VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

In Europe, it is estimated that more than 10% of people are affected by kidney disease. The number of patients with end-stage kidney disease is estimated to continue to rise at a rate of 5% to 8% each year in developed countries. People with chronic (long-term) kidney disease are at high risk for end-stage kidney disease and may benefit from treatment with peritoneal dialysis. The peritoneal cavity is the cavity in the belly where dialysis solution can be placed to allow removal of water and waste products from the blood. Without treatment to remove water and waste products from the blood, patients with end-stage kidney disease can die. Peritoneal dialysis is a well-known treatment for end-stage kidney disease, especially for long-term treatment.

VI.2.2 Summary of Treatment Benefits

A kidney transplant is the best treatment for end-stage kidney disease, but kidney transplants are not always possible and may not happen right away. Instead of a kidney transplant, or while a patient waits for a kidney transplant, a patient can be placed on PD to help them live. The goals of PD therapy are to maintain the condition of the peritoneum and to maintain adequate exchange of waste and fluids, which helps to keep patients on PD long-term, in order to prevent serious outcomes, including death, due to end-stage kidney disease.

PD solutions with dextrose (sugar) in them have been commonly used for the last 35 years. Optimal use of PD solutions with dextrose in them is limited to two to eight hours at a time. EXTRANEAL does not have dextrose in it; instead, the main ingredient in EXTRANEAL is called icodextrin. Because EXTRANEAL has icodextrin in it, it can be

used for a longer period of time (6 to 12 hours in continuous ambulatory peritoneal dialysis and 14 to 16 hours in automated peritoneal dialysis).

The main EXTRANEAL clinical studies included 776 patients aged between 18 and 86 years old. The studies showed that EXTRANEAL works just as well as a dextrose (sugar) based solution called DIANEAL. Also, one study, which included 26 patients with diabetes, showed that EXTRANEAL works the same in patients with diabetes as it does in the patients without diabetes.

VI.2.3 Unknowns Relating to Treatment Benefits

EXTRANEAL clinical studies did not exclude subjects of certain ethnicities, but the majority of patients studied were Caucasian or Black. The numbers of Hispanic, Asian, and patients of other populations were too small to study. It is unlikely that the safety or benefits of EXTRANEAL are affected by race.

EXTRANEAL clinical studies excluded children and pregnant or breastfeeding females. The potential risks and benefits for each specific patient must be carefully considered before using EXTRANEAL.

VI.2.4 Summary of Safety Concerns

Table 38. Important Identified Risks

Risk	What is Known	Preventability
Peritonitis (Cloudy effluent/Aseptic peritonitis)	Peritonitis is a known risk of PD therapy and may be severe. At the start of peritonitis, a patient may have cloudy peritoneal fluid. Peritonitis is usually due to an infection and is confirmed by testing the peritoneal fluid. If the peritoneal fluid test does not show an infection, then the peritonitis is called aseptic or sterile peritonitis.	The EXTRANEAL SmPC and PL include information regarding the risk of peritonitis. Baxter has put in place different steps that lower the risk of peritonitis happening due to parts of bacteria (for example, parts of bacteria called peptidoglycans or endotoxins) in EXTRANEAL. Patients should follow all instructions from their doctor, nurse, or clinic, and should use aseptic technique during every PD exchange. It is important to know that the risk of peritonitis is not completely removed by these actions. Patients should tell their doctor immediately if they think they have peritonitis.
Blood sugar tests that show a higher blood sugar level than the	Blood sugar tests and test strips that show a higher blood sugar	Only certain glucometers and test strips should be used on patients

Table 38. Important Identified Risks

Risk	What is Known	Preventability
actual blood sugar level (Falsely elevated glucose readings due to use of GDH-PQQ-, GDO-, or some GDH-FAD-based glucometers and test strips)	level than the actual blood sugar level can lead to severe consequences. This happens when the wrong blood sugar tests (glucometers) and/or test strips are used for patients who use EXTRANEAL.	using EXTRANEAL. Patients who use EXTRANEAL are given special tools to help them and their caregivers know which glucometers and test strips are safe to use. Baxter makes it clear in the EXTRANEAL SmPC and PL that falsely elevated glucose readings can occur with the use of certain glucometers and test strips.
Allergic reactions (Hypersensitivity reactions)	Allergic reactions may be mild, moderate, or severe.	Baxter makes it clear in the EXTRANEAL SmPC and PL that an allergic reaction to EXTRANEAL can happen. Patients should not use EXTRANEAL if they are allergic to any ingredients in the medicine. Patients must tell their doctor immediately if they have an allergic reaction. The doctor/ patient may need to stop EXTRANEAL treatment.
Not enough fluid in the body (Hypovolemia)	EXTRANEAL can cause too much fluid to be taken from the body, possibly resulting in not enough fluid left in the body.	Patients should be monitored for underhydration. An accurate record of the patient's fluid intake and output should be kept and the patient's body weight monitored. The EXTRANEAL SmPC and PL include information regarding the risk of hypovolemia.
Low sodium levels in the blood (Hyponatremia)	EXTRANEAL can cause decreased sodium levels in the blood.	Blood sodium levels should be evaluated periodically. The EXTRANEAL SmPC and PL include information regarding the risk of hyponatremia.
The belly's protective and filtering layer becomes thick and hard and as a result does not allow for the flow of the PD solution. EPS causes inflammation in the abdomen (belly) and thickening of the intestines that may be associated with abdominal pain, abdominal distention, or vomiting.	How EPS happens exactly is not known. It is possible that experiencing peritonitis many times and/or using peritoneal dialysis solutions for a long time may increase the risk for EPS. Patients can get EPS with any kind of PD treatment.	It is difficult to detect EPS at an early stage. Patients who are suspected of having EPS should switch to hemodialysis therapy. The EXTRANEAL SmPC and PL include information regarding the risk of EPS.

Table 38. Important Identified Risks

Risk	What is Known	Preventability
(Encapsulating peritoneal sclerosis (EPS))		

Table 39. Important Potential Risks

Risk	What is Known (Including Reason Why it is Considered a Potential Risk)
High levels of lactic acid in the blood (Lactic acidosis, especially in patients with conditions known to increase the risk of lactic acidosis)	EXTRANEAL can cause increased lactic acid levels in the blood.

Table 40. Missing Information

Risk	What is Known
Lack of studies in children younger than 18 years of age	No studies of EXTRANEAL have been performed in children younger than 18 years of age. EXTRANEAL is not recommended for use in children younger than 18 years of age.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists, and other healthcare professionals with details on how to use the medicine, the risks, and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measures).

These additional risk minimization measures are for the following risk:

Table 41. Blood sugar tests that show a higher blood sugar level than the actual blood sugar level (Falsely elevated glucose readings due to use of GDH-PQQ-, GDO-, or some GDH-FAD-based glucometers and test strips)

Risk Minimization Measure(s): - Communicate the risks of using glucometers which should not be used with EXTRANEAL to patients and caregivers.
Objective and Rationale: By providing patients and caregivers with the tools described below, the instances of hypoglycemic events related to using glucometers and/or test strips which should not be used with EXTRANEAL can be minimized.
Summary description of main additional risk minimization measures: Agreements to share information on reports of these cases (called safety data exchange agreements) have been made with key global manufacturers of glucometers known to interfere with EXTRANEAL. The following tools and a website have been provided by Baxter: - EXTRANEAL Wallet Card to communicate the risk of potential incorrect blood glucose reading to healthcare professionals (potentially on behalf of an unconscious patient) - EXTRANEAL Hospital Admission Kit to provide information to HCPs (including paramedics where appropriate) - EXTRANEAL Glucose Wearable Warning Item to provide a constant patient reminder of the warning and to communicate the warning information to HCPs - Website content to include downloadable versions of warning message on glucose monitor interference, links to existing EXTRANEAL labeling, letters for clinicians and paramedics, a Country Specific Glucose Monitor List, and a contact link. All information on the website is translated into all official languages spoken within each country or region.

VI.2.6 Planned Post-Authorization Development Plan

Table 42. List of Studies in Post-Authorization Development Plan

Study/Activity (Including Study Number)	Objectives	Safety Concerns/ Efficacy Issue Addressed	Status	Planned Date for Submission of (Interim and Final) Results
Effectiveness check survey study	• To assess understanding of the EXTRANEAL risk minimization tools • To determine whether the respondents of the survey	Falsely elevated glucose readings due to use of GDH-PQQ-, GDO-, or some GDH-FAD-based glucometers and test strips	Planned	The effectiveness check study protocol will provide more detailed timelines.

Table 42. List of Studies in Post-Authorization Development Plan

Study/Activity (Including Study Number)	Objectives	Safety Concerns/ Efficacy Issue Addressed	Status	Planned Date for Submission of (Interim and Final) Results
	understand instruction and would take appropriate action as a result of the tools			

Studies which are a Condition of the Marketing Authorization

There are no studies which are conditions of the marketing authorization.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Table 43. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety concerns	Comment
1	15 FEB 2007	Cloudy effluent	Included in initial RMP
		Hypoglycemic events	Included in initial RMP
3	31 OCT 2007	Cloudy effluent/aseptic peritonitis	Revised wording of previous identified risk to include aseptic peritonitis
		Hypoglycemia events/ interference with glucose monitoring systems	Revised wording of previous identified risk to specify interference with glucose monitoring systems
4	22 FEB 2012	Falsely elevated glucose readings due to use of GDH-PQQ-, GDO-, or GDH-FAD-based glucometers and test strips	Revised wording of previous identified risk, “Hypoglycemic events/ interference with glucose monitoring systems”
		Hypersensitivity reactions Toxic epidermal necrolysis (TEN) Angioedema Erythema multiforme Vasculitis	Added as an important identified risk

Table 43. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety concerns	Comment
		Hypervolemia/ Hypovolemia	Added as an important identified risk
		Hyponatremia	Added as an important identified risk
		Lactic acidosis, especially in patients with conditions known to increase the risk of lactic acidosis	Added as an important potential risk
		Encapsulating peritoneal sclerosis (EPS)	Added as an important potential risks
		Lack of clinical data in pediatric population (<18 years of age)	Added as important missing information
5	22 FEB 2013	There were no changes to the safety concerns for EXTRANEAL.	--
6	08 OCT 2015	Cloudy effluent/Aseptic peritonitis	Additional risk minimization measures were fulfilled
		Hypersensitivity reactions	Revised wording of previous identified risk to be comprehensive of all manifestations of hypersensitivity reactions
		Hypovolemia	Revised wording per Good Pharmacovigilance Practices definitions
		Encapsulating peritoneal sclerosis (EPS)	Revised from important potential risk to important identified risk