ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State EU/EEA	Marketing autorisation Holder	Invented Name	Strength	Pharmaceutical form	Route of administration
Austria	Baxter Vertriebs GmbH Landstraßer Hauptstraße 99/Top2A 1031 Wien Austria	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
Belgium	Baxter S.A. Boulevard R. Branquart 80 7680 Lessines Belgium	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
Denmark	Baxter A/S Gydevang 43 3450 Allerød Denmark	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
Finland	Baxter Oy P.O. Box 270 Valimotie 15A 00381 Helsinski Finland	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
France	Baxter S.A.S 6 av. Louis Pasteur 78310 Maurepas France	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
Germany	Baxter Deutschland GmbH Edissontrasse 3-4 85716 Unterschleissheim Germany	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
Greece	Diophar A.E. Kiphissias 368 15233 Halandri Athens Greece	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use

Ireland	Baxter Healthcare Ltd Caxton Way Thetford IP24 3SE United Kingdom	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
Italy	Baxter S.p.A. Piazzale dell'Industria 20 00144 Roma Italy	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
Luxembourg	Baxter S.A. Boulevard R. Branquart 80 7680 Lessines Belgium	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
Netherlands	Baxter B.V Kobaltweg 49 3542 CE Utrecht The Netherlands	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
Portugal	Baxter Médico Farmacêutica Lda Sintra Business Park, Zona Industrial da Abrunheira, Edificio 10 2710-089 Sintra Portugal	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
Spain	Baxter S.L Poligono Industrial Sector 14 c/Pouet de Camilo, 2 46394 Ribarroja del Turia (Valencia) Spain	Extraneal	Icodextrina 7.5%	Solution for peritoneal dialysis	Intraperitoneal use
Sweden	Baxter AB Box 63 16494 Kista Sweden	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use

United Kingdom	Baxter Healthcare Ltd Caxton Way, Thetford IP24 3SE United Kingdom	Extraneal	Icodextrin 7.5%	Solution for peritoneal dialysis	Intraperitoneal use

ANNEX II

SCIENTIFIC CONCLUSIONS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF EXTRANEAL

Introduction

Extraneal is an isotonic solution of 7.5% icodextrin. The product also contains as active ingredients sodium lactate, sodium chloride, calcium chloride and magnesium chloride. It is presented as a sterile solution in 1.5, 2.0 and 2.5 liter bags and it is intended for peritoneal dialysis.

Extraneal is recommended as a once daily replacement for a single glucose exchange as part of a continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) regimen for the treatment of chronic renal failure, particularly for patients who have lost ultrafiltration on glucose solutions, because it can extend time on CAPD therapy in such patients.

Following occurrence of increased reported cases of Aseptic Peritonitis (AP) in 2002 and then in 2007, Baxter committed to the Reference Member State (UK) to vary the marketing authorisation in order to include a peptidoglycan test to the drug product specification. Accordingly, the variation application was submitted to update the finished product specification by including the peptidoglycan test. Previously this limit was not part of the finished product specification.

UK as RMS had clearly highlighted the limitations associated with the proposed method as being insensitive to control the level of PG in the finished product in a meaningful way, considering that the proposed limit of PG in the finished product was higher than the toxin level seen in the 2007 cluster of AP. The NL brought to the attention of the UK, towards the end of the procedure, the existence of a more sensitive version of the SLP method (SLP-HS) that would be capable of detecting the PG levels down to 0.5 ng/ml in the finished product. In addition NL requested the manufacturing process of the active substance (icodextrin) to be improved in order to limit possible future contamination with peptidoglycans and related occurrence of sterile peritonitis. Both issues were considered potential serious risks to public health and were the basis for triggering the referral.

As no agreement was reached by NL on 9 July 2009 on the draft decision of the RMS, the procedure was referred to the CHMP according to Article 6(12) and the Referral procedure was initiated on 23 July 2009 with the adoption of a CHMP List of Questions to be addressed by the MAHs.

Quality issues

Investigation revealed that the presence of elevated levels of peptidoglycan (PG) in Extraneal batches was associated with the reports of aseptic peritonitis. All batches used icodextrin material supplied by the same manufacturer. Peptidoglycans originate from the breakdown of the cell wall of thermophilic, gram-positive bacteria that are commonly found in maltodextrin, a maize starch derivative that is used as raw material for the manufacture of icodextrin.

The proposed method of analysis to determine the level of peptidoglycans (PG) in the finished product using Wako Silk Worm Larvae Plasma **(**SLP) method has been assessed. It was concluded that the method of analysis was not able to detect the PG level precisely, accurately and consistently and hence does not support the proposed limit in the finished product. Tighter control of PG in the finished product can be achieved by controlling the active substance. Historically the cause of PG induced peritonitis has always been linked with contaminated active substance. Controls over the active substance were therefore likely to limit the occurrence of peritonitis and ensure better control the finished product. The variation to include a limit for PG in the finished product was considered beneficial in considering the possibility of an unexpected rise in PG in the finished product.

The limit proposed by the applicant was higher than the level of PG observed to be associated with the 2007 cluster of AP, therefore there was clinical evidence that the limit proposed for the finished product specification was too high. It has become apparent that a more sensitive analytical method is

available i.e. Wako High Sensitivity Silk Worm Larvae Plasma assay or (SLP –HS). This method is able to detect lower amounts of PG (i.e. 0.5 ng/ml) in the finished product. The applicant was asked therefore to set acceptable limits for PG with the improved method.

Baxter agreed setting tighter specification limit for PG in the finished product together with a lower limit for PG in the active substance, to allow patients adequate safety margins. In addition the new SLP-HS method will be implemented by the end of December 2009.

In view of the circumstances, the proposed limit for peptidoglycans in the aactive substance was considered acceptable until the end of the year. It corresponds to the limit of quantitation of the current SLP test. It is expected that the peptidoglycan levels in the drug product are indirectly controlled as well as the active substance currently appears to be the only source of this contamination. Nevertheless, in order to rule out contamination with PG from sources other than the API, peptidoglycan levels should be controlled at the lowest possible level in the drug product as well.

In addition the MAH committed to implement the more sensitive SLP-HS assay by the end of the year in order to better control the quality of the active substance and finished product. It should allow on peptidoglycan limit for the drug product which is considered to be sufficiently low from a chemical-pharmaceutical and toxicological point of view.

Moreover since it has not been possible to improve in short term manufacturing process of the active substance in one of currently approved manufacturing sites, this site will be removed by the end of the year for the European market and globally by the end of next year. The issue was resolved from a chemical-pharmaceutical point of view. However considering the decreased risk established by mitigating measures: the MAH has to put every effort in minimising availability problems. Patient demand being unfulfilled is unacceptable. The MAH should put every effort in upgrading the production to prevent shortage.

The overall conclusion is that proposed plan presented by Baxter is acceptable. The MAH has agreed to implement the more sensitive assay in a timely manner, has agreed to cease use of the active substance from the manufacturing site where manufacturing process could not be improved.

At the time of the CHMP opinion, there were minor unresolved quality issues, which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measure after the opinion, within an agreed timeframe.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

The National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions relating to quality aspects are fulfilled by the Marketing Authorisation Holders within the specified time frame:

- Variations to add the new SLP-HS method and limits to the active substance (API) and finished product specifications will be submitted no later than the end of December 2009;
- The Roquette Frères manufacturing site for the active substance will be removed from EU licences via appropriate variation procedure by February 2010.