Turkey as additional manufacturing sites to the marketing authorisations of the respective

[4] Production of all products using the affected lines at the Castlebar plant ceased on 26 January 2011.
[5] There were no supply shortages identified for sodium chloride 0.9% solution for haemodialysis and Monosol solution for haemodialysis.

peritoneal dialysis solutions. A first opinion on the inclusion of these three sites was issued by the Committee in April, and the corresponding decision from the Commission was issued on 12 May 2011. A second opinion was then issued in May to recommend the inclusion of the site located in USA as an additional manufacturing site. The corresponding decision from the Commission was issued on 13 July 2011.

The issues on changeover to products from alternative sites were thus addressed in the two initial opinions. Regarding the manufacturing site located in Castlebar, investigations into the root cause of the out-of-specifications for endotoxins, the measures proposed to prevent its reoccurrence, future supply to Europe, pharmacovigilance and communication were also thoroughly reviewed in the framework of this Article 31. The CHMP considers that sufficient information is now available to issue a third and final opinion for the article 31 procedure recommending the variation of the marketing authorisations for dialysis solutions from Baxter group of companies and associated companies produced at Castlebar, subject to conditions set out in the Annex III of the opinion. The specificities of this procedure are discussed below.

2.2. Quality

The CHMP considered the responses provided by the MAH, the feedback from the GMDP IWG on the root cause investigation and prevention of future biofilm problems, and the input from the supervisory authority on performed or ongoing local reviews or inspections.

2.2.1. Root cause

Further to the out-of-specification endotoxin results observed in batches manufactured in one area of the Castlebar manufacturing site (mainline twinbag mix/fill complex area), an investigation into the root cause of the findings was initiated. Inspection of tank F identified cracks and a reservoir of solution between the tank skin and the leg support panel, and the tank was removed from service. The leg of the tank was drilled and the solution from the leg was analysed. Tank G was also identified as having cracks and thus removed from service. Throughout the initial investigation Gram negative organisms, namely *Stenotrophomonas maltophilia* and *Sphingomonas paucimobilis*, and Gram positive organisms, namely *Cellulomonas/Microbacterium sp.*, were identified. After initial cleaning designed to sterilise the tanks and lines and replacement of some parts the issue re-emerged with further out-of-specifications for endotoxins. The impacted lines were shut down and, with the agreement of the supervisory authority (the Irish Medicines Board, IMB), the decision was taken to not restart production until the investigation was completed and a corrective action plan implemented. Based on the available data, the most likely cause of the presence of endotoxins was considered to be a biofilm that developed in the tank cavity and subsequently contaminated tanks and lines.

Cleaning and systematic dismantling and inspection of the lines (including product contact and non-product contact surfaces) were undertaken using a six sigma DMAIC (define, measure, analyse, improve, control) based root cause investigation. This included facilities and equipment, raw materials, water systems, methods, procedures and personnel. Observations for signs of wear, microbiological swabs and testing of residual water for bioburden and endotoxins were performed. Imaging techniques used in areas where unusual observations were made included scanning electron microscopy, polarised light, Fourier transform infrared (FT-IR), energy dispersive x-ray spectroscopy and coupled plasma spectroscopy. A description of the manufacturing complex at Castlebar was submitted to better understand the layout of the affected lines, including its in-process controls, sampling regimens and limits applied. The suitability of the steps in place for batch and campaign manufacture were reviewed, including any potential risks of microbial contamination. Special attention was given to cleaning regimens and hold and processing times including periods of time the equipment was left wet or filled with solutions.

Based on the results provided, microorganisms originating from cracks in tanks F and G in a difficult to clean location may have been the original cause, with potential spreading leading them to become established throughout the entire solution transmission system. It was noted that the microbiological monitoring programme was not sufficiently sensitive or targeted to quickly detect the impact of the mechanical failures. An analysis of historical records (since 2006) of endotoxin testing for relevant dialysis fluids was performed. All routine finished product endotoxin results for the released batches were below the limit of detection (LoD) of the test. Therefore, no clear marker for endotoxin was found until November 2010, when the first out-of-specification emerged. The CHMP considered however that

the test used was unreliable and a more sensitive kinetic turbidimetric limulus amebocyte lysate (LAL) method for endotoxin testing should be introduced. This would allow the detection of much lower levels of contamination, give better trend analysis and enable better process control. In addition, as it is known that other bacterial toxins can cause aseptic peritonitis (e.g. peptidoglycan) a [redacted] was proposed. The sampling strategy was also reviewed. As both Gram positive and negative organisms were found at Castlebar, a [redacted] will be implemented during the requalification phase.
The root cause investigation also made reference to water pooling in some parts of the pipe work and the slope of pipes not being adequate to facilitate drainage. The pooling of water was considered a potential contributor to the incident. In addition, the volumes of liquid used at Castlebar mean that mixing and filling take periods of time in which microorganisms can proliferate. An upgrade of equipment, including its re-design was therefore proposed.

Overall, it was confirmed that protein/biofilm were not found upon dismantling the line. However it was noted that the analysis was conducted after extraordinary cleaning which could have removed the evidence. In conclusion, a combination of factors may have played a role. This would include inadequately designed equipment, mechanical failure of equipment (cracks), methods of microbial monitoring not applied routinely and not state of the art, including outdated methods for monitoring endotoxins, and an inadequate cleaning and sanitisation regimen.

2.2.2. Corrective actions

Based on the apparent combination of factors which led to the findings of endotoxins in dialysis solutions produced at the affected line, improvements to the manufacturing process and additional controls are being introduced.
The refit of the pipework, changeboards, pumps, valves and filling equipment was undertaken with the intention to eliminate areas where pooling of water/solutions could occur. Pipe slopes were also reset to ensure that these are free draining. [redacted] Modern rapid microbial methods (RMM) applied on site (such as ATP bioluminescence as well as flow cytometry) to raw materials, excipients and finished product should reduce variability, increase turn around time and improve the quality of information. A more sensitive kinetic turbidimetric limulus amebocyte lysate (LAL) method for endotoxin testing should also be applied, and its limit of detection will be tightened for both finished product and excipients. Cleaning/sanitisation procedures were also reviewed and installation and qualification of all of the above should be reviewed by the supervisory authority through inspections before any solutions produced in these lines can be released to the market. Once this process is completed, the MAH should submit variations to the national competent authorities to update the marketing authorisations of the affected dialysis solutions, in accordance with the change management plan agreed by CHMP.

It is considered that the proposed enhancements may be adequate in preventing the occurrence of future biofilm/microbial contamination problems. Once the process qualification is reviewed by the supervisory authority, a 12 month monitoring should be undertaken. This is an intensive period of monitoring to establish that the site is performing to acceptable standards. All changes to processes, frequencies or limits resulting from the evaluation should also be submitted to the national competent authorities.

On the basis of the proposed measures, the CHMP was reassured that corrective actions are being implemented and should be subject of further monitoring. Before any release of products from Castelbar, the CHMP requests that the inspection of the Castlebar site be performed by the end of December 2011 and that the outcome of the inspection be provided to national competent authorities.

Considering the global implications of the findings at Castlebar, and proposed improvements at this manufacturing site, global corrective and preventive actions (CAPA) should be drawn up and used to audit other sites producing dialysis solutions. The MAH proposed a change management plan which was agreed by the CHMP. The outcome of global CAPA should be provided to the national competent authorities and any changes considered necessary to implement all lessons learned at Castlebar in other sites should be addressed through the appropriate change management protocols and subsequent regulatory procedures at a national level, as applicable.

2.2.3. Continuous supply

Following the initial endotoxin findings, the level of risk associated with potentially affected batches from Castlebar was addressed. This included the probability of dialysis solutions bags being affected and the clinical issues relative to aseptic peritonitis, including the severity of patient harm if presented with aseptic peritonitis.
Although it was noted that the risk of a patient using a potentially affected bag was low, measures were immediately put in place to minimise the use of affected product from Castlebar.
The CHMP expressed concern about the critical dependence of the supply of these specialist medicines on one site, from one manufacturer supplying a large percentage of the EU market. In view of severe supply limitations, in particular for DIANEAL, EXTRANEAL and NUTRINEAL, and the risk involved with switching patients to alternative PD solutions or therapies, the use of comparable products produced by Baxter at alternative manufacturing sites outside the EEA was prioritised. The MAH immediately recalled the two other products produced at the affected line (Monosol and sodium chloride 0.9% solution for haemodialysis) as there were no supply shortages identified and alternatives were available.

In the framework of this article 31 review procedure four alternative sites (located in Canada, Poland, Turkey and USA) were authorised as additional manufacturing sites for peritoneal dialysis solutions[6]. This ensured supply demands were met whilst the root cause and the future re-instatement of supply from Castlebar was being investigated.
This alternative sourcing plan was defined based, primarily on the volume demand per country, product connectology and import from one source if possible to simplify customer and patient information. The complexities of the changeover to products from alternative sites, in particular the different connectors used for different PD systems were noted by the CHMP. It was highlighted that the development of standard connectors across PD solutions and even PD solutions manufacturers could prove beneficial.
In addition, the CHMP would recommend that appropriate steps are taken to harmonise national marketing authorisations across the EU/EEA.

In addition considerations were given to the future supply strategy of PD solutions from Baxter for Europe and a contingency plan was developed taking into account the worst case scenario (e.g. a catastrophic event at Castlebar preventing its reinstatement or the production of PD solutions, raw materials' shortages). The strategy submitted by the MAH included a plan for maintenance of existing manufacturing sites, registration of additional manufacturing sites located in Italy and the UK, expansion of different sites to increase its capacity and contingency for sufficient alternative providers/stocks for raw materials. This was endorsed by the CHMP. The MAH should submit variations to increase the diversity of supply to national competent authorities in accordance with agreed timelines.

2.3. Clinical safety

The CHMP considered all responses provided by the MAH and the feedback from the PhVWP on the pharmacovigilance issues.

2.3.1. Aseptic peritonitis monitoring

Heightened pharmacovigilance, including active surveillance of all adverse drug reactions (ADRs), was undertaken by the MAH.

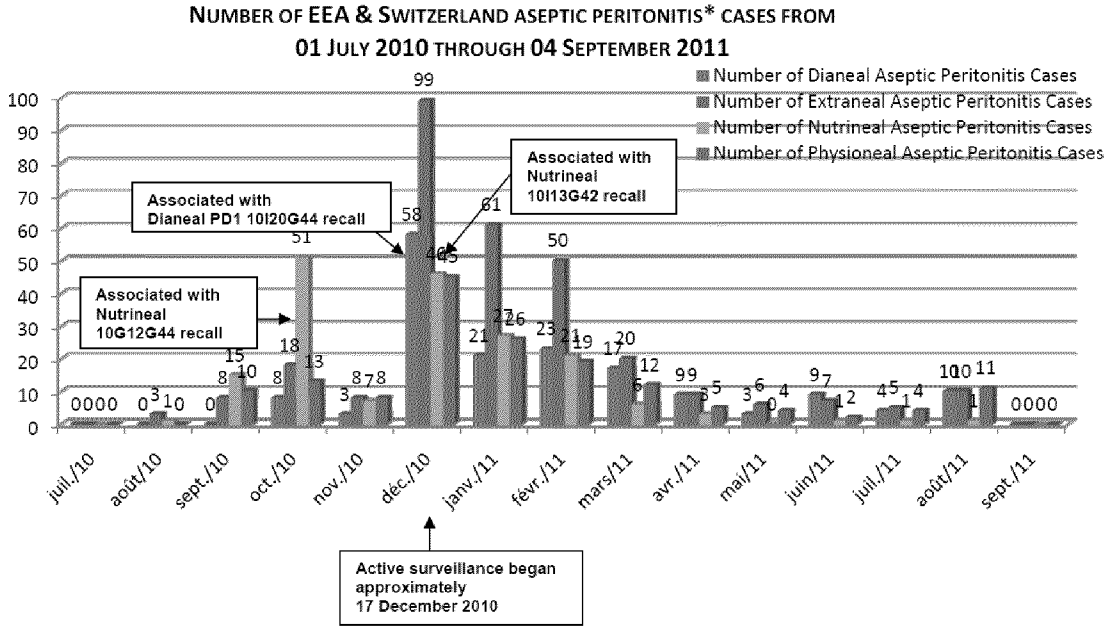
The harm induced from out-of-specifications for endotoxins in the PD solutions is the potential to develop sterile inflammation of the peritoneum, aseptic peritonitis. The peritoneal membrane is a selective semi-permeable membrane and the molecular weight of endotoxin (> 10kDa) means that only a proportion will be absorbed, making systemic effects unlikely. The most important likely clinical event associated with increased endotoxin levels in PD solutions is that the patient will observe cloudy effluent, abdominal pain, nausea, vomiting and sometimes fever, and present to their clinic where a

[6]. A first opinion on the inclusion of the sites located in Canada, Poland and Turkey as additional manufacturing sites to the marketing authorisations of the respective peritoneal dialysis solutions was issued by the Committee in April 2011, and the corresponding decision from the Commission was issued on 12 May 2011. A second opinion was issued in May 2011 to recommend the inclusion of the site located in USA as an additional manufacturing site. The corresponding decision from the Commission was issued on 13 July 2011.

presumptive diagnosis of peritonitis will be made and antibiotics will be administrated and investigations initiated. Therefore, patients who experience aseptic peritonitis not only are exposed to the symptoms associated with aseptic peritonitis but also are needlessly exposed to antibiotics (with potential unwanted side effects and the contribution to antibiotic resistance) and the risks involved with removing the PD catheter. More serious complications of aseptic peritonitis include changes to the peritoneal membrane with an acute inflammation which may affect its permeability. Patients may develop decreased ultrafiltration leading to fluid overload and associated complications.

All cases of aseptic peritonitis identified using the MedDRA (Medical Dictionary for Regulatory Activities) preferred terms peritonitis, peritoneal cloudy effluent and chemical peritonitis were reviewed within weekly reports. A review of ADRs and batch signal data was undertaken in accordance with agreed criteria[7] for batch recall in case a signal arose from the use of the dialysis solutions being monitored. The MAH presented all cases reported from use of product produced at Castlebar and PD solutions originating from alternative manufacturing sites (Canada, Poland, Turkey and USA).

The total number of aseptic peritonitis cases in the EEA associated with DIANEAL, EXTRANEAL, NUTRINEAL (and Physioneal) by month until 4 September 2011 is presented below.



* aseptic peritonitis according to the MedDRA preferred terms as defined above.

Aseptic peritonitis is included in the summary of product characteristics (SmPC) as an adverse reaction for PD solutions and was the most commonly reported adverse reaction during the period noted above. The risk for aseptic peritonitis was expected to increase if a patient was using one or several affected bags of batch/batches containing increased levels of endotoxin as this could lead to an inflammatory response affecting the peritoneum (see the period from December 2010 to March 2011 above). Most PD solutions produced in Castlebar were successfully recalled from the market by end of April 2011, and the number of reports of aseptic peritonitis decreased.

Data within the weekly reports on Monosol and sodium chloride 0.9% solution for haemodialysis did not suggest any signal. Data were limited since potentially affected products were immediately recalled from the market as no supply shortages identified for these products intended for systemic administration[8].

[7] A signal for an individual batch was defined as a number of aseptic peritonitis reports that was greater or equal to an aggregate of 5 reports assessed as probably associated or an aggregate of 10 reports assessed as possibly associated with one batch during active surveillance (with 1 probable case being the equivalent to 2 cases assessed as possibly associated).
[8] Cases of endotoxin induced systemic response could be identified using the MedDRA preferred terms pyrexia, chills, hypotension, tachycardia, tachyarrhythmia, tachypnoea, myalgia, headache and nausea. Monosol and 0.9% sodium chloride for haemodialysis products produced at the affected lines were withdrawn from the market.

The CHMP was of the agreement that weekly reports could cease, with the MAH providing assurance that they should promptly report any data suggestive of a signal with the dialysis solutions presently on the market to the appropriate national competent authorities, as defined in the risk management plan.

Cumulative review of cases with fatal outcome
The MAH provided a review of cases received with fatal outcomes from 1st September 2010 to 30th June 2011. During this period 141 cases were received but there was no suggestion that this number of cases was different from that expected under normal conditions of use i.e. without potential exposure to endotoxins. Furthermore the causes of death were similar to what is expected for this patient population.
Detailed summaries of all cases with fatal outcomes were provided and also reviewed within weekly reports. There was no clear pattern to suggest that exposure to endotoxin was associated with any other serious adverse reaction besides aseptic peritonitis including systemic reactions or that cases of aseptic peritonitis were life threatening.

The CHMP considered that there is still limited information on the cases with fatal outcomes. It was noted that information on causes of death for all cases with fatal outcomes would be sought in the proposed observational study (see section 2.3.2 below).

For completeness, the CHMP considered that a pharmacovigilance inspection should be carried out as a condition to the outcome of this article 31 procedure. Focus should be given to the timeliness of communication of safety signals to healthcare professionals or competent authorities, and the accuracy and consistency of the systems in place to collect safety information and provide it to the regulatory networks.

2.3.2. Proposed studies

In order to gather data to examine trends in peritonitis rates from 2010 through 2011 and its clinical outcomes two epidemiological studies were proposed by the MAH:

1. Clinical audit of peritonitis events across member states in order to collect data on number of events. This will entail a follow up of cases of peritonitis gathered from representative renal centres in member states (five PD units will be contacted in smaller member states and up to 20 PD units in larger countries). The total number of events, the number of culture positive peritonitis events, the number of negative peritonitis events and the number of suspected aseptic peritonitis events will be considered. Standard case definitions will be used.

2. Observational (registry type) study of endotoxin related aseptic peritonitis. This study aims to assess the severity of peritonitis episodes (including fatal outcomes) and the impact on longer term clinical outcome. This study will describe the initial clinical presentation and 6 and 12 month follow up data (in particular, membrane transport and PD therapy changes) in a group of patients experiencing likely endotoxin related aseptic peritonitis. This study will recruit and follow up patients in centres that used 3 recalled batches of PD fluids (DIANEAL, EXTRANEAL and NUTRINEAL) to maximise recruitment of patients experiencing endotoxin related aseptic peritonitis and match them as closely as possible with patients in the same centres (thus receiving similar PD therapies) who did not experience an aseptic peritonitis event. Inclusion and exclusion criteria were defined and a protocol submitted.

The CHMP agreed with the proposed studies, although some concerns were raised regarding the limited sample size of the observational study as this may not make the study sufficiently powered to draw robust conclusions, but this was accepted based on study feasibility and overall design. The MAH should submit the relevant data to national competent authorities for review, in line with the agreed milestones for evaluation and reporting as described in the RMP.

2.4. Risk management plan

The MAH submitted a consolidated risk management plan (version 2.0 dated 21 September 2011) addressing the identified risk of aseptic peritonitis and the potential risk of endotoxin related systemic inflammatory response resulting from the out-of-specifications for endotoxins, which included a risk minimisation plan.

Table summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
CLOUDY EFFLUENT / ASEPTIC PERITONITIS (DIANEAL, EXTRANEAL and NUTRINEAL)	1. Enhanced pharmacovigilance activities in line with the active surveillance implemented in December 2010 including weekly updates, direct healthcare professionals (DHPC) letter with adverse event (AE) questionnaire and weekly pharmacovigilance (PV) signalling meetings for 8 weeks after re-launch of solutions concerned by Castlebar manufacturing endotoxin issue. Baxter will provide weekly PV reports for 8 weeks after re-launch of solutions concerned by Castlebar manufacturing endotoxin issue and thereafter monthly reports for another 4 months. 2. Any data suggestive of a signal with imported or re-launched PD solutions will be promptly reported to the national competent authorities. 3. Expedited reporting of all spontaneous aseptic peritonitis independent of seriousness to all concerned member states. 4. Studies Study 1: A clinical audit which will collect data on the numbers of peritonitis events in renal centres. Study 2: An observational study which aims to examine aseptic peritonitis cases (occurring in relation to the recalled batches) in detail and will describe the severity of initial peritonitis episodes (aseptic and bacterial) and the impact on longer term clinical outcome.	Measures to reinforce reporting of batch number for PD solutions to ensure best possible capture of any batch related issue. Further DHPC and attached AE questionnaire. Quality risk minimisation activities: i. Implementation of the Kinetic Turbidimetric test for Endotoxin. ii. Update of the manufacturing process specifically related to cleaning, sanitisation and hold times. iii. Update of in-process sampling and testing specifically related to monitoring endotoxin and bioburden throughout the manufacturing process. iv. Corrective and Preventive Action (CAPA).
ENDOTOXIN INDUCED SYSTEMIC INFLAMMATORY	1. Enhanced pharmacovigilance activities in line with the active surveillance implemented in	Measures to reinforce reporting of batch number for Monosol and 0.9% sodium chloride for haemodialysis to

Safety issue	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
RESPONSE (MONOSOL and 0.9% SODIUM CHLORIDE for HAEMODIALYSIS)	December 2010 including weekly updates, DHPC letter and weekly PV signalling meetings for 8 weeks after re-launch of solutions concerned by Castlebar manufacturing endotoxin issue. Baxter will provide weekly PV reports for 8 weeks after re-launch of solutions concerned by Castlebar manufacturing endotoxin issue and thereafter monthly reports for another 4 months. 2. Any data suggestive of a signal with the re-launched Monosol and 0.9% sodium chloride for haemodialysis solutions will be promptly reported to the national competent authorities. 3. Expedited reporting of all cases suggestive of an endotoxin induced systemic inflammatory response independent of seriousness to all concerned member states.	ensure best possible capture of any batch related issue. DHPC. Quality risk minimisation activities: i. Implementation of the Kinetic Turbidimetric test for Endotoxin. ii. Update of the manufacturing process specifically related to cleaning, sanitisation and hold times. iii. Update of in-process sampling and testing specifically related to monitoring endotoxin and bioburden throughout the manufacturing process. iv. Corrective and Preventive Action (CAPA).

The CHMP, having considered the data submitted, is of the opinion that no additional risk minimisation activities are required beyond those identified above and in the risk management plan.

2.5. Overall benefit/risk assessment

An article 31 referral procedure of Directive 2001/83/EC was initiated by the European Commission (EC) following receipt of information from Baxter indicating that their manufacturing problem related to out-of-specifications results for endotoxins in dialysis solutions produced at Castlebar was not resolved and the root cause had not been identified. Products manufactured at the affected lines in Castlebar included peritoneal dialysis (PD) solutions DIANEAL, EXTRANEAL and NUTRINEAL; and Monosol and 0.9% sodium chloride for haemodialysis.

Taking into account the crucial nature of these medicinal products, and the need for unaffected batches of dialysis solutions to be made available to patients across the EU in the shortest possible timeframe, alternatives were sought. In view of severe supply limitations for DIANEAL, EXTRANEAL and NUTRINEAL and the risk of switching patients to alternative PD solutions or therapies, the CHMP considered that the use of comparable products produced by Baxter at alternative manufacturing sites outside the EEA (European Economic Area) should be prioritised, as these products were assessed to be therapeutically equivalent to the EU products, and there was sufficient reassurance regarding their quality. These dialysis solutions were thus imported from Canada, Singapore, Turkey and USA. To meet supply demands, the unprecedented importation of PD solutions from Canada, Turkey and USA increased. The Singaporean manufacturing plant was only used once and no longer considered as an alternative.
Monosol and 0.9% sodium chloride for haemodialysis solutions were promptly recalled from the market as alternatives were available.

Considering the likelihood of prolonged use of large quantities of imported PD solutions on the EU market, and in order to ensure continued supply of licensed medicinal products to the European Union, the necessary data packages to support the inclusion of additional manufacturing sites were expedited within the article 31 referral procedure. Whilst all data to finalise the article 31 was not available, a

stepwise approach was followed for the assessment, resulting in subsequent opinions being adopted by the CHMP.
Two initial opinions were issued. The first on the inclusion of the sites located in Canada, Poland and Turkey as additional manufacturing sites to the marketing authorisations of the respective peritoneal dialysis solutions was issued by the Committee in April 2011, and the corresponding decision from the Commission was issued on 12 May 2011. A second opinion was then issued in May 2011 to recommend the inclusion of the site located in USA as an additional manufacturing site. The corresponding decision from the Commission was issued on 13 July 2011.

The CHMP is now in a position to issue a third and final opinion on the article 31 review procedure focusing on the issues at the Castlebar site.

Further to the out-of-specification endotoxin results observed in batches manufactured in one area of the Castlebar manufacturing site, an investigation into the root cause was undertaken. Although protein/biofilm were not found upon dismantling the line, Gram positive and Gram negative microorganisms were identified. Overall, a combination of factors may have played a role in the findings, such as inadequately designed equipment, mechanical failure of equipment (cracks having been detected in some tanks used in the affected lines), methods of microbial monitoring not applied routinely and not state of the art, including outdated methods for monitoring endotoxins, and an inadequate cleaning and sanitisation regimen.
Enhancements of the affected line were proposed in order to prevent the occurrence of future biofilm/microbial contamination problems. New re-designed equipment was installed with the intention of minimising areas where pooling of water/solutions could occur. Modern rapid microbial methods should be applied on site to raw materials, excipients and finished product, to reduce variability, improve turn around time and improve the quality of information. A more sensitive method for endotoxin testing should be implemented and its limit of detection will be tightened for both finished product and excipients. This should allow early detection of low levels of endotoxin and trend analysis which should provide an early safety warning. Cleaning/sanitisation procedures were also reviewed and installation and qualification of all of these enhancements should be reviewed by the supervisory authority through inspections before any solutions produced in these lines can be released to the market. Once this process is completed, the marketing authorisation holder (MAH) should submit variations to the national competent authorities to update the marketing authorisations of the affected dialysis solutions. A 12 month monitoring should also be undertaken upon qualification. This will be an intensive period of monitoring to establish that the site is performing to acceptable standards. All changes to processes, frequencies or limits resulting from the evaluation should also be submitted to the national competent authorities through appropriate regulatory procedures.

On the basis of the proposed measures, the CHMP was reassured that corrective actions are being implemented and will be subject of further monitoring. The CHMP requests that the inspection of the Castlebar site be performed by the end of December 2011 and that the outcome of the inspection be provided to national competent authorities.

Considering the global implications of the findings at Castlebar, and proposed improvements at this manufacturing site, global corrective and preventive actions (CAPA) should be drawn up and used to audit other sites producing dialysis solutions, including those authorised in the framework of this procedure at the time of the first and second opinions. The MAH proposed a change management plan on the development of the CAPA which was agreed by the CHMP. The outcome of global CAPA will be provided to the national competent authorities and any changes considered necessary should be addressed through the appropriate change management protocols and subsequent regulatory procedures at a national level, as applicable.

In addition to the programme of quality improvement, future assured supply steps were developed. A plan for maintenance of existing manufacturing sites, registration of additional sites located in Italy and the UK, expansion of different sites to increase its capacity and contingency for sufficient alternative providers/stocks for raw materials was agreed. The MAH should submit variations to increase the diversity of supply, to national competent authorities in line with agreed timelines.

During the article 31, several measures were put in place in order to monitor the risk of developing aseptic peritonitis, identified as the primary risk following the use of dialysis solutions manufactured at the affected manufacturing lines in Castlebar. Weekly reports of adverse drug reactions and batch signal data was undertaken, and a batch recall performed in case a signal arose with a particular batch. This heightened pharmacovigilance was applied to products from alternative sites supplying Europe. It was noted that the risk for aseptic peritonitis increased if a patient was using one or several affected

bags of batch/batches containing increased levels of endotoxin. Further to the replacement of the product from Castlebar, mostly completed in April 2011, a decline in the number of aseptic peritonitis cases reported was observed. Following continued review until September 2011, the CHMP now considers that weekly reports can cease, and the MAH should promptly inform the appropriate national competent authorities of any data suggestive of a signal with the dialysis solutions on the market.

The product information for dialysis solutions includes the risk of peritonitis. As an additional measure, a consolidated risk management plan (RMP) specific for the re-launch of dialysis solutions manufactured at the Castlebar lines affected by the endotoxin issue has been submitted. Weekly reports will be reintroduced for eight weeks followed by four monthly reports once solutions from the Castlebar plant using the new manufacturing lines are produced. Other enhanced pharmacovigilance activities include the clinical audit that will collect data on the number of peritonitis events in the EU and an observational study to assess the severity of peritonitis episodes (including fatal outcomes) and the impact on longer term clinical outcome. Additional risk minimisation activities focus on reporting of batch numbers, communication via a direct healthcare professional communication and an adverse event questionnaire in addition to quality risk minimisation activities. The CHMP agreed with the proposed studies. The MAH should submit the relevant data to national competent authorities for review, in line with the agreed milestones for evaluation and reporting as described in the RMP.

For completeness, the CHMP considered that a pharmacovigilance inspection should be carried out. Focus should be given to the timeliness of communication of safety signals to healthcare professionals and competent authorities, and the accuracy and consistency of the systems in place to collect safety information and provide it to the regulatory networks.

In view of the above, the Committee considers that the benefit risk balance of dialysis solutions from Baxter produced at Castlebar under review through this procedure, is positive under normal conditions of use and therefore recommends the variation to the terms of the marketing authorisations, subject to the following conditions:

- **CONDITIONS TO BE FULFILLED BY THE MAH:**

1. The MAH shall update the marketing authorisations of the affected dialysis solutions with the improved microbiological analytical methodologies and inclusion of new sites for increasing the diversity of supply in accordance with the change management plan and its timelines. Variations should be submitted for assessment by the national competent authorities.

2. The MAH shall perform a 12 month monitoring after site qualification by the supervisory authority (IMB) in Castlebar. Within 90 days of the finalisation of said monitoring period, a change management plan shall be submitted to the national competent authorities. The plan shall detail all changes to processes, frequencies or limits resulting from the monitoring.

3. The MAH shall draw up global corrective and preventive actions (CAPA) and use them to prevent endotoxin contamination at other sites producing dialysis solutions. The outcome of the global CAPA shall be provided to the national competent authorities and any changes considered necessary shall be addressed through the appropriate change management protocols and regulatory procedures at a national level, as applicable.

4. The MAH shall submit to the national competent authorities, at the time of the next Periodic Safety Update Report (PSUR), a risk management plan (RMP) for all affected products using the agreed consolidated RMP, version 2.0 of 21 September 2011, which describes the products' safety concerns (cloudy effluent/aseptic peritonitis with peritoneal dialysis solutions and endotoxin induced systemic inflammatory response with haemodialysis solutions) and their risk minimisation which includes a direct healthcare professional communication and quality activities. This RMP shall follow the EU RMP template (as referenced in Volume 9a of The Rules Governing Medicinal Products in the European Union) and shall include the measures to assess the effectiveness of the risk minimisation in the agreed consolidated RMP.

5. The MAH shall perform epidemiological studies consisting of a clinical audit that will collect data on the number of peritonitis events in the EU in 2010 and 2011 and an observational study to assess the nature of peritonitis and non-peritonitis cases (including fatal outcomes) and their outcome, in accordance with the milestones for evaluation and reporting described in the consolidated RMP.

- **CONDITIONS TO BE IMPLEMENTED BY THE MEMBER STATES:**

1. The inspection of the Castlebar site by the supervisory authority (IMB) shall be performed by end of December 2011 before the solutions can be re-launched. The outcome of the inspection shall be provided to national competent authorities.

2. A pharmacovigilance inspection shall be carried out by the competent authority by end of September 2012. The outcome of the inspection shall be provided to national competent authorities.

3. During inspections of the local sites located under their territories, member states shall ensure that the MAH has appropriately transposed the experience acquired in Castlebar, in accordance with the global CAPA. Care should be taken to ensure consistency with the inspections of the Castlebar site. The outcome of the inspection shall be provided to national competent authorities.

2.6. Communication plan

Communications with healthcare professionals and EU patient organisations and provision of patient training material was undertaken by the MAH during the procedure in order to address the risks associated with the use of dialysis solutions potentially containing endotoxins and to guide transfer to product from alternative manufacturing sites. Appropriate training instructions and guidance on prioritisation of patients was provided, as applicable. Healthcare professionals were also requested to report ADRs associated with all solutions including imported products.

The MAH proposed that a Direct Healthcare Professional Communication (DHPC) letter with an adverse event questionnaire would be sent upon re-launch of dialysis solutions produced at Castlebar. The CHMP agreed with the proposed measure. The wording of the proposed communication will need to be agreed by the national competent authorities, prior to placing the product on the market.

No additional communication is required at this point in time.

2.7. Changes to the product information

There were no changes to the product information.

3. Overall conclusion

Having considered the overall submitted data provided by the MAH in writing and in the oral explanations, the CHMP concluded that the data are sufficient to conclude on the endotoxin findings at the manufacturing site located in Castlebar (Ireland).

Therefore, the CHMP recommended the variation to the terms of the marketing authorisation for the medicinal products referred to in Annex I of the Opinion.

The conditions affecting the marketing authorisations are set out in Annex III of the Opinion.

This opinion is the third and final opinion[9] issued by the Committee on the article 31 regarding out-of-specifications for endotoxins in dialysis solutions from Baxter group of companies and associated companies produced at Castlebar.

[9] A first opinion on the inclusion of the sites located in Canada, Poland and Turkey as additional manufacturing sites to the marketing authorisations of the respective peritoneal dialysis solutions was issued by the Committee in April 2011, and the corresponding decision from the Commission was issued on 12 May 2011. A second opinion was then issued in May 2011 to recommend the inclusion of the site located in USA as an additional manufacturing site. The corresponding decision from the Commission was issued on 13 July 2011.

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.