EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 April 2011
EMA/404194/2011

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

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]).

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

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, as amended. 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 produced at Castlebar by Baxter group of companies and associated companies.

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[2].

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[3], (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.

[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] 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

[3] The IMB raised concerns that cleaning solution from Tank M had been transferred to tanks used in the manufacture of Physioneal on a weekly basis thereby suggesting a possible risk with Physioneal. However, no out-of-specifications for endotoxin was reported for Physioneal.

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, as amended 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.

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. 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 ongoing 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 is expected to become fully operational soon, was also expedited. In light of the current 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 submission, and this was considered acceptable.
A combined assessment for all PD solutions is 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.

[4] Production of all products using the affected lines at the Castlebar plant ceased on 26 January 2011. In order to eliminate the biofilm the MAH proposed to replace all solution contact points and surfaces in the manufacturing line (Twinbag/mainline Mix/Fill Complex) in addition to resurfacing and polishing all tanks.
[5] There were no supply shortages identified for sodium chloride 0.9% solution for haemodialysis and Monosol solution for haemodialysis.

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. At this stage of the article 31 review procedure, sufficient data is available to recommend the variation to the marketing authorisations consisting in the inclusion of Canada, Poland and Turkey as additional manufacturing sites, as no major quality issues were identified at these sites. Presently, the information available on the USA site is insufficient to conclude on its addition, pending the outcome of a recent inspection carried out at this site. Furthermore, the opinion on the Castlebar site cannot be finalised at this stage as issues remained for resolution by the marketing authorisation holder.

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

Therefore, without prejudice to the ongoing article 31 procedure, the CHMP considers that sufficient information is available to issue a first opinion for this Article 31 procedure recommending the addition of Canada, Poland and Turkey manufacturing sites to the existing PD solutions' marketing authorisations, subject to conditions set out in the Annex IV of the opinion.
The specificities of authorisation for each site are discussed below.

2.2. Scientific discussion on chemical, pharmaceutical and biological aspects

2.2.1. Addition of Canadian finished product manufacturing site

The administrative details for the Canadian site are shown below.

Name:	Baxter Healthcare Corporation
Address:	Alliston, BAXTER CORPORATION 89 Centre Street Alliston, Ontario CANADA, L9R 1W7
Peritoneal dialysis produced at the site	Dianeal PD4 (Glucose 1.36%) Dianeal PD4 (Glucose 2.27%) Dianeal PD4 (Glucose 3.86%) Extraneal Nutrineal

Good manufacturing practice (GMP)
A GMP inspection was not performed or required in connection to the inclusion of this site. A mutual recognition agreement (MRA) exists between the EU and Canada. Therefore, the EU recognises Canadian GMP certificates and inspection findings. A Canadian GMP certificate issued on 14 January 2010 has been supplied in support of this application. Inspection of the plant occurred in May and July 2009. The site is therefore considered GMP compliant.

Drug substance
The name and address of the supplier and drug substance specification for each active substance was provided. Some active suppliers are common to the EU products, e.g. Icodextrin is supplied by [redacted] In the case of active substances common to EU no further data was required. Some suppliers of active substance have not been used in EU products and active substance master files (ASMF's) or equivalent data were not submitted for these suppliers. It is to be noted that the product

currently supplied to the Canadian market complies with the USP. Although minor differences in quality standards may be highlighted, the product currently released into the EU market through importation complies with the EU requirements. The appropriate data should be submitted to formally harmonise specifications in accordance with the current EU standards.
Summary details of relevant new sources of drug substances (and relevant differences between products) were provided and are described below.

Dianeal

Dextrose Monohydrate

Dianeal PD4 made at Alliston Canada uses Dextrose monohydrate [redacted] This is a new source of active, not present in EU approved product, and should be supported by an ASMF or equivalent data package to be submitted. The product is in compliance with the USP. An appropriate change management plan should be submitted.

Dextrose sourced from [redacted] is also used in Dianeal made at Alliston. The [redacted] source of dextrose is the same source as licensed in EU approved Dianeal and is tested to the Ph. Eur.

Extraneal

Icodextrin

The source of icodextrin is [redacted] and the drug substance from this site was previously approved. Further information was not considered necessary.

Nutrineal

[redacted] (amino acid mix)

is a blend of 15 amino acids. Nutrineal made at Alliston, Canada uses [redacted] made at [redacted]. This is a new source of active, not present in the EU approved product, and should be supported by a ASMF or suitable data package. An appropriate change management plan should be submitted. It is to be noted that the individual aminoacids that are used in the manufacture of [redacted] are manufactured by the same company for Alliston as they are for Castlebar.

All PD solutions

Sodium Chloride

[redacted] are proposed as additional suppliers for Sodium Chloride not previously licensed in the EU approved PD solutions. In order to support their inclusion in the licence an ASMF or equivalent data package should be provided for sodium chloride produced at 1) [redacted] (a Ph. Eur. compliant alternate supplier) and 2) [redacted] (a USP compliant alternate supplier).

Sodium S-Lactate

[redacted] is proposed as additional supplier for Sodium S-Lactate solution and this was not previously licensed in the EU approved PD solutions. An ASMF or data package in support of this active substance should be provided. The product complies with the USP. Lactic Acid, used as starting material for production of Sodium S-Lactate, is tested in compliance with USP. Tests for the following are not performed as they are performed on the starting material: reducing sugars and sucrose; methanol; chloride; oxalate and phosphate; and sulphate. It is considered necessary to fully explain the control of the lactic acid starting material, including the comparability of assay limits to the Ph. Eur. Aluminium and barium are not controlled in Sodium S-lactate from [redacted] Unless justified these tests should be added to the specification for Sodium S-Lactate. An appropriate change management plan should be submitted.

Calcium Chloride and Magnesium Chloride

Calcium Chloride and Magnesium Chloride are made by the same manufacturers as Castlebar. These sources are accepted and therefore further information was not considered necessary.

Control of microbial contamination / endotoxins
Some of the salt starting materials contain water for crystallisation or water, which can be risk factor for microbial contamination / microbial impurities. In addition, Ph. Eur. 5.1.1 states 'Microbiological monitoring and setting of suitable action limits may be advisable for ingredients which are liable to be contaminated because of their origin, nature or method of preparation.'
Given the concerns raised regarding the product manufactured at Castlebar (possibly associated with biofilm) together with the difficulties so far in identifying the root cause, the CHMP considered that routine microbial monitoring of all the starting materials (including excipients) should be undertaken and the appropriate change management plans submitted.

Drug product

Description and composition of the drug product

The composition of Dianeal PD4 drug product is presented in the table below.

Comparison of composition of Dianeal PD4 manufactured at Castlebar and Alliston

Glucose concentration	**1.36 % (anhydrous glucose corresponding to 1.5 % glucose monohydrate)**		**2.27 % (anhydrous glucose corresponding to 2.5 % glucose monohydrate)**		**3.86 % (anhydrous glucose corresponding to 4.25 % glucose monohydrate)**		**%age of Castlebar**
Manufacturing site	Castlebar	Alliston	Castlebar	Alliston	Castlebar	Alliston	
Active ingredients	Per 1000 ml	Per 1000 ml	Per 1000 ml	Per 1000 ml	Per 1000 ml	Per 1000 ml	
Glucose monohydrate / dextrose monohydrate	15.0 g	15.0 g	25.0 g	25.0 g	42.50 g	42.50 g	same
Sodium chloride	5.38 g	5.38 g	5.38 g	5.38 g	5.38 g	5.38 g	same
Calcium chloride dehydrate	0.184 g	0.183 g	0.184 g	0.183 g	0.184 g	0.183 g	99.45%
Magnesium chloride Hexahydrate	0.051 g	0.051 g	0.051 g	0.051 g	0.051 g	0.051 g	same
Sodium S-lactate solution	4.48 g	4.48 g	4.48 g	4.48 g	4.48 g	4.48 g	same
Water for injection	To 1000 ml	qs	To 1000 ml	qs	To 1000 ml	qs	same

As shown in the table above, the composition of Dianeal PD4 manufactured in Castlebar and in Alliston is equivalent. There is a minor difference in the quantity of Calcium Chloride dehydrate, which is less than 1% and considered insignificant.

Extraneal

The composition of Extraneal drug product is presented in the table below.

	Product manufactured in Castlebar	**Product manufactured in Alliston**		**% of Castlebar**
Name of ingredients	**Formula in g/l (100 % formulation)**	[redacted]	**Formula in g/l (100 % formulation corresponding to label claim)**	**-**
Icodextrin	75.0		75	100%
Sodium chloride	5.4		5.35	99.07 %
Calcium chloride dihydrate	0.257		0.257	100%
Magnesium chloride hexahydrate	0.051		0.051	100%
Sodium lactate solution	4.5		4.48	99.55 %
Water for injection	To 1000 ml		To 1000 ml	
Sodium hydroxide or Hydrochloric acid	qs to required pH*		qs to required pH*	

A slight difference in sodium chloride and Sodium S-Lactate concentrations was noted but the difference is less than 1% and considered insignificant.

Nutrineal

The composition of Nutrineal drug product is presented in the table below.

Comparison of composition of Nutrineal manufactured at Castlebar and Alliston

	Product manufactured in Castlebar	**Product manufactured in Alliston**	**%of Castlebar**
Name of ingredients	**Weight in g/l**	**Quantity per unit (g/1000 mL)**	
Tyrosine	0.300	0.300	100%
Tryptophan	0.270	0.270	100%
Phenylalanine	0.570	0.570	100%
Threonine	0.646	0.645	100%
Serine	0.510	0.509	99.8%
Proline	0.595	0.595	100%
Glycine	0.510	0.509	99.8%
Alanine	0.951	0.951	100%
Valine	1.393	1.393	100%
Methionine	0.850	0.849	99.8%
Isoleucine	0.850	0.849	99.8%
Leucine	1.020	1.019	99.9%
Lysine (hydrochloride)	0.955	0.955	100%
Histidine	0.714	0.714	100%
Arginine	1.071	1.071	100%
Calcium chloride dehydrate	0.184	0.183	99.5%
Magnesium chloride hexahydrate	0.051	0.0508	99.6%
Sodium S-Lactate	4.48	4.48	100%
Sodium Chloride	5.38	5.38	100%
Hydrochloric acid	0.203	qs	qs
Water for injection	To 1000 ml	qs	qs

The composition of Nutrineal manufactured in Castlebar and in Alliston are equivalent although minor differences are observed for the quantity of magnesium chloride, calcium chloride and some amino acids. The percentage difference is less than 1% in each case and not considered significant.

Pharmaceutical development
The development pharmaceutics are the same as those currently approved.

Manufacture

Manufacturing, chemical testing, packaging
BAXTER
CORPORATION
89 Centre Street
Alliston, Ontario
CANADA L9R
1W7

Chemical testing, packaging, final release
BAXTER HEALTHCARE SA
Moneen Road
Castlebar, County Mayo
Republic of Ireland

Testing
[redacted]

Batch formula

Dianeal PD4
The scale of manufacture at Alliston is between [redacted]
The scale of manufacture at Castlebar is [redacted]

Extraneal
The scale of manufacture at Alliston is [redacted]
The scale of manufacture at Castlebar is [redacted]

Nutrineal
The scale of manufacture at Alliston is between [redacted]
The scale of manufacture at Castlebar is [redacted]

Description of Manufacturing Process and Process Controls
The method of preparation is essentially the same as for other sites. Dissolution and mixing of ingredients occurs. The solution is [redacted] and filled into pre-printed PVC bags. The bags are sterilised by moist heat.
The drug product is terminally sterilised. The units are subject to a steam sterilisation cycle that should ensure that a minimum F_0 of [redacted] is delivered to the product at a cycle temperature of 121°C. An F_0 of [redacted] complies with the requirements of the Ph. Eur and is the same as delivered to bags sterilised at Castlebar.
The same type of autoclaves are used at Castlebar and Canada. Heat distribution studies showed temperatures below 250°F (121.1°C) in three batches where a value of 248.42°F (120.23°C) was shown. There is concern that temperatures below 250°F/ 121°C are permissible. There is concern that an inadequate F_0 will be delivered. Alliston has been producing PD solutions without incident for some time and is licensed [redacted] This gives assurance with regard to sterility. The MAH should clarify how autoclave validation was obtained. This is to be addressed by an appropriate change management plan.
The maximum processing time between the start of mixing and the start of sterilisation is [redacted] (Extraneal). The maximum holding time in the mix tank and processing time for Dianeal and Nutrineal, (Alliston Canada) should be stated.
It is noted that a different biological indicator than that required by the Ph. Eur. is used in the validation of sterilisation at Alliston, in accordance with the USP. The sterilisation process should be re-validated using the biological indicators as per Eur. Ph. 5.1.1. and 5.1.2. An appropriate change management plan should be provided.

Controls of critical steps and intermediates
In-process controls are similar to Castlebar. Bioburden limits are the same order of magnitude at both sites [redacted] generally accepted in the EU for moist heat sterilisation. Overall the same process controls are applied to all products at Alliston. [redacted]

Control of excipients
The following excipients are present in both Dianeal and Extraneal: water for injection; hydrochloric acid; and sodium hydroxide. The excipients are controlled according to the USP.
Water for injections is produced by distillation but presently not tested for compliance with the Ph.Eur. It complies with the USP.
Hydrochloric acid complies with the Ph.Eur. and sodium hydroxide is not presently tested to the Ph.Eur., but complies with the USP.
All excipients should be tested to the Ph.Eur. Given the concerns over control of bioburden and endotoxin, this should be tested for all excipients.

Control of drug product
Baxter provided tables and EU specifications for Alliston products. Some tests have been omitted in the US specification and some limits are wider than allowable in the EU specification.
It is to be noted that licensed medicines being imported into the EU from a non-EU country are tested according to the EU specifications, [redacted] As previously agreed at CHMP in the framework of the ongoing article 31 for all imported products, batches which do not meet in their totality the approved EU specifications are not released to the market. The appropriate efforts should be undertaken by the MAH to harmonise specifications across sites with EU requirements.

Dianeal PD 4
Batch analysis was provided for 9 batches. All batches comply with the specifications.

Extraneal
Batch analysis was provided for 10 batches. All batches comply with the specification.

Nutrineal
Batch analysis was provided for 9 batches. All batches comply with the specifications except for two sodium values which are just below the EU specification.

Container closure system
Dianeal, Extraneal and Nutrineal are packed in bags made of the same material. The compositions of the bags used in Canada are slightly different to those licensed in the EU. Both formulations are identical with the exception of the stabiliser and the lubricant.

[redacted]

The new packaging raises no safety concerns and is considered acceptable. The container has been on the market for many years.

Stability
In all cases, summary stability data are provided.

Dianeal PD 4
Up to 24 months data was presented for various presentations and all remained within specification. Weight loss remained within [redacted]

	Europe	Alliston
Shelf life	24 months	24 months
Storage statement	Do not store above 25°C	Room temperature (25 °C, 77 °F); avoid excessive heat; brief exposure to 40 °C does not adversely affect the product

Extraneal
Four batches were stored for up to 12 months at 25 ± 2°C. All parameters remained within specification. Weight loss results were within the limits [redacted] at 25°C/40%RH.

	Europe	Alliston
Shelf life	24 months	12 months
Storage statement	Do not store below 4 °C	Store at room temperature (15-25°C).

Nutrineal
Six batches were stored for up to 21 months at 25 ± 2°C. All parameters remained within specification. Weight loss remained within 2%.

	Europe	Alliston
Shelf life	24 months	18 months
Storage statement	Do not store below 4 °C	Store between 15-30 °C. Protect from light until ready to use.

It is noted that there are differences in the shelf life for the products manufactured in Canada to those manufactured at Castlebar. The shelf-life expiration dating of peritoneal dialysis (PD) solutions is primarily dependent on the rate of water loss over time. This is because flexible container systems are water vapor permeable and the resultant water loss contributes to the concentration of solutes over time. The thickness of the [redacted] overpouches used for these products also affects water loss from the primary containers. Other contributing factors to water loss are container geometry, container surface area to solution volume, sterilisation heat history, loading pattern, and container fill volumes. Actual product weight loss for specific products varies between facilities due to differences in container configurations (e.g., fill volume), container surface area to solution volume, sterilisation heat history and loading pattern.
The stability data from the products manufactured at Alliston provides reassurance on their stability profile. However, as stability data of these products manufactured in compliance with EU requirements is currently not available, a conservative approach of recommending a 12 month shelf-life across all products produced at Alliston was agreed. Stability data, including long term and accelerated in product produced in accordance with EU specifications should be provided. A change management plan should be submitted by the MAH.
The real time stability data from product produced at Alliston have shown similar trends with the approved products manufactured at Castlebar. On this basis, then the special storage conditions remain unchanged.

Regional information
Not applicable.

Product information
Product information (PI) will be provided in all the relevant EU languages. However, due to the undertaking by the MAH to ensure EU supply from sites originally supplying non-EU markets, a delay in the availability of the PI according to EU languages is expected. In the meantime, the current agreed standards for importation of product into EU, should continue to be followed.
Information on changes to the PI can be found in section 2.4.

Conclusions on quality on adding Canada as an additional manufacturing site
The CHMP considered that the data provided was acceptable and showed that inclusion of the Canadian site does not present major quality concerns.

However, the MAH should address the following:

1. All drug substances should be supported by active substance master files or appropriate data and comply with European Pharmacopoeia (Ph. Eur.) requirements.

Suppliers of active substance listed below have not previously been used in EU product and active substance master files (ASMF's) or equivalent data packages should be submitted for these suppliers. A change management plan, including timelines for implementation should be submitted within one week of Commission Decision. In addition, where applicable, they should be tested and shown to comply with the European Pharmacopoeia (Ph.Eur.), prior to the release of PD solutions to the EU market under the EU marketing authorisation.
In particular:

- Dextrose monohydrate from [redacted] made at [redacted]
- sodium chloride produced at 1) [redacted] and 2) [redacted]
- Sodium S-Lactate from [redacted]

2. The excipients water for injections and sodium hydroxide are controlled according to the United States Pharmacopoeia. These should be tested and results submitted to shown they comply with the Ph. Eur. prior to the release of PD solutions to the EU market under the EU marketing authorisation.

3. The current minimum standards for critical process parameters and limits e.g. for terminal sterilisation should be reviewed and improved, in compliance with process capabilities and best practice. Terminal sterilisation has to be expressed as a minimum exposure time to a minimum temperature as per Ph. Eur. and should be harmonised at all involved sites. Consequently bioburden specifications of the filled containers should also be harmonised. The sterilisation process should be re-validated using biological indicators as per Ph. Eur. A change management plan, including timelines for implementation should be submitted within one week of Commission Decision.

4. Routine microbial monitoring of all the starting materials (including excipients) should be undertaken and the appropriate change management plan, including timelines for implementation should be submitted within one week of Commission Decision.

5. Stability data, including long term and accelerated in products produced in accordance with EU specifications should be provided. An appropriate change management plan should be submitted within three weeks of Commission Decision.

6. Standard QP release should apply for all products released under the terms of EU marketing authorisations; in particular the QPs must be satisfied that the active substances are manufactured in accordance with EU GMP requirements. The declaration should be provided prior to the release of PD solutions to the EU market under the EU marketing authorisation.

Pending conclusion of the ongoing Article 31, the MAH should implement in all its sites the outcome of lessons learned from the findings at Castlebar, to ensure a safe product supply. In particular

7. A more sensitive kinetic turbidimetric limulus amebocyte lysate (LAL) method for endotoxin testing should be introduced. A change management plan, including timelines for implementation should be submitted within three weeks of Commission Decision.

8. The full description of manufacture (3.2.P.3) for all sites together with its critical review should be submitted. A change management plan, including timelines for implementation should be submitted within three week of Commission Decision.

Additional measures may be requested subsequently for all sites, but pending conclusion of the ongoing article 31 these cannot be identified.

2.2.2. Addition of Polish finished product manufacturing site

The administrative details for the Polish site are shown below.

Name:	Baxter Manufacturing Sp.z.o.o.
Address:	42 B Wojciechowska Str., 20-704, Lublin, Poland
Peritoneal dialysis produced at the site	Dianeal PD1 (Glucose 1.36%) Dianeal PD1 (Glucose 2.27%) Dianeal PD1 (Glucose 3.86%) Dianeal PD4 (Glucose 1.36%) Dianeal PD4 (Glucose 2.27%) Dianeal PD4 (Glucose 3.86%)

Good manufacturing practice (GMP)
A satisfactory GMP certificate dated 31 August 2010 has been supplied.

A QP declaration, dated 3 February 2011, asserted that the active pharmaceutical ingredients (APIs) suppliers operate in compliance with guidelines on GMP. This is accepted.

Lublin will carry out all of the manufacturing processes of the finished product: solution preparation, mixing, filling, sterilisation, final packaging, quality control, release; similar to the Castlebar manufacturing plant.
The drug product specifications, the analytical methods and the manufacturing process will remain the same as for Castlebar.

Drug substance
Summary details of relevant new sources of drug substances were provided and are described below.

Two sources of glucose are proposed:
(a) [redacted]
This has previously been approved for Dianeal produced at Castlebar. Further information was not considered necessary.

(b) [redacted]
This drug substance supplier has been approved for Physioneal and has a certificate of suitability (CEP R1-CEP 1997-059-Rev00). Further information was not considered necessary.

The same sources of Sodium Chloride, Calcium chloride and Magnesium chloride as used in Castlebar Dianeal are used in Lublin Dianeal. Further information was not considered necessary.

Sodium S-Lactate is sourced from [redacted]. Drug substance from this site was previously approved thus further information was not considered necessary.

Control of microbial contamination / endotoxins
Some of the salt starting materials contain water for crystallisation or water, which can be risk factor for microbial contamination / microbial impurities. In addition, Ph Eur 5.1.1 states 'Microbiological monitoring and setting of suitable action limits may be advisable for ingredients which are liable to be contaminated because of their origin, nature or method of preparation.'
Given the concerns raised regarding the product manufactured at Castlebar (possibly associated with biofilm) together with the difficulties so far in identifying the root cause, the CHMP considered that routine microbial monitoring of all the starting materials (including excipients) should be undertaken and the appropriate change management plans submitted.

Drug product

Description and composition of the drug product
The formulations produced in Poland are identical to the currently approved.

Pharmaceutical development
The development pharmaceutics are the same as those currently approved.

Manufacture
Baxter Manufacturing Sp. z.o.o.
42 B Wojciechowska Str.
20-704 Lublin
Poland

The Lublin site carries out the same functions (solution preparation, mixing, filling, sterilisation, final packaging, quality control and release) as the registered manufacturing plant in Castlebar.
A sterility assurance level (SAL) of 10^{-6}, or better, is achieved with a minimum F_0 of [redacted] (T= 121°C± 1°C).

Description of Manufacturing Process and Process Controls
The manufacturing process is equivalent to the manufacturing process performed in Castlebar. Information on the maximum batch size at Lublin was outstanding and should be stated. Validation data for these batch sizes should be provided.

Control of excipients
Water for injections complies with the Ph. Eur and satisfactory limits for bioburden and endotoxin are applied. Specifications for the excipients sodium hydroxide and hydrochloric acid should be stated along with the results of analysis. As for the active substances, the control of bioburden and endotoxin should be provided along with typical results.

Control of drug product
The specifications are broadly similar to Castlebar and satisfactory batch analysis was provided.

Container closure system
No information was present on the container. Stability data states that the same material as used at Castlebar is used, therefore this was considered appropriate.

Stability
The batches selected are representative of the product range: highest and lowest volumes/ concentrations have been selected. These solutions are packed in bags of 2L nominal volume (twin bag), for a 1500 ml fill volume and of 5L nominal volume, for a 5000 ml fill volume. The filled units are wrapped in a transparent over pouch [redacted] for all configurations.

The stability studies reported refer to 6 batches of Dianeal PD1 solution and 6 batches of Dianeal PD4. The MAH provided 12 months data when stored at 25°C/40%RH and 6 months data when stored at 40°C/25%RH. Storage conditions are appropriate for semi-permeable containers. All batches remain within specification. Weight loss of up to [redacted] is seen after 12 months. A maximum of [redacted] is permitted. From the data provided the batches seem likely to remain within specification over 24 months. As the product is similar to Castlebar dialysis fluids and packed in the same containers differences in stability would not be expected. The shelf-life and storage conditions are the same as licensed for Castlebar.

Regional information
Not applicable.

Product information
Information on changes to the PI can be found in section 2.4.

<u>Conclusions on quality on adding Poland as an additional manufacturing site</u>
The CHMP considered that the data provided was acceptable and showed that inclusion of the Polish site does not present major quality concerns.
However, the MAH should address the following:

1. Routine microbial monitoring of all the starting materials (including excipients) should be undertaken and the appropriate change management plan, including timelines for implementation should be submitted within one week of Commission Decision.

2. The maximum batch size at Lublin should be stated and the actual validation data for these batch sizes should be provided within three weeks of Commission Decision.

3. Specifications for the excipients sodium hydroxide and hydrochloric acid should be stated along with the results of analysis. This should be submitted prior to the release of PD solutions to the EU market under the EU marketing authorisation.

Pending conclusion of the ongoing Article 31, the MAH should implement in all its sites the outcome of lessons learned from the findings at Castlebar, to ensure a safe product supply. In particular

4. A more sensitive kinetic turbidimetric limulus amebocyte lysate (LAL) method for endotoxin testing should be introduced. A change management plan, including timelines for implementation should be submitted within three weeks of Commission Decision.

5. The full description of manufacture (3.2.P.3) for all sites together with its critical review should be submitted. A change management plan, including timelines for implementation should be submitted by within three weeks of Commission Decision.

Additional measures may be requested subsequently for all sites, but pending conclusion of the ongoing article 31 these cannot be identified.

2.2.3. Addition of Turkish finished product manufacturing site

The administrative details for the Turkish site are shown below.

Name:	Eczacibasi-Baxter Hastane Eczacibasi-Baxter Hastane Ürünleri San ve Tic AS
Address:	Cendere Yolu, Pirnal KeceliBahcesi, Ayazaga 3490 Istanbul, Turkey
Peritoneal dialysis produced at the site[6]	Extraneal Nutrineal[1] Dianeal PD1 (Glucose 1.36%) Dianeal PD1 (Glucose 2.27%) Dianeal PD1 (Glucose 3.86%) Dianeal PD4 (Glucose 1.36%) Dianeal PD4 (Glucose 2.27%) Dianeal PD4 (Glucose 3.86%)

[1]Nutrineal PD solutions will only be manufactured in 'Viaflex' containers at this manufacturing site.

Good manufacturing practice (GMP)

A GMP inspection was not performed or required in connection to the inclusion of this site. The site of manufacture and assembly is supported by a Certificate of GMP Compliance issued by the Hungarian competent authority (CA), based on an inspection performed in December 2010. The certificate refers to Dianeal and Extraneal peritoneal dialysis solutions, but not Nutrineal. However, given the similarity in the manufacturing processes for all the MAH's peritoneal dialysis solutions, the certificate was accepted for all solutions listed.

It was noted that batch data for this site refer to [redacted] with respect to the sterility of the drug product. This is not supported by the EU Certificate of GMP Compliance, therefore all products will be released on passing the relevant sterility testing as mentioned in the product specifications. [redacted] will not be performed prior to the approval of a suitable variation supported by a specific EU GMP inspection.

Drug substances

The name and address of the supplier and drug substance specification for each active substance was provided. Although minor differences in quality standards may be highlighted, the product currently released into the EU market through importation complies with the EU requirements. The appropriate data should be submitted to formally harmonise specifications in accordance with the current EU standards.

Summary details of relevant new sources of drug substances (and relevant differences between products) were provided and are described below.

Dianeal

Glucose

Two sources of this drug substance were proposed:

[6] The quality data submitted for each dialysis solution was similar, except that for Dianeal information on a new source of glucose drug substance was provided. The data for new sources of other drug substances were essentially the same.

(a) [redacted]
This drug substance as glucose monohydrate was previously approved. Further information was not considered necessary.

(b) [redacted]
This drug substance as glucose anhydrous had not previously been approved. However, it is supported by a satisfactory 'European Directorate for the Quality of Medicines and HealthCare' (EDQM) Certificate of Suitability (R0-CEP 2004-274-Rev 00).
The certificate also includes additional tests as follows:

Isomaltose:	0.1%
Fructose:	0.05%
Sucrose:	0.05%
Lactose:	0.05%
Total impurities:	0.5%

The certificate includes a retest period of 3 years, when stored in polyethylene (PE) bags, inside kraft paper bags, placed into a complex plastic woven container.

Batch data were provided for three batches showing compliance with the European Pharmacopoeia (Ph. Eur).
The endotoxin limit set by [redacted] is equivalent to [redacted]. Considering the specified limit of [redacted] in the drug product, it is considered that the limit test for endotoxin in the drug substance should be tightened. Updated certificates of analysis will be provided by the MAH.

Extraneal
Icodextrin
The source of icodextrin is [redacted] and the drug substance from this site was previously approved. Further information was not considered necessary.

Nutrineal
Amino Acids
The sources of amino acids remain unchanged. Further information was not considered necessary.

All PD solutions
Sodium Chloride Ph Eur
Two sources of this drug substance were provided:
(a) [redacted]
Drug substance from this site was previously approved thus further information was not considered necessary.

(b) [redacted] Drug substance from this source had not previously been approved. However, it is supported by a satisfactory EDQM Certificate of Suitability (R0-CEP 2008-105-Rev 00).

The certificate did not include information concerning the container, storage conditions and shelf life. However the MAH provided acceptable information concerning the container closure system. The primary container is a double layered plastic bag.
No stability data were provided, on the grounds that it is known that this drug substance is stable e.g. there are no degradation products in the Ph. Eur. monograph. A 12-month retest period is set for this material. When the retest period has expired the active substance is retested for compliance with approved specifications and then used immediately. This was considered acceptable.

Batch data were provided for three batches showing compliance with the Ph Eur.
No microbiological test data were provided (except the text for endotoxin required when used for parenteral forms).

Calcium Chloride Dihydrate Ph Eur
Two sources of this drug substance were provided:
(a) [redacted]
Drug substance from this site was previously approved thus further information was not considered necessary.

(b) [redacted]

This was supported by a satisfactory EDQM Certificate of Suitability (R0-CEP 2006-263-Rev 01).
The certificate includes a retest period of 48-months, when stored in PE bags, inside paper bags, cardboard drums or PP texture big-bags. This was considered sufficient and acceptable.
Batch data were provided for three batches showing compliance with the Ph Eur.
No microbiological test data were provided.

Magnesium Chloride Hexahydrate Ph Eur
Two sources of drug substance were provided:
(a) [redacted]
Drug substance from this site was previously approved thus further information was not considered necessary.

(b) [redacted]
This was supported by a satisfactory EDQM Certificate of Suitability (R0-CEP 2006-264-Rev 01).
The certificate includes a retest period of 36-months, when stored in PE bags, inside paper bags, cardboard drums or PP texture big-bags. This is considered sufficient and acceptable.
Batch data were provided for three batches showing compliance with the Ph Eur.
No microbiological test data were provided.

Sodium S-Lactate solution
The source of this drug substance is [redacted] Drug substance from this site was previously approved thus further information was not considered necessary.

Control of microbial contamination / endotoxins
Batch data showed that no microbiological bioburden testing is undertaken for the new sources of drug substances.
Some of the salt starting materials contain water for crystallisation or water, which can be risk factor for microbial contamination / microbial impurities. In addition, Ph Eur 5.1.1 states 'Microbiological monitoring and setting of suitable action limits may be advisable for ingredients which are liable to be contaminated because of their origin, nature or method of preparation.'
Given the concerns raised regarding the product manufactured at Castlebar (possibly associated with biofilm) together with the difficulties so far in identifying the root cause, the CHMP considered that routine microbial monitoring of all the starting materials (including excipients) should be undertaken and the appropriate change management plans submitted.

Drug product

Description and composition of the drug product
The formulations produced in Turkey are identical to the currently approved.

Pharmaceutical development
The development pharmaceutics are the same as those currently approved.

Manufacture
Eczacibasi-Baxter Hastane Ürünleri San ve Tic AS
Cendere Yolu, Pirnal KeceliBahcesi, Ayazaga 3490 Istanbul, Turkey

Control and release in the EEA by:
Baxter Healthcare SA
Moneen Road
Castlebar, County Mayo
Republic of Ireland

Alternative testing can be performed at following contract-lab:
[redacted]

Batch formula

Dianeal
For all the PD1 and PD4 solutions, satisfactory batch formulas are provided for both glucose monohydrate and glucose anhydrous drug substances at 1,000L.
The scale of manufacture is from [redacted]

Extraneal
The scale of manufacture at Istanbul is [redacted]
The scale of manufacture at Castlebar is [redacted]

Nutrineal
The scale of manufacture at Istanbul is between about [redacted]
The scale of manufacture at Castlebar is [redacted]

Description of Manufacturing Process and Process Controls
No other information concerning the manufacturing process than the described below was provided and it was therefore considered to be the same as that currently approved.

It was noted that the minimum target lethality of the autoclave cycle is set to Fo = [redacted] minutes, this is an acceptable lethality according to current EU guidance. Validation data for the terminal sterilisation was provided and the proposed autoclave process was accepted as the autoclave conditions are similar to those already approved.
It is noted that a different biological indicator than that required by the Ph. Eur. is used in the validation of sterilisation in Turkey, in accordance with the USP. The sterilisation process should be re-validated using the biological indicators as per Eur. Ph. 5.1.1. and 5.1.2. An appropriate change management plan should be provided.

Control of excipients
Water for injections is produced by distillation and is compliant with the Ph. Eur. No further information was therefore required.

Control of drug product
Only batch data were provided and this was considered acceptable under the understanding that the tests employed are as currently approved.

Dianeal
Batch data are provided for three batches of all strengths of PD1 and PD4 solutions, for the 2/2 pack, manufactured in between June 2010 and February 2011. All batches comply with the specifications.

Extraneal
Batch data are provided for three batches, of [redacted] manufactured on 14 and 15 February 2011. All batches comply with the specifications.

Nutrineal
Batch data are provided for one batch of [redacted] and two batches of about [redacted] manufactured between 25 January and 5 February 2011. All batches comply with the specifications.

All PD solutions
The batch data complies with the current approved Finished Product Specifications and are considered acceptable, although no sterility tests were performed.
The data were compared with batches manufactured at Castlebar – batches from both sites are similar. Once approved, product manufactured at the Turkish site will be tested for release using the specifications and analytical methods currently approved in Europe.

Container Closure System
A module 3.2.P.7 was not provided. This was accepted, given that the packaging is essentially unchanged.

Luer Connector for continuous ambulatory peritoneal dialysis (CAPD)
The luer connector currently used in CAPD bags manufactured in Istanbul [redacted]

Since the configuration of the CAPD system is such that the solution is not in contact with the luer connector until the patient begins the transfer, and the ability to sterilise the connector has been fully validated, it can be concluded that this connector has no impact on the finished product quality. This was considered acceptable.

Stability
In all cases, summary stability data are provided.
The stability study quality specification includes appropriate weight/water loss studies.
The data support a 24-month shelf life, in line with that currently approved for all the PD solutions.

Regional information
Certificate of European Pharmacopeia (CEPs) for calcium chloride dihydrate, magnesium chloride hexahydrate and sodium chloride were provided. These were acceptable.

Product information
Product information will be provided in all the relevant EU languages. However, due to the undertaking by the MAH to ensure EU supply from sites originally supplying non-EU markets, a delay in the availability of the PI according to EU languages is expected. In the meantime, the current agreed standards for importation of product into EU, should continue to be followed.
The writing on the bag is presently in Turkish; however the essential information, e.g. type of fluid (Dianeal, Extraneal, and Nutrineal), glucose strength (1.36%, 2.27% or 3.86%), expiry date, and volume (e.g. 2000 ml) are clearly written and recognisable.
Training material has been developed in conjunction with the CHMP for importation and provided to healthcare professionals to advise and reassure patients on this fact since these are the items patients are trained to routinely check with each PD exchange. A small difference in the luer connector for CAPD patients causes no risk to public health. The adaptations could even provide benefits in clinical use by removing the step to use a connection shield (Clam Shell) to cover the connection and reduce the risk of touch contamination. This is covered in the training material provided.
Information on changes to the PI can be found in section 2.4.

Conclusions on quality on adding Turkey as an additional manufacturing site
The CHMP considered that the data provided was acceptable and showed that inclusion of the Turkish site does not present major quality concerns.
However, the MAH should address the following:

1. For glucose anhydrous from [redacted] the limit test for endotoxin in the drug substance should be tightened prior to the release of PD solutions to the EU market under the EU marketing authorisation. Updated certificates of analysis should also be provided.

2. Routine microbial monitoring of all the starting materials (including excipients) should be undertaken and the appropriate change management plan, including timelines for implementation should be submitted within one week of Commission Decision.

3. The current minimum standards for critical process parameters and limits e.g. for terminal sterilisation should be reviewed and improved, in compliance with process capabilities and best practice. Terminal sterilisation has to be expressed as a minimum exposure time to a minimum temperature as per Ph. Eur. and should be harmonised at all involved sites. Consequently bioburden specifications of the filled containers should also be harmonised. The sterilisation process should be re-validated using biological indicators as per Ph. Eur. A change management plan, including timelines for implementation should be submitted within one week of Commission Decision.

4. Standard QP release should apply for all products released under the terms of EU marketing authorisations; in particular the QPs must be satisfied that the active substances are manufactured in accordance with EU GMP requirements. The declaration should be provided prior to the release of PD solutions to the EU market under the EU marketing authorisation.

Pending conclusion of the ongoing Article 31, the MAH should implement in all its sites the outcome of lessons learned from the findings at Castlebar, to ensure a safe product supply. In particular

5. A more sensitive kinetic turbidimetric limulus amebocyte lysate (LAL) method for endotoxin testing should be introduced. A change management plan, including timelines for implementation should be submitted within three weeks of Commission Decision.

6. The full description of manufacture (3.2.P.3) for all sites together with its critical review should be submitted. A change management plan, including timelines for implementation should be submitted by within three weeks of Commission Decision.

Additional measures may be requested subsequently for all sites, but pending conclusion of the ongoing article 31 these cannot be identified.

2.3. Overall conclusion

An article 31 referral procedure of Directive 2001/83/EC, as amended 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 peritoneal dialysis produced at Castlebar was not resolved and the root cause had not been identified.
Taking into account the crucial nature of these medicinal products, and the need for unaffected batches of PD 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. 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.

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 ongoing 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 is expected to become fully operational soon, was also expedited. In light of the current 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.

The CHMP reviewed all the data available for each of the four sites concerned. At this stage of the article 31 review procedure, sufficient data is available to recommend the variation to the marketing authorisations consisting in the inclusion of Canada, Poland and Turkey as additional manufacturing sites, as no major quality issues were identified at these sites. Presently, the information available on the USA site is insufficient to conclude on its addition, pending the outcome of a recent inspection carried out at this site. Furthermore, the opinion on the Castlebar site cannot be finalised at this stage as issues remained for resolution by the marketing authorisation holder.

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

Therefore, without prejudice to the ongoing article 31 procedure, the CHMP considers that sufficient information is available to issue a first opinion for this Article 31 procedure recommending the addition of Canada, Poland and Turkey manufacturing sites to the existing PD solutions' marketing authorisations, subject to conditions set out in the Annex IV. Overall, the following should be taken into account:

- All drug substances should be supported by active substance master files or appropriate data and comply with Ph Eur requirements.

- All starting materials (including excipients) should be subject to satisfactory routine control of microbial contamination and, unless justified, endotoxin testing.

- Water for injections, and other excipients, should fully comply with Ph Eur monograph requirements, where applicable.

- The current minimum standards for critical process parameters and limits e.g. for terminal sterilisation should be reviewed and improved, in compliance with process capabilities and best practice. Terminal sterilisation has to be expressed as a minimum exposure time to a minimum temperature as per Ph. Eur. and should be harmonised at all involved sites. Consequently bioburden specifications of the filled containers should also be harmonised.
The sterilisation process should be re-validated using biological indicators as per Ph. Eur..

Standard QP release should apply for all products released under the terms of EU marketing authorisations; in particular the QPs must be satisfied that the active substances are manufactured in accordance with EU GMP requirements.

Pending conclusion of the ongoing Article 31, it is expected that the MAH implements in all its sites the outcome of lessons learned from the findings at Castlebar, to ensure a safe product supply. The introduction of a more sensitive kinetic turbidimetric limulus amebocyte lysate (LAL) method for endotoxin testing and the re-submission of the full description of the manufacturing processes for all sites together with its critical review should thus be undertaken. Additional measures may be requested subsequently for these sites, but pending conclusion of the ongoing article 31 these cannot be identified.

The CHMP considers of extreme importance to retain coordination of the review of the conditions presently identified for the sites in Canada, Poland and Turkey. A harmonised European approach to supply has been in place since identification of the concern at Castlebar and the article 31 procedure remains ongoing pending resolution of the outstanding issues. The present opinion is the first of a series of entwined opinions, which may result subsequently in additional measures being requested for the sites subject of the current opinion. The coordinated review of the conditions by the CHMP will enable the appropriate harmonious adjustments with minimum impact on supply of PD solutions to the EU market.

2.4. Changes to the product information

Proposed minor amendments to the PI take into account the quality particulars in relation to the addition of the sites to the marketing authorisations, in particular the shelf-life and nature and contents of container differences. The CHMP agreed with the amendments to the product information, as detailed below:

Changes are shown as greyed boxed wording

Summary of Product Characteristics

DIANEAL PD4
6.3 Shelf life

The shelf life of the product as packaged for sale is 24 months
12 months (for medicinal product manufactured at Alliston, Canada only).
The product, once removed from its overpouch, should be used immediately

EXTRANEAL
6.3 Shelf Life

2 years.
12 months (for medicinal product manufactured at Alliston, Canada only)
The product, once removed from its overpouch should be used immediately.

6.5 Nature and Contents of Container

Flexible PVC container holding 1.5, 2.0 or 2.5 litres.

The lineo connector that may equip the Y transfer line of the twin bag, contains 10.5% of Povidone iodine ointment

1.5 L 6 units per box Single bag Sy II (luer connector)
1.5 L 6 units per box Single bag Sy III (spike connector)
1.5 L 6 units per box Twin bag Sy II (luer connector)
1.5 L 6 units per box Twin bag Sy III (spike connector)
1.5 L 6 units per box Twin bag (lineo connector)
2.0 L 8 units per box Single bag Sy II (luer connector)
2.0 L 8 units per box Single bag Sy III (spike connector)
2.0 L 8 units per box Twin bag Sy II (luer connector)
2.0 L 8 units per box Twin bag Sy III (spike connector)
2.0L 6 units per box Twin bag Sy II (luer connector)
2.0L 6 units per box Twin bag Sy III (spike connector)
2.0 L 5 units per box Single bag Sy II (luer connector)
2.0 L 5 units per box Single bag Sy III (spike connector)
2.0 L 5 units per box Twin bag Sy II (luer connector)
2.0 L 5 units per box Twin bag Sy III (spike connector)
2.0 L 5 units per box Twin bag (lineo connector)
2.5L 5 units per box Single bag Sy II (luer connector)
2.5L 5 units per box Single bag Sy III (spike connector)
2.5L 5 units per box Twin bag Sy II (luer connector)
2.5L 5 units per box Twin bag Sy III (spike connector)
2.5 L 4 units per box Single bag Sy II (luer connector)
2.5 L 4 units per box Single bag Sy III (spike connector)
2.5 L 4 units per box Twin bag Sy II (luer connector)
2.5 L 4 units per box Twin bag Sy III (spike connector)
2.5 L 4 units per box Twin bag (lineo connector)

Not all pack sizes may be marketed

NUTRINEAL
6.3 Shelf Life
2 years.
12 months (for medicinal product manufactured at Alliston, Canada only)

Patient Information Leaflet

EXTRANEAL
5. How to store extraneal

- Keep out of the reach and sight of children.
- Store in the original package.
- Do not store below 4°C.
- Do not use EXTRANEAL after the expiry date. The date is stated on the carton label and on the bag after the abbreviation Exp. and the symbol ⌛. The expiry date refers to the last day of that month.
- Dispose Extraneal as you have been trained

Volume	Number of units per box	Product configuration	Type of connector(s)
1.5L	6	Single bag (APD)	luer /spike
1.5L	6	Twin bag (CAPD)	luer / spike /lineo
2.0L	8	Single bag (APD)	luer/spike
2.0L	8	Twin bag (CAPD)	luer/spike
2.0L	6	Twin bag (CAPD)	luer/spike
2.0L	5	Single bag (APD)	luer / spike
2.0L	5	Twin bag (CAPD)	luer / spike / lineo
2.5L	5	Single bag (APD)	luer/spike
2.5L	5	Twin bag (CAPD)	luer/spike
2.5L	4	Single bag (APD)	luer / spike
2.5L	4	Twin bag (CAPD	luer / spike /lineo

The Lineo connector contains iodine.
Not all configurations may be marketed.

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanations, the CHMP concluded that the data are sufficient to support inclusion of the additional manufacturing sites located in Canada, Poland and Turkey into the existing marketing authorisations of Baxter PD solutions.

Therefore, the CHMP recommends the variations to the terms of the marketing authorisation for the medicinal products referred to in Annex I concerning the addition of three manufacturing sites (Canada, Turkey and Poland) as set out in the Annex II and for which the relevant sections of the summary of product characteristics and package leaflet, are set out in Annex III of the opinion. The conditions affecting the marketing authorisations are set out in Annex IV of the opinion.

This opinion will be followed by subsequent opinions pending resolution of the issues for inclusion of an additional manufacturing site in the USA, and the outstanding manufacturing issues at Castlebar (Ireland).

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.