PRODUCT MONOGRAPH

# EXTRANEAL

Icodextrin, Sodium Chloride, Sodium Lactate, Calcium Chloride, Magnesium Chloride

75 g/L Icodextrin
5.35 g/L Sodium Chloride
4.48 g/L Sodium Lactate
257 mg/L Calcium Chloride
51 mg/L Magnesium Chloride

Peritoneal Dialysis Solution

BAXTER CORPORATION
Mississauga, Ontario L5N 0C2

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Icodextrin, Sodium Chloride, Sodium Lactate, Calcium Chloride, Magnesium Chloride

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | All Nonmedicinal Ingredients |
|---|---|---|
| Intraperitoneal | 75 g/L icodextrin<br>5.35 g/L sodium chloride<br>4.48 g/L sodium lactate<br>257 mg/L calcium chloride<br>51 mg/L magnesium chloride | Hydrochloric acid (For pH adjustment)<br>Sodium Hydroxide (For pH adjustment)<br>Water for Injection |

### INDICATIONS AND CLINICAL USE

EXTRANEAL (icodextrin, sodium chloride, sodium lactate, calcium chloride, magnesium chloride) is indicated for use as an osmotic agent for long dwell, up to 12 hours, in continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD), where it can be used for 14 and up to 16 hours.

### CONTRAINDICATIONS

- EXTRANEAL is contraindicated for use in patients with:
  - acute renal failure
  - an allergy to starch-based polymers (e.g., corn starch) and/or icodextrin
  - maltose or isomaltose intolerance.
  - glycogen storage disease
  - pre-existing severe lactic acidosis
  - uncorrectable mechanical defects that prevent effective PD or increase the risk of infection
  - documented loss of peritoneal function or extensive adhesions that compromise peritoneal function

- The product is also contra-indicated in patients with a history of abdominal surgery in the month preceding commencement of therapy, patients with abdominal fistulae, tumors, open wounds, herniae or other conditions which compromise the integrity of the abdominal wall, abdominal surface or intra-abdominal cavity - in common with other peritoneal dialysis fluids until healing is complete. In patients with impaired respiratory function or potassium deficiency, peritoneal dialysis may also be contraindicated.

- EXTRANEAL is not recommended for use in children.

**Use in Pregnancy & Lactation**

- No data from animal studies on the effects of EXTRANEAL on reproduction or lactation are available and therefore, EXTRANEAL solution should not be used during pregnancy or lactation. Women of childbearing potential should be treated with EXTRANEAL solution only when adequate contraceptive precautions have been taken. Potential effects on male and female fertility are unknown.

## WARNINGS AND PRECAUTIONS

### Warnings

**General**

Blood glucose measurement in patients receiving EXTRANEAL must be done with a glucose-specific method (monitor and test strips) to avoid interference by maltose or other metabolites of EXTRANEAL[1]. Maltose interference results in inaccurate blood glucose measurement which could lead to errors in the administration of insulin to any Extraneal patient, and also in the overall management of diabetes in diabetic Extraneal patients. Glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase (GDO)-based methods must not be used. Also, the use of some glucose monitors and test strips using glucose dehydrogenase flavin-adenine dinucleotide (GDH-FAD) methodology has resulted in falsely elevated glucose readings due to the presence of maltose. The manufacturer(s) of the monitor and test strips should be contacted to determine if icodextrin or maltose causes interference or falsely elevated glucose results.

If GDH-PQQ, GDO, or GDH-FAD-based methods are used, using EXTRANEAL may cause a falsely high glucose reading which could result in the administration of more insulin than needed. Administration of more insulin than needed has caused hypoglycemia, which has resulted in loss of consciousness, coma, neurological damage and death. Additionally, falsely elevated blood glucose measurements due to maltose interference may mask true hypoglycemia and allow it to go untreated with similar consequences.

Falsely elevated glucose levels may be measured up to two weeks following cessation of EXTRANEAL(icodextrin) therapy when GDH-PQQ, GDO, or GDH-FAD-based blood glucose monitors and test strips are used.

Because GDH-PQQ, GDO, and GDH-FAD-based blood glucose monitors may be used in hospital settings, it is important that the health care providers of all peritoneal dialysis patients using EXTRANEAL(icodextrin) carefully review the product information of the blood glucose testing system, including that of test strips, to determine if the system is appropriate for use with

EXTRANEAL(icodextrin).

To avoid improper insulin administration, educate all patients on EXTRANEAL therapy to alert health care providers of this interaction whenever they are admitted to the hospital.

Encapsulating peritoneal sclerosis (EPS) is considered to be a known, rare complication of peritoneal dialysis therapy. EPS has been reported in patients using peritoneal dialysis solutions including EXTRANEAL. Fatal outcomes of EPS have been reported with EXTRANEAL.

If peritonitis occurs, the choice and dosage of antibiotics should be based upon the results of identification and sensitivity studies of the isolated organism(s) when possible. Prior to identification of the involved organism(s), broad-spectrum antibiotics may be indicated.

Rarely, serious hypersensitivity reactions to EXTRANEAL have been reported such as toxic epidermal necrolysis, angioedema, serum sickness, erythema multiforme and vasculitis. Anaphylactic/anaphylactoid reactions may occur. Stop the infusion immediately and drain the solution from the peritoneal cavity if any signs or symptoms of a suspected hypersensitivity reaction develop. Appropriate therapeutic countermeasures must be instituted as clinically indicated.

Patients with severe lactic acidosis should not be treated with lactate-based peritoneal dialysis solutions. It is recommended that patients with conditions known to increase the risk of lactic acidosis [e.g. severe hypotension or sepsis, hepatic failure and/or renal failure, inborn errors of metabolism, treatment with drugs such as metformin[2] and nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)[3]] must be monitored for occurrence of lactic acidosis before the start of treatment and during treatment with lactate-based peritoneal dialysis solutions.

When prescribing the solution to be used for an individual patient, consideration should be given to the potential interaction between the dialysis treatment and therapy directed at other existing illnesses. Serum potassium levels should be monitored carefully in patients treated with cardiac glycosides. For example, rapid potassium removal may create arrhythmias in cardiac patients using digitalis or similar drugs; digitalis toxicity may be masked by hyperkalemia, hypermagnesemia, or hypocalcemia. Correction of electrolytes by dialysis may precipitate signs and symptoms of digitalis excess. Conversely, toxicity may occur at suboptimal dosages of digitalis if potassium is low or calcium high.

## Precautions

### General

EXTRANEAL is intended for intraperitoneal administration only. Not for intravenous administration.

Do not administer if the solution is discoloured, cloudy, contains particulate matter or shows

evidence of leakage or if seals are not intact.

The drained fluid should be inspected for the presence of fibrin or cloudiness which may indicate the presence of peritonitis.
Safety and effectiveness in pediatric patients have not been established.

Protein, amino acids, water-soluble vitamins and other medicines may be lost during peritoneal dialysis and may require replacement.

Peritoneal dialysis should be done with caution in patients with: 1) fecal fistula, colostomy, large polycystic kidneys, or other conditions that compromise the integrity of the abdominal wall, abdominal surface, or intra-abdominal cavity; and 2) other conditions including aortic graft placement.

Patients should be carefully monitored to avoid over- and under hydration. An accurate fluid balance record should be kept and the patient's body weight monitored.

Overinfusion of an EXTRANEAL volume into the peritoneal cavity may be characterized by abdominal distension, feeling of fullness and/or shortness of breath.

Treatment of EXTRANEAL overinfusion is to drain the EXTRANEAL from the peritoneal cavity.

Potassium is omitted from EXTRANEAL solutions due to the risk of hyperkalemia.

- In situations in which there is a normal serum potassium level or hypokalemia, the addition of potassium chloride (up to a concentration of 4 mEq/L) may be indicated to prevent severe hypokalemia and should be made after careful evaluation of serum and total body potassium, only under the direction of a physician. (**See Monitoring and Laboratory Tests).**

In diabetic patients, blood glucose levels should be regularly monitored and the dosage insulin or other treatment for hyperglycemia should be adjusted following initiation of treatment with EXTRANEAL. Appropriate monitoring of blood glucose should be performed and insulin dosage adjusted if necessary.

Because the use of EXTRANEAL interferes with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase based blood glucose measurements, diabetic patients should be instructed to use only glucose-specific glucose monitors and test strips. (**See Monitoring and Laboratory Tests)**.

Fluid, haematology, blood chemistry and electrolyte concentrations should be monitored periodically, including, magnesium and bicarbonate. If serum magnesium levels are low, oral magnesium supplements or peritoneal dialysis solutions containing higher magnesium concentrations may be used. Decreases in serum sodium and chloride have been observed in patients using EXTRANEAL.

**Monitoring and Laboratory Tests**

Blood glucose measurement must be done with a glucose-specific method to prevent maltose interference. Glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase (GDO)-based methods must not be used[2]. Also, the use of some glucose monitors and test strips using glucose dehydrogenase flavin-adenine dinucleotide (GDH-FAD) methodology has resulted in falsely elevated glucose readings due to the presence of maltose (**See WARNINGS AND PRECAUTIONS)**.

An apparent decrease in serum amylase activity has been observed in patients administered EXTRANEAL[4].

## ADVERSE REACTIONS

### Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

| **Clinical Trial Adverse Reactions**[†] | | | |
|---|---|---|---|
| **System Organ Class (SOC)** | **Preferred MedDRA Term** | **Frequency*** | **Frequency Percentage or Ratio N=493** |
| **INFECTIONS AND INFESTATIONS** | Influenza | Uncommon | 0.6 |
| | Furuncle | Uncommon | 0.2 |
| | Infection | Uncommon | 0.2 |
| **BLOOD AND LYMPHATIC SYSTEM DISORDERS** | Anemia | Uncommon | 0.4 |
| | Leukocytosis | Uncommon | 0.6 |
| | Eosinophilia | Uncommon | 0.2 |
| **ENDOCRINE DISORDERS** | Parathyroid disorder (Increased intact-PTH) | ** | ** |
| **METABOLISM AND NUTRITION DISORDERS** | Dehydration | Common | 2.0 |
| | Hypovolemia | Common | 1.0 |
| | Hypoglycemia | Uncommon | 0.4 |
| | Hyponatremia | Uncommon | 0.4 |
| | Hyperglycemia | Uncommon | 0.2 |
| | Hypervolemia | Uncommon | 0.8 |
| | Anorexia | Uncommon | 0.8 |
| | Hypochloremia | Uncommon | 0.8 |
| | Hypomagnesemia | Uncommon | 0.4 |
| | Hypoproteinemia | Uncommon | 0.4 |
| **PSYCHIATRIC DISORDERS** | Thinking abnormal | Uncommon | 0.2 |
| | Anxiety | Uncommon | 0.2 |
| | Nervousness | Uncommon | 0.2 |

| | | | |
|---|---|---|---|
| **NERVOUS SYSTEM DISORDERS** | Dizziness | Common | 1.8 |
| | Headache | Common | 1.4 |
| | Hyperkinesia | Uncommon | 0.2 |
| | Parathesia | Uncommon | 0.6 |
| | Ageusia | Uncommon | 0.2 |
| **EAR AND LABYRINTH DISORDERS** | Tinnitus | Common | 3.6 |
| **CARDIAC DISORDERS** | Cardiovascular disorder | Uncommon | 0.2 |
| | Tachycardia | Uncommon | 0.2 |
| **VASCULAR DISORDERS** | Hypotension | Common | 3.2 |
| | Hypertension | Common | 2.6 |
| | Orthostatic hypotension | Uncommon | 0.2 |
| **RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS** | Pulmonary edema | Uncommon | 0.2 |
| | Dyspnea | Uncommon | 0.4 |
| | Cough | Uncommon | 0.2 |
| | Hiccups | Uncommon | 0.2 |
| | Lung disorder | Uncommon | 0.4 |
| **GASTROINTESTINAL DISORDERS** | Abdominal pain | Common | 1.6 |
| | Abdominal distension | ** | ** |
| | Intestinal obstruction | Uncommon | 0.2 |
| | Peritonitis | Uncommon | 0.6 |
| | Bloody peritoneal effluent | Uncommon | 0.2 |
| | Diarrhea | Uncommon | 0.6 |
| | Gastric ulcer | Uncommon | 0.2 |
| | Gastritis | Uncommon | 0.2 |
| | Gastrointestinal disorder | Uncommon | 0.4 |
| | Vomiting | Uncommon | 0.2 |
| | Constipation | Uncommon | 0.4 |
| | Dyspepsia | Uncommon | 0.6 |
| | Nausea | Uncommon | 0.2 |
| | Dry mouth | Uncommon | 0.4 |
| | Flatulence | Uncommon | 0.2 |
| **SKIN AND SUBCUTANEOUS DISORDERS** | Dermatitis exfoliative | Common | 1.6 |
| | Rash | Common | 5.5 |
| | Pruritus | Common | 1.4 |
| | Urticaria | Uncommon | 0.2 |
| | Dermatitus bullous | Uncommon | 0.2 |
| | Psoriasis | Uncommon | 0.4 |
| | Rash, maculo-papular | Uncommon | 0.2 |
| | Skin ulcer | Uncommon | 0.2 |
| | Eczema | Uncommon | 0.2 |
| | Nail disorder | Uncommon | 0.6 |
| | Skin disorder | Uncommon | 0.2 |

| | | | |
|---|---|---|---|
| | Dry skin<br>Skin discolouration | Uncommon<br>Uncommon | 0.2<br>0.2 |
| **MUSCULOSKLETAL, CONNECTIVE TISSUE DISORDERS** | Bone pain<br>Muscle spasms<br>Myalgia<br>Neck Pain | Uncommon<br>Uncommon<br>Uncommon<br>Uncommon | 0.1<br>0.4<br>0.4<br>0.4 |
| **RENAL AND URINARY DISORDERS** | Renal pain | Uncommon | 0.2 |
| **GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS** | Edema peripheral<br>Asthenia<br>Chest pain<br>Catheter-related complication<br>Face edema<br>Edema<br>Pain | Common<br>Common<br>Uncommon<br>Uncommon<br>Uncommon<br>Uncommon<br>Uncommon | 1.4<br>1.2<br>0.4<br>0.2<br>0.2<br>0.6<br>0.2 |
| **INVESTIGATIONS** | Urine output decreased<br>Laboratory test abnormal<br>Alanine aminotransferase increased<br>Aspartate aminotransferase increased<br>Blood alkaline phosphatase increased<br>Liver function test abnormal<br>Weight decreased<br>Weight increased | **<br>Common<br>Uncommon<br>Uncommon<br>Uncommon<br>Uncommon<br>Uncommon<br>Uncommon | **<br>2.6<br>0.4<br>0.4<br>0.6<br>0.6<br>0.2<br>0.6 |
| **INJURY, POISONING, AND PROCEDURAL COMPLICATIONS** | Injury | Uncommon | 0.2 |

*Frequency has been evaluated using the following criteria: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

†This table represents an integration of safety data from the following clinical trials of 493 patients: RD-97-CA-130, RD-97-CA-131, ML/IB/001, PRO-Renal-Reg-035, ML/IB/020 (DELIA), ML/IB/011 (DIANA), ML/IB/004 (Midas-2), RD-99-CA-060, and ML/IB/014. The table also includes adverse events from clinical study BLR-PG21. Additionally, safety data from studies BLR-PG22, RD-00-CA-050 and RD-00-CA-022 were reviewed and did not require additions to the clinical trial data presented.

**Reported in 1 of 18 patients who were exposed to EXTRANEAL in clinical trial BLR-PG21. Therefore, estimation of frequency not presented due to limited patient population in clinical trial BLR-PG21.

## Post-Market Adverse Drug Reactions

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post marketing experience. These reactions are listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity.

INFECTIONS AND INFESTATIONS: Fungal peritonitis, Peritonitis bacterial, Catheter site infection, Catheter related infection

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Thrombocytopenia, Leukopenia

IMMUNE SYSTEM DISORDERS: Vasculitis, Serum sickness, Hypersensitivity

METABOLISM AND NUTRITION DISORDERS: Shock hypoglycemia, Fluid overload, Fluid imbalance

NERVOUS SYSTEM DISORDERS: Hypoglycemic coma, Burning sensation

EYE DISORDERS: Vision blurred

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Bronchospasm, Stridor

GASTROINTESTINAL DISORDERS: Encapsulating peritoneal sclerosis, Aseptic peritonitis*, Peritoneal cloudy effluent, Ileus, Ascites, Inguinal hernia, Abdominal discomfort

SKIN AND SUBCUTANEOUS DISORDERS: Toxic epidermal necrolysis, Erythema multiforme, Angioedema, Urticaria generalized, Toxic skin eruption, Swelling face, Periorbital edema, Exfoliative rash, Skin exfoliation, Prurigo, Rash (including macular, papular, erythematous), Dermatitis (including allergic and contact), Drug eruption, Erythema, Onychomadesis, Skin chapped, Blister

MUSCULOSKELETAL, CONNECTIVE TISSUE DISORDERS: Arthralgia, Back pain, Musculoskeletal pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: Penile edema, Scrotal edema

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Discomfort, Pyrexia, Chills, Malaise, Drug effect decreased, Drug ineffective, Catheter site erythema, Catheter site inflammation, Infusion related reaction (including Infusion site pain, Instillation site pain)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: Device interaction

*Lower level term

## DRUG INTERACTIONS

### Overview

No interaction studies have been conducted with EXTRANEAL. The blood concentration of dialyzable drugs may be reduced by peritoneal dialysis.

### Drug-Drug Interactions

Some drug additives may be incompatible with EXTRANEAL.

Addition of Potassium
Potassium is omitted from EXTRANEAL solutions because dialysis may be performed to correct hyperkalemia. In situations where there is a normal serum potassium level or hypokalemia, the addition of potassium chloride (up to a concentration of 4 mEq/L) may be indicated to prevent severe hypokalemia. The decision to add potassium chloride should be made by the physician after careful evaluation of serum potassium.

Addition of Insulin
Addition of insulin to EXTRANEAL was evaluated in 6 insulin-dependent diabetic patients undergoing CAPD for end stage renal disease. No interference of EXTRANEAL with insulin absorption from the peritoneal cavity or with insulin's ability to control blood glucose was observed (SEE WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests). Appropriate monitoring of blood glucose should be performed when initiating EXTRANEAL in diabetic patients and insulin dosage adjusted if needed[5] (SEE WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

Addition of Heparin
No human drug interaction studies with heparin were conducted. In *vitro* studies demonstrated no evidence of incompatibility of heparin with EXTRANEAL.

Addition of Antibiotics
Compatibility has been demonstrated with vancomycin[6], cefazolin[7], ceftazidime[7], gentamicin[6], and netilmicin[8]. However, aminoglycosides should not be mixed with penicillins due to chemical incompatibility[9, 10].

Minimum Inhibitory Concentration (MIC)
No formal clinical data interaction studies have been performed. *In vitro* studies with EXTRANEAL and the following antibiotics have demonstrated no effects with regard to minimum inhibitory concentration (MIC): vancomycin, cefazolin, ampicillin, ampicillin/flucoxacillin, ceftazidime, gentamicin, and amphotericin.

## Drug-Laboratory Interactions

Blood glucose measurement must be done with a glucose-specific method to prevent maltose interference. Glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ)- or glucose-dye-oxidoreductase (GDO)-based methods must not be used[1]. Also, the use of some glucose monitors and test strips using glucose dehydrogenase flavin-adenine dinucleotide (GDH-FAD) methodology has resulted in falsely elevated glucose readings due to the presence of maltose (**See WARNINGS AND PRECAUTIONS)**.

An apparent decrease in serum amylase activity has been observed in patients administered EXTRANEAL[4].

# DOSAGE AND ADMINISTRATION

## Dosing Considerations

**EXTRANEAL is intended for intraperitoneal administration only. Not for intravenous administration.**

Treatment should be initiated under the supervision of a physician. The mode of therapy, frequency of treatment, exchange volume, duration of dwell and length of dialysis should be initiated and supervised by the physician.

Do not administer if the solution is discoloured, cloudy, contains particulate matter or shows evidence of leakage, or if seals are not intact.

EXTRANEAL is recommended for single use only. Discard any unused remaining solution.

## Recommended Dose and Dosage Adjustment

EXTRANEAL is available in either a 2000 mL or a 2500 mL bag. The volume administered is based on the patient's need for adequate dialysis, as determined by the prescribing physician.

**Adults:** By intraperitoneal administration as a single daily exchange for the long dwell, up to 12 hours, in CAPD or 14 and up to 16 hours in APD. Aseptic technique should be employed throughout the peritoneal dialysis procedure.

The contents of a 2000 mL or 2500 mL bag (as appropriate for the patient's dialysis needs) should be instilled over a period of approximately 10 to 20 minutes at a rate which the patient finds comfortable. The recommended dwell time is between 6 and 12 hours in CAPD and 14-16 hours in APD. Drainage of CAPD fluid is by gravity and APD fluid is by a process which simulates gravity. Both should be at a rate comfortable for the patient.

The drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of infection.
**Elderly:** As for adults.

**Children:** Not recommended for use in children (less than 18 years of age).

**Administration**

EXTRANEAL is intended for intraperitoneal administration only.

Aseptic technique should be employed throughout the peritoneal dialysis procedure.

To reduce discomfort on administration, the solution may be warmed to a temperature of 37°C (98.6°F) prior to use. This should be done using dry heat ideally using a warming plate or heating pad specially designed for the purpose. **The bag should not be immersed in water to warm it to avoid contamination of connectors. Do not microwave.**

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No data is available on the effects of overdosage. However, continuous administration of more than one bag of EXTRANEAL in 24 hours would increase plasma levels of carbohydrate metabolites and maltose. The effects of such an increase are unknown but an increase in plasma osmolality may occur. Treatment could be managed by icodextrin free peritoneal dialysis or haemodialysis.

## ACTION AND CLINICAL PHARMACOLOGY

**Mechanism of Action**

EXTRANEAL is a water-soluble α–1,4 and α–1,6 linked glucopyranose (cyclic form of glucose) polymer with an average molecular weight range of 12,000 to 20,000 daltons. When administered intraperitoneally icodextrin acts as a colloid osmotic agent, leading to net fluid movement from blood to dialysate. Icodextrin is approximately iso-osmolar (284 mOsmol/L) to serum. As an osmotic agent it is 5.5 times more effective than glucose 1.36% solution and as effective as glucose 3.86% solution.

Icodextrin does not appear to be metabolized within the peritoneal cavity and is only slowly absorbed from the peritoneal cavity, mostly by the lymphatic system[6]. The extent of absorption depends on the dwell time of the solution; about 20% of the total carbohydrate is absorbed in 8 hours, and this rises to 34% in 12 hours. This translates into mean carbohydrate absorption for the icodextrin 29.5 ± 5g vs 62 ± 5g for glucose 4.25% solution per 12 hour dwell. The reduced

absorption of glucose leads to reduced potential for hyperglycemia, hyperinsulemia and caloric load[12].

Absorbed icodextrin has been shown to be degraded to smaller oligosaccharides (principally maltose and maltotriose) by serum α-amylase [13]. In subjects with normal renal function, these metabolites are further degraded by kidney enzymes[14]. In dialysis patients, the clearance of the icodextrin and its metabolites is slower and the levels of the metabolites increase, however there is no effect on serum osmolality[12, 13, 15]. With daily use of icodextrin solution, steady state concentrations of total icodextrin, maltose and metabolites of higher molecular weight are achieved within 7-10 days. In the MIDAS study, steady-state levels were 4.6 mg/mL for total icodextrin derived material, 1.2 mg/mL for maltose, 1.8 mg/mL for oligosaccharides between 3 and 9 glucose units (G3-G9), and 1.8 mg/ml for metabolites larger than G9. Plasma levels return to baseline values within approximately two weeks following cessation of icodextrin administration[4]. The long-term effects of raised plasma levels of maltose and glucose polymer are unknown, but there is no reason to suspect these to be harmful.

In APD (automated peritoneal dialysis), EXTRANEAL solution used for the long daytime dwell allows greater flexibility in fluid intake compared to glucose solutions.

Toxicity studies show no evidence of local damage or irritation of the peritoneum, nor any evidence of storage of the polymer.

## STORAGE AND STABILITY

Store at room temperature (15-25°C). Do not store below 4°C. Do not use unless the solution is clear and the container undamaged. Any unused portion of the solution should be discarded.

## SPECIAL HANDLING INSTRUCTIONS

SEE STORAGE AND STABILITY

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Dosage Forms

EXTRANEAL is available in Viaflex® Single or TwinBag containers holding 2000 mL or 2500 mL.

### Composition

EXTRANEAL is a sterile, peritoneal dialysis fluid containing icodextrin at a concentration of 7.5% w/v in an electrolyte solution containing the following:

| | mmol/litre (approx) | mEq/litre (approx) |
|---|---|---|
| Sodium | 132 | 132 |
| Calcium | 1.75 | 3.5 |
| Magnesium | 0.25 | 0.5 |
| Chloride | 96 | 96 |
| Lactate | 40 | 40 |

### Each one litre contains

| | |
|---|---|
| Icodextrin | 75 g |
| Sodium Chloride, PhEur or USP | 5.35 g |
| Sodium Lactate, DAB or USP | 4.48 g |
| Calcium Chloride Dihydrate, PhEur or USP | 257 mg |
| Magnesium Chloride Hexahydrate, PhEur or USP | 51 mg |
| Water for Injection, PhEur or USP | q.s. |
| Theoretical osmolarity | 284 milliosmoles per litre |
| pH | 5.2 |

### Packaging

See Dosage Forms.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

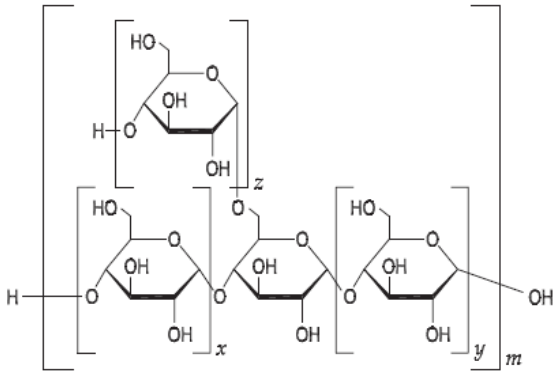
### Drug Substance

Proper name: Icodextrin

Chemical name: α-1,4, poly glucopyranose

Molecular formula and molecular mass: $[C_6H_{10}O_5]_n$
n = number of glucose units in polydisperse glucose polymer

Structural formula:



Physicochemical properties: Icodextrin is a glucopyranose (cyclic form of glucose) polymer (linked by α -1,4 and α -1,6 bonds, but predominantly α -1,4) produced by the hydrolysis of starch and fractionated by membrane separation technology to produce material with the desired molecular weight distribution. Icodextrin has a weight average molecular weight between 12,000 and 20,000 Daltons and a number average molecular weight between 5,000 and 6,500 Daltons. It bears a close structural relationship to glycogen, the natural storage polymer in the human body [15].

## DETAILED PHARMACOLOGY

Colloid osmosis is the predominant basis of action of icodextrin [16, 17]. In biological systems, a transport mechanism similar to that elicited by that of icodextrin in CAPD exists naturally across the permeable membranes of capillaries. Albumin (68,000 daltons) is an effective osmotic agent

whose passage across the capillary wall is restricted. It exerts a colloid osmotic pressure, even though its molar concentration (0.66 mmol/L) is a fraction of the total plasma osmolarity (295 mmol/L). Icodextrin is a glucose polymer composed of glucose residues joined largely through 1-4 links with a small degree of branching through 1,6 links with an average molecular weight at the range of 12,000 to 20,000 daltons.

Carbohydrates with structures like icodextrin are substrates for α-amylase which is found in pancreatic juice, saliva and plasma. Alpha-amylase hydrolyses these carbohydrates to oligosaccharides, maltose, isomaltose and maltotriose. These are hydrolyzed to glucose by maltase and isomaltase found in the small intestine, kidney and a variety of other tissues[13]. An assay was developed to separate and detect icodextrin and its hydrolysis products (G1-glucose to G10 and high molecular weight structure >G10) in body fluids[18]. The fate of intraperitoneally administered icodextrin is determined by its stability in the peritoneal cavity, the degree of absorption into systemic circulation and renal and metabolic elimination. The results of pharmacokinetic studies in animals are limited by the fact that most animal models have normal kidney function. The kidney is a major site for further metabolism of oligosaccharides by maltase. The animal studies can provide information on the absorption from the peritoneal cavity and on rates of non-renal clearance, but may not give all the desired information on metabolism and distribution. In addition, rats and dogs metabolize (due to higher levels of maltase) and excrete the product much faster than humans, as demonstrated in a 28-day study where icodextrin was not detected in the plasma of rats or dogs and was rapidly eliminated.

**Table 1: Comparative Pharmacokinetic data for Icodextrin**

| Species | Dose Details | Sample Time (n) | Mean Plasma Levels (mg/mL) G2 | G3-G10 | G>10 |
|---|---|---|---|---|---|
| Rat | 4.0 & 6.0 g/kg IP twice daily for 28 days | | None detected | | |
| Dog | 6.0 g/kg IP twice daily for 28 days (12g/kg/day) | Pre-dose (8)<br>Day 1:5h (8)<br>Day 1:24h (8)<br>Day 21:5h (8)<br>Day 21:24h (8)<br>Day 28:5h (8)<br>Day 28:24h (8) | 0.02<br>0.11<br>0.02<br>0.05<br>0.02<br>0.03<br>0.02 | 0.02<br>0.52<br>0.22<br>0.33<br>0.24<br>0.28<br>0.26 | 0.10<br>0.17<br>0.13<br>0.18<br>0.16<br>0.14<br>0.16 |
| Man | 150 g once daily IP for 6 months (2.14g/kg/day) | Pre-dose (91)<br>1 month (80)<br>3 months (72)<br>6 months (53) | 0.04<br>1.20<br>1.00<br>1.06 | 0.02<br>1.84<br>1.67<br>1.76 | 0.29<br>1.83<br>1.73<br>1.84 |

Pharmacokinetics: There is evidence of slow constant absorption of icodextrin from the peritoneal cavity via the lymphatic system[16, 17]. In the systemic circulation it is metabolized by amylase to smaller oligosaccharides (principally maltose and maltotriose) which are detectable in serum and are cleared by metabolism and peritoneal dialysis. Following the use of icodextrin on a daily basis

for overnight exchange, maltose levels reach steady-state (1.2 mg/mL) after 7-10 days. Plasma levels of icodextrin and maltose were measured in 12 patients who stopped once a day treatment with icodextrin after approximately two years. Icodextrin related material (4.8 mg/mL) and maltose (1.1 mg/mL) fell to pretreatment levels in 7-10 days[19].

Clinical trials: The MIDAS[15] 6 month clinical trial was set up to compare and evaluate the efficacy and safety of icodextrin with glucose (weak 1.36%/1.5% and strong 3.86%/4.25%) in 8 hours of CAPD. On weeks 4, 13 and 21, the hours were extended for 12 hours. The results indicate that icodextrin was well-tolerated and produced up to 5.5 times more ultrafiltration than 1.36% glucose and the same ultrafiltration as a 3.86% glucose solution.

**Table 2: Mean Volume (mL) of Net Ultrafiltration for 8 Hour Dwell by Glucose Concentration***

| Week | Control Mean SD (N) | Icodextrin Mean SD (N) |
|---|---|---|
| Weak (1.36%) | | |
| Week 3 | 150.6 ± 328.7 (50) | 497.4 ± 228.3 (42)* |
| Week 12 | 141.8 ± 309.6 (40) | 480.7 ± 208.3 (42)* |
| Week 20 | 153.2 ± 313.0 (38) | 516.9 ± 234.7 (37)* |
| Medium (2.27%) or Strong (3.86%) | | |
| Week 3 | 615.4 ± 288.8 (30) | 528.1 ± 241.0 (28) |
| Week 12 | 553.0 ± 357.2 (29) | 515.2 ± 211.7 (23) |
| Week 20 | 464.6 ± 379.2 (24) | 461.8 ± 198.5 (19) |
| *p<0.0001 | | |

**Table 3: Mean Volume (mL) of Ultrafiltrate for Special Weeks (12 hr Dwell) by Glucose Concentration**

| Special Week | Control Mean SD (N) | Icodextrin Mean SD (N) |
|---|---|---|
| 1.5% Dextrose | | |
| 4 | 72.7 339.0 (51) | 529.6 290.2 (42)* |
| 13 | 49.3 302.0 (41) | 496.9 288.9 (40)* |
| 21 | 125.9 324.3 (38) | 552.1 309.3 (36)* |
| 4.25% Dextrose | | |
| 4 | 498.4 418.5 (31) | 610.4 238.8 (28) |
| 13 | 458.3 434.1 (29) | 593.5 223.8 (23) |
| 21 | 427.0 461.4 (25) | 509.5 205.5 (21) |
| *p<0.0001 | | |

In the icodextrin group, 7% of the patients experienced negative ultrafiltration (UF), while in the control group, up to 41% of the patients experienced negative UF. Over the 12-hour dwell, net ultrafiltration was similar in patients receiving icodextrin solution and the controls who were using 4.25% dextrose solution for the long dwell.

Safety: The side effects in this study were reported by half of the patients and were equally distributed between the two groups. They were mainly related to preexisting cardiovascular disease. Excluding peritonitis, the most common reported were respiratory, musculoskeletal and gastrointestinal events. There was no difference in severity of the side effects between the two groups. The icodextrin patients experienced symptomatic improvement in abdominal fullness, fatigue and shortness of breath. There were no differences in the insulin dose for diabetic patients (n=26) in both groups. The mean carbohydrate absorption for the icodextrin group (29 ± 5g) was lower than with 4.25% dextrose (62 ± 5g). The icodextrin group mean serum maltose and metabolite levels (total GHO-G1) rose to a steady-state level.

**Table 4: Serum Levels of Maltose and Total Icodextrin and Metabolites**

| | | Visit 2 Baseline | Visit 6 | Visit 9 | Visit 12 |
|---|---|---|---|---|---|
| Maltose (mg/mL) | Control | 0.0300.02 (91) | | | 0.030.01 (64) |
| | Icodextrin | 0.040.04 (91) | 1.200.38 (91) | 1.010.35 (80) | 1.090.39 (67) |
| Total CHO-G1 (mg/mL) | Control | 0.320.10 (98) | | | 0.350.09 (64) |
| | Icodextrin | 0.350.15 (91) | 4.871.55 (80) | 4.411.36 (73) | 4.621.46 (67) |

The elevated levels of maltose did not appear to have any clinical side effects. Some patients in the UK who elected to continue using icodextrin have been doing so for more than 5 years without any adverse effects related to icodextrin accumulation.

## TOXICOLOGY

Recommended human dose 2-3 g/kg/day.

Animal toxicology testing was limited by several factors, notably by restrictions on the volume/viscosity of icodextrin which could be administered intraperitoneally, lack of renal failure animal models and by differences in the degree and speed of metabolism and excretion of icodextrin, especially in the rat and in the dog. The chronic toxicity studies were not done for the same reasons. Therefore, the results of animal toxicology studies are mostly useful for their information on the local effects of icodextrin.

Acute toxicity: Single i.v. and i.p. dose of icodextrin had no systemic or local effect in the mouse or the rat. No effect on the CNS was observed. Subacute 28-day toxicity testing in the rat (12 g/kg/day) and the dog (12 g/kg/day) revealed rapid elimination and limited exposure by icodextrin in the rat and similarly, rapid metabolism and excretion in the dog (blood levels 10-20% lower than humans), with exposure to icodextrin metabolites similar to humans despite a much higher dose.

There was no apparent effect on the peritoneum in the rat or the dog and only small changes in electrolytes, BUN and MCV, consistent with the anticipated physiological effect of peritoneal dialysis even in the presence of normal renal function. A sharp decline in the production of urine and production of more concentrated urine in the dog was consistent with the effect of peritoneal dialysis. Plasma glucose has shown dose-related increases of up to 25-30%, which is attributed to the hydrolysis of icodextrin as it is released from the peritoneal “reservoir”. The dog has also high

levels of circulating maltose and maltotriose. All changes had largely or completely disappeared after the 14-day recovery period.Mutagenicity: Using the Ames test, no effect was found at up to (icodextrin) 10,000g/plate.

In a very full test, (icodextrin) had no clastogenic effect in concentrations up to 200 mg/mL, in the presence and absence of S9 microsomes.

This concentration did not affect the osmolality of the culture medium. It had no cytotoxic action.

In a mouse micronucleus test, mice of both sexes were given (icodextrin) up to 6 g/kg i.p. In samples of bone marrow taken at several times, no micronuclei were found.

Icodextrin does not possess chemical structures known to be capable of being metabolized to mutagenic electrophilic groups. No further experiments have been done *in vitro* or *in vivo* because of the chemical nature of icodextrin, the lack of activity even in very high concentrations in the *in vitro* studies, and because it is metabolized *in vivo* to compounds normally present in the body.

Local Toxicity Studies: In terms of irritancy, clinical and necropsy observations in the acute toxicity tests did not show any features of local irritation. In a 28-day experiment in the dog, residual peritoneal fluid was sometimes obtained in *vivo* and at autopsy. It did show a variable, low leukocyte count and protein content in most instances, often exceeded by the values in fluid from animals receiving 5% glucose i.p. The latter might have been anticipated in view of the know irritancy (in man) of 5% glucose.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICATION**

# PART III: PATIENT MEDICATION INFORMATION

**EXTRANEAL solution**
**(icodextrin, sodium chloride, sodium lactate, calcium chloride, magnesium chloride)**

**This leaflet is part III of a three-part "Product Monograph" published when EXTRANEAL solution was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about EXTRANEAL solution. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**

- EXTRANEAL solution is a sterile peritoneal dialysis solution used in patients whose kidneys are not working properly. It removes waste products and water from the blood. EXTRANEAL solution can be used up to 12 hours for continuous peritoneal dialysis in mobile patients or 14 and up to 16 hours for automated peritoneal dialysis procedures.

**What it does:**

EXTRANEAL solution contains icodextrin, which is made from cornstarch. It draws fluid and wastes from your blood stream into your peritoneal cavity (the space inside your abdomen). The fluids and wastes are removed from your body when the EXTRANEAL solution solution is drained.

**When it should not be used:**

**Do not use EXTRANEAL solution:**

- If you have been treated for acute renal failure
- If a doctor has ever told you that you have a glycogen storage disease
- If you are allergic to cornstarch or have had an allergic reaction to icodextrin
- If you have maltose or isomaltose intolerance
- If a doctor has told you that you have pre-existing severe lactic acidosis
- If you have had abdominal surgery within the last month
- If you are allergic to any of the nonmedicinal ingredients (see What the nonmedicinal ingredients are:)
- If you have impaired respiratory function or potassium deficiency
- If you are told having a surgically uncorrectable problem affecting your abdominal wall or cavity or uncorrectable problem that increases risk of abdominal infections such as abdominal fistulae, tumors, open wounds, herniae or other conditions until healing is complete
- If you have documented loss of peritoneal function due to severe peritoneal scarring
- If you are pregnant or plan to become pregnant
- If you are breastfeeding

**What the medicinal ingredients are:**

Icodextrin
Sodium Chloride
Sodium Lactate
Calcium Chloride
Magnesium Chloride

**What the nonmedicinal ingredients are:**

Hydrochloric acid (For pH adjustment)
Sodium Hydroxide (For pH adjustment)
Water for Injection

**What dosage forms it comes in:**

EXTRANEAL solution is available in Viaflex® Single or TwinBag containers holding 2000 mL or 2500 mL**.**

## WARNINGS AND PRECAUTIONS

**If you monitor your blood glucose, you must use a glucose specific monitor and test strips. If your glucose monitor or test strips use a GDH-PQQ*GDO**or GDH-FAD***-based method, using EXTRANEAL solution may cause a falsely high glucose reading or may mask a very low actual glucose reading. A false high blood glucose reading could cause you to give more insulin than you need. Getting more insulin than you need can cause serious reaction including loss of consciousness, coma, neurological damage and death. If you have true low blood sugar but are using a monitor that is not specific, you may inadvertently delay taking appropriate measure to correct the low blood sugar. A false elevated reading may be measured up to two weeks following the discontinuance of EXTRANEAL solution.**

***GDH-PQQ: glucose dehydrogenase pyrroloquinolinequinone**
****GDO: glucose-dye-oxidoreductase**
*****GDH-FAD: glucose dehydrogenase flavin-adenine dinucleotide**

**If you are ever hospitalized or admitted to the emergency room, notify** the hospital staff that you are using EXTRANEAL solution and that icodextrin and maltose may give a false high glucose reading with some types of glucose monitors or test strips.

**Tell your doctor if you:**

- Use cardiac glycosides, such as digoxin. Your doctor may need to monitor your blood levels of calcium,

potassium and magnesium
- Have recently had surgery to repair a weakness in an abdominal artery
- Suspect you are having an allergic reaction to EXTRANEAL solution or any ingredient in EXTRANEAL solution

Patients on EXTRANEAL solution may experience high or low levels of potassium, calcium, or magnesium in their blood. Your doctor will monitor your blood test results.

Tell your doctor about any other conditions you have that may affect the inside, outside or the wall of your abdomen.

If you are allergic to corn or corn products, undesirable allergic reactions, including development of rash, hives, throat and/or facial swelling, wheezing, shortness of breath, low blood pressure, and other anaphylactic/anaphylactoid reactions, may occur. Stop the infusion immediately and drain the solution from the peritoneal cavity if any signs or symptoms of a suspected allergic reaction develop and contact your doctor immediately.

## INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist all the medications you are taking including all prescription, non-prescription and natural health products.

The blood concentration of drugs that can be removed from the body using dialysis may be reduced by peritoneal dialysis.

Talk with your doctor about any drugs prescribed as an additive to EXTRANEAL solution.

Tell your doctor about all the medicines you take, including insulin and blood pressure medicines. Your dose of these medicines may need to be changed when you use EXTRANEAL solution.

## PROPER USE OF THIS MEDICATION

**Usual dose**
- EXTRANEAL solution is used for the long dwell exchange, up to 12 hours, in CAPD. EXTRANEAL solution is used for the long dwell exchange (14 to 16 hours) in APD. Do not perform more than one exchange in 24 hours.
- To do your EXTRANEAL solution exchange, it is very important that you follow the steps shown to you in your peritoneal dialysis training. All surfaces and connecting parts must be clean to avoid serious infection. If you need more help or have any questions you should contact your dialysis center or doctor.
- Before use, always check to make sure the bags are not leaking and the date for using the solution (expiration date) has not passed. Do not use EXTRANEAL solution after the expiration date shown on the carton and product label.
- Make sure the solution is clear and does not contain particles. Do not use bags that are cloudy, leaking or that contain particles.
- EXTRANEAL solution is for single use only. Discard any unused remaining solution.
- EXTRANEAL solution is only for intraperitoneal administration.
- Sometimes, too much EXTRANEAL solution can get into your peritoneal cavity. If you experience abdominal distention, feeling of fullness and, or shortness of breath, contact your doctor or peritoneal dialysis unit.
- To make using EXTRANEAL solution more comfortable, you can warm it to 37°C (98.6°F) before use. This should only be done using dry heat, such as a heating pad.
- To avoid increased risk of infection, do not place EXTRANEAL solution in water to heat the bags.
- Do not microwave EXTRANEAL solution.
- EXTRANEAL solution should be infused based on your need for adequate dialysis, as determined by your doctor. When draining the fluid after the dwell, always check your drained fluid for cloudiness or fibrin. Fibrin looks like clumps or stringy material in the drained solution. Cloudy drained fluid or fibrin may mean you have an infection. Call your doctor if your drained fluid is cloudy or contains fibrin.
- Carefully monitor your fluid balance. Keep an accurate fluid record. Carefully monitor your body weight to avoid too much or too little fluid in your body (over or under hydration) which may have serious effects.
- Talk to your doctor before adding any other medicines to EXTRANEAL solution.

**Overdose**

There is no information available on the effects of overdosage. Only one exchange is recommended in a 24-hour period. Contact your doctor if a suspected overdosage has been administered.

In case of a suspected drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Rash is the most common side effect of EXTRANEAL solution. It usually appears during the first 3 weeks of treatment and goes away when treatment stops.

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom / effect** | | **Talk with your doctor or pharmacist** | | **Stop taking drug and seek immediate emergency medical attention** |
| | | **Only if severe** | **In all cases** | |
| **Common** | • Allergic Reactions: swelling of the face, throat, lips, difficulty swallowing or breathing, skin peeling, itching, hives or rash | | ✓ | ✓ |
| | • Dehydration: dizziness, weakness or fainting, low or drop in blood pressure, thirst, dry mouth, constipation | ✓ | | |
| | • Ringing in your ears | ✓ | | |
| | • Headache | ✓ | | |
| | • Swelling in different parts of the body such as the hands, feet, face and abdomen | ✓ | | |
| | • Decreased urine production | | ✓ | |
| | • High blood pressure | ✓ | | |
| **Uncommon** | • Peritonitis (an infection in the peritoneal cavity): cloudy or bloody drained fluid, abdominal pain, fever, redness, nausea, upset stomach, vomiting, lack of appetite, weight loss, constipation) | | ✓ | |
| | • High / low blood sugar | ✓ | | |
| | • Shortness of breath, chest pain | | ✓ | |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom / effect** | | **Talk with your doctor or pharmacist** | | **Stop taking drug and seek immediate emergency medical attention** |
| | | **Only if severe** | **In all cases** | |
| | • Flu-like symptoms, cold, cough | ✓ | | |

***This is not a complete list of side effects. For any unexpected effects while taking EXTRANEAL solution, contact your doctor or pharmacist.***

## HOW TO STORE IT

Store at room temperature (15 - 25°C). Do not store below 4°C. Do not use unless the solution is clear and the container undamaged. Any unused portion of the solution should be discarded.

*Keep out of reach and sight of children.*

**REPORTING SUSPECTED SIDE EFFECTS**

**You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.**
**3 ways to report:**

- **Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);**
- **By calling 1-866-234-2345 (toll-free);**
- **By completing a Consumer Side Effect Reporting Form and sending it by:**
  - **Fax to 1-866-678-6789 (toll-free), or**
  - **Mail to: Canada Vigilance Program**
    **Health Canada,Postal Locator 0701E**
    **Ottawa, ON**
    **K1A 0K9**

**Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).**

***NOTE: Contact your health professional if you need information about how to manage your side effects. . The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

If you want more information about EXTRANEAL solution:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc-gc.ca/index-eng.php); Baxter Corporation's website (http://www.baxter.ca), or by contacting the sponsor, BAXTER CORPORATION, at:1-800-387-8399

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