

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EXTRANEAL safely and effectively. See full prescribing information for EXTRANEAL.

EXTRANEAL (icodextrin) peritoneal dialysis solution
Initial U.S. Approval: 2002

WARNING: UNRECOGNIZED HYPOGLYCEMIA RESULTING FROM DRUG-DEVICE INTERACTION

See full prescribing information for complete boxed warning

- Use of non-specific glucose monitors has resulted in falsely elevated glucose readings due to maltose interference leading to inappropriate insulin administration or withholding of hypoglycemia treatment. Permanent neurological damage and death have been reported. (5.1)
- Only use glucose-specific monitoring systems in patients using EXTRANEAL (see glucosafety.com). (5.1)
- Blood glucose monitoring devices using glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ), glucose-dye-oxidoreductase (GDO), or some glucose dehydrogenase flavin-adenine dinucleotide (GDH-FAD)-based methods must not be used. (5.1)
- Falsely elevated glucose levels may be measured up to two weeks following cessation of EXTRANEAL therapy. (5.1, 12.3)
- Educate all patients to alert health care providers of this interaction whenever they are admitted to the hospital. (5.1, 17)
- Because of the risk of unrecognized hypoglycemia that could result from drug-device interaction, EXTRANEAL is available only through a restricted program. (5.2)

INDICATIONS AND USAGE

- For a single daily exchange for the long (8- to 16- hour) dwell during continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) for the management of end-stage renal disease. (1)
- To improve (compared to 4.25% dextrose) long-dwell ultrafiltration and clearance of creatinine and urea nitrogen in patients with high average or

greater transport characteristics, as defined using the peritoneal equilibration test (PET). (1)

DOSAGE AND ADMINISTRATION

For intraperitoneal administration only. Not for intravenous injection. Administer as a single daily peritoneal dialysis (PD) exchange for the long dwell. Dosage should be individualized by the prescribing physician experienced in the treatment of end-stage renal disease with PD. (2.1)

DOSAGE FORMS AND STRENGTHS

7.5% icodextrin (75 grams icodextrin per 1000 milliliters) in an electrolyte solution containing 40 mEq/L lactate (3)

- 2 L and 2.5 L AMBU-FLEX II containers (APD)
- 2 L and 2.5 L ULTRABAG containers (CAPD)

CONTRAINDICATIONS

- Known allergy to cornstarch or icodextrin (4.1)
- Maltose or isomaltose intolerance (4.2)
- Glycogen storage disease (4.2)
- Pre-existing severe lactic acidosis (4.3)

WARNINGS AND PRECAUTIONS

- Encapsulating peritoneal sclerosis (5.3)
- Peritonitis: Initiate appropriate antimicrobial therapy. (5.3)
- Hypersensitivity reactions: Serious reactions have been reported. Discontinue use of EXTRANEAL if serious reaction is suspected. (5.4)
- Monitor for lactic acidosis in patients at risk (5.5)
- Monitor for electrolyte, fluid, and nutrition imbalances (5.7)

ADVERSE REACTIONS

The most common adverse reaction (incidence > 5%) was rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2016

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FULL PRESCRIBING INFORMATION

WARNING: UNRECOGNIZED HYPOGLYCEMIA RESULTING FROM DRUG-DEVICE INTERACTION

- **Only use glucose-specific monitors and test strips to measure blood glucose levels in patients using EXTRANEAL (icodextrin) Peritoneal Dialysis Solution. Blood glucose monitoring devices using glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase (GDO)-based methods must not be used. In addition, some blood glucose monitoring systems using glucose dehydrogenase flavin-adenine dinucleotide (GDH-FAD)-based methods must not be used. Use of GDH-PQQ, GDO, and GDH-FAD-based glucose monitors and test strips has resulted in falsely elevated glucose readings (due to the presence of maltose) [see Warnings and Precautions (5.1)]. Falsely elevated glucose readings have led patients or health care providers to withhold treatment of hypoglycemia or to administer insulin inappropriately. Both of these situations have resulted in unrecognized hypoglycemia, which has led to loss of consciousness, coma, permanent neurological damage, and death. Plasma levels of EXTRANEAL (icodextrin) and its metabolites return to baseline within approximately 14 days following cessation of EXTRANEAL (icodextrin) administration. Therefore falsely elevated glucose levels may be measured up to two weeks following cessation of EXTRANEAL (icodextrin) therapy when GDH-PQQ, GDO, and GDH-FAD-based blood glucose monitors and test strips are used.**
- **To avoid improper insulin administration, educate all patients to alert health care providers of this interaction particularly in hospital settings.**
- **The manufacturer(s) of the monitor and test strips should be contacted to determine if icodextrin or maltose causes interference or falsely elevated glucose readings. For a list of toll free numbers for glucose monitor and test strip manufacturers, please contact the Baxter Renal Clinical Help Line 1-888-RENAL-HELP or visit www.glucosafety.com.**
- **Because of the risk of unrecognized hypoglycemia that could result from a drug-device interaction, EXTRANEAL is available only through a restricted program (5.2).**

1. INDICATIONS AND USAGE

EXTRANEAL (icodextrin) is indicated for a single daily exchange for the long (8- to 16- hour) dwell during continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) for the management of end-stage renal disease. EXTRANEAL is also indicated to improve (compared to 4.25% dextrose) long-dwell ultrafiltration and clearance of creatinine and urea nitrogen in patients with high average or greater transport characteristics, as defined using the peritoneal equilibration test (PET) [see *Clinical Pharmacology (12)*, *Clinical Studies (14)*].

2. DOSAGE AND ADMINISTRATION

2.1 Basic Dosing Information

EXTRANEAL is intended for intraperitoneal administration only. Not for intravenous injection. Administer as a single daily exchange for the long dwell in continuous ambulatory peritoneal dialysis or automated peritoneal dialysis. The recommended dwell time is 8- to 16- hours. Administer over a period of 10-20 minutes at a rate that is comfortable for the patient.

The mode of therapy, frequency of treatment, exchange volume, duration of dwell, and length of dialysis should be initiated and supervised by the prescribing physician experienced in the treatment of end-stage renal disease with peritoneal dialysis. It is recommended that patients being placed on peritoneal dialysis should be appropriately trained in a program that is under supervision of a physician.

2.2 Directions for Use

For complete CAPD and APD system preparation, see directions accompanying ancillary equipment.

Aseptic technique should be used throughout the peritoneal dialysis procedure.

For single-dose only.

Storage

Store in moisture barrier overwrap and in carton until ready to use [*see How Supplied/Storage and Handling (16)*].

Warming

For patient comfort, EXTRANEAL can be warmed to 37°C (98.6°F). Only dry heat should be used (e.g., heating pad, warming plate). Do not immerse EXTRANEAL in water for warming. Do not use a microwave oven to warm EXTRANEAL. Do not heat above 40°C (104°F).

To Open

To open, tear the overwrap down at the slit and remove the solution container. Some opacity of the plastic, due to moisture absorption during the sterilization process, may be observed. This does not affect the solution quality or safety and may often leave a slight amount of moisture within the overwrap.

Inspect for Container Integrity and Solution Appearance

Do not use EXTRANEAL if it is cloudy or discolored, if it contains particulate matter, or if the container is leaking.

Inspect the patient connector to ensure the pull ring is attached. Do not use if pull ring is not attached to the connector. Inspect the EXTRANEAL container for signs of leakage and check for minute leaks by squeezing the container firmly. If the container has frangible(s), inspect that they are positioned correctly and are not broken. Do not use EXTRANEAL if the frangible(s) are broken or leaks are suspected as sterility may be impaired.

For EXTRANEAL in ULTRABAG, inspect the tubing and drain container for presence of solution. Small droplets are acceptable, but if solution flows past the frangible prior to use, do not use and discard the units.

Adding Medications

The decision to add medication should be made by the physician after careful evaluation of the patient [*see Drug Interactions (7), Clinical Pharmacology (12.3)*].

If the re-sealable rubber plug on the medication port is missing or partly removed, do not use the product.

To add a medication:

1. Put on mask. Clean and/or disinfect hands.
2. Prepare medication port site using aseptic technique.
3. Using a syringe with a 1-inch long, 25- to 19-gauge needle, puncture the medication port and inject additive.
4. Reposition container with container ports up and evacuate medication port by squeezing and tapping it.
5. Mix solution and additive thoroughly.

Preparation for Administration

1. Put on mask. Clean and/or disinfect hands.
2. Place EXTRANEAL on work surface.
3. For ULTRABAG system for manual exchange, uncoil tubing and drain bag. Ensure the patient transfer set is closed. Break the connector (Y-set) frangible.
4. Remove pull ring from connector of solution container. If continuous fluid flow from connector is observed, discard solution container. Once the pull ring has been removed, do not reuse the solution or container.
5. Immediately attach the solution container to patient connector (transfer set) or appropriate peritoneal dialysis set.
6. For AMBU-FLEX II, continue with therapy set-up as instructed in user manual or directions accompanying tubing sets for automated peritoneal dialysis.

7. For ULTRABAG, follow the below steps:
 - Clamp solution line and then break frangible near solution bag. Hang solution container and place the drainage container below the level of the abdomen.
 - Open transfer set to drain the solution from abdomen. If drainage cannot be established, contact your clinician. When drainage complete, close transfer set.
 - Remove clamp from solution line and flush new solution to flow into the drainage container for 5 seconds to prime the line. Clamp drain line after flush complete.
 - Open transfer set to fill. When fill complete, close transfer set and clamp solution line.
 - Put on mask. Clean and/or disinfect hands.
 - Disconnect ULTRABAG from transfer set and apply MINICAP.

Completion of Therapy

1. Following use, the drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of peritonitis.
2. Discard unused portion.

3. DOSAGE FORMS AND STRENGTHS

EXTRANEAL is a clear, colorless peritoneal dialysis solution containing icodextrin as the primary osmotic ingredient at a concentration of 7.5% (7.5 grams icodextrin per 100 milliliters) in an electrolyte solution with 40 mEq/L lactate.

EXTRANEAL is available in the following containers and fill volumes:

| Container | Fill Volume | Peritoneal Dialysis Modality |
|------------------|--------------------|-------------------------------------|
| ULTRABAG | 2 L, 2.5 L | CAPD |
| AMBU-FLEX II | 2 L, 2.5 L | APD |

4. CONTRAINDICATIONS

4.1 Allergy to Cornstarch or Icodextrin

EXTRANEAL is contraindicated in patients with a known allergy to cornstarch or icodextrin.

4.2 Metabolic Diseases

EXTRANEAL is contraindicated in patients with maltose or isomaltose intolerance and in patients with glycogen storage disease.

4.3 Severe Lactic Acidosis

EXTRANEAL is contraindicated in patients with severe lactic acidosis. EXTRANEAL contains lactate which may contribute to worsening acidosis if conversion to bicarbonate is impaired and may be associated with hyperventilation, lethargy, hypotension or irregular heart rhythms.

5. WARNINGS AND PRECAUTIONS

5.1 Unrecognized Hypoglycemia Resulting From Drug-Device Interaction

Only use glucose-specific monitors and test strips to measure blood glucose levels in patients using EXTRANEAL (icodextrin) Peritoneal Dialysis Solution. Blood glucose monitoring devices using glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase (GDO)-based methods must not be used. In

addition, some blood glucose monitoring systems using glucose dehydrogenase flavin-adenine dinucleotide (GDH-FAD)-based methods must not be used. Use of GDH-PQQ, GDO, and GDH-FAD-based glucose monitors and test strips has resulted in falsely elevated glucose readings (due to the presence of maltose). Falsely elevated glucose readings have led patients or health care providers to withhold treatment of hypoglycemia or to administer insulin inappropriately. Both of these situations have resulted in unrecognized hypoglycemia, which has led to loss of consciousness, coma, permanent neurological damage, and death. Plasma levels of EXTRANEAL (icodextrin) and its metabolites return to baseline within approximately 14 days following cessation of EXTRANEAL (icodextrin) administration. Therefore falsely elevated glucose levels may be measured up to two weeks following cessation of EXTRANEAL (icodextrin) therapy when GDH-PQQ, GDO, and 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 to alert health care providers of this interaction whenever they are admitted to the hospital.

The manufacturer(s) of the monitor and test strips should be contacted to determine if icodextrin or maltose causes interference or falsely elevated glucose readings. For a list of toll free numbers for glucose monitor and test strip manufacturers, please contact the Baxter Renal Clinical Help Line 1-888-RENAL-HELP or visit www.glucosafety.com.

5.2 REMS Program for EXTRANEAL

Because of the risk of unrecognized hypoglycemia resulting from a drug-device interaction, EXTRANEAL is available only through a restricted program under a REMS [*see Warnings and Precautions (5.1)*]. Required components of the EXTRANEAL REMS Program include the following:

- Dialysis clinic staff must be trained about the risk of undetected hypoglycemia resulting from a drug-device interactions involving EXTRANEAL in order to manage the treatment of patients prescribed EXTRANEAL.
- Patients must be educated at a trained dialysis center before their initial EXTRANEAL treatment.

Further information, including a listing of blood glucose monitor compatibility information provided by the manufacturers of blood glucose monitors, is available by visiting www.glucosafety.com or by calling Baxter Renal Clinical Help Line 1-888-RENAL-HELP.

5.3 Peritonitis and Encapsulating Peritoneal Sclerosis

Infectious and aseptic peritonitis has been associated with EXTRANEAL use. Following EXTRANEAL use, inspect the drained fluid for the presence of fibrin or cloudiness, which may indicate the presence of peritonitis. Improper clamping or priming sequence may result in infusion of air into the peritoneal cavity, which may result in abdominal pain and/or peritonitis. If peritonitis occurs, treat with appropriate therapy.

Encapsulating peritoneal sclerosis (EPS), sometimes fatal, is a complication of peritoneal dialysis therapy and has been reported in patients using EXTRANEAL.

5.4 Hypersensitivity Reactions

Serious hypersensitivity reactions to EXTRANEAL have been reported such as toxic epidermal necrolysis, angioedema, serum sickness, erythema multiforme and vasculitis [*see Adverse Reactions (6.1, 6.2)*]. Anaphylactic or 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. Institute appropriate therapeutic countermeasures as clinically indicated.

5.5 Lactic Acidosis

Monitor patients with conditions known to increase the risk of lactic acidosis [e.g., severe hypotension or sepsis that can be associated with acute renal failure, inborn errors of metabolism, treatment with drugs such as nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)] for lactic acidosis before the start of treatment and during treatment with EXTRANEAL [see *Contraindications (4.3)*].

5.6 Overinfusion

Overinfusion of peritoneal dialysis solution volume into the peritoneal cavity may be characterized by abdominal distention, feeling of fullness and/or shortness of breath. Drain the peritoneal dialysis solution from the peritoneal cavity to treat overinfusion.

5.7 Electrolyte, Fluid, and Nutrition Imbalances

Peritoneal dialysis may affect a patient's protein, water-soluble vitamin, potassium, sodium, chloride, bicarbonate, and magnesium levels and volume status [see *Adverse Reactions (6)*]. Monitor electrolytes and blood chemistry periodically and take appropriate clinical action.

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.

Monitor fluid status to avoid hyper- or hypovolemia and potentially severe consequences including congestive heart failure, volume depletion, and hypovolemic shock.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

EXTRANEAL was originally studied in controlled clinical trials of 493 patients with end-stage renal disease who received a single daily exchange of EXTRANEAL for the long dwell (8-to 16- hours). There were 215 patients exposed for at least 6 months and 155 patients exposed for at least one year. The population was 18-83 years of age, 56% male and 44% female, 73% Caucasian, 18% Black, 4% Asian, 3% Hispanic, and it included patients with the following comorbid conditions: 27% diabetes, 49% hypertension and 23% hypertensive nephropathy.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Rash was the most frequently occurring EXTRANEAL-related adverse reaction (5.5%, EXTRANEAL; 1.7% Control). Seven patients on EXTRANEAL discontinued treatment due to rash, and one patient on EXTRANEAL discontinued due to exfoliative dermatitis. The rash typically appeared within the first three weeks of treatment and resolved with treatment discontinuation or, in some patients, with continued treatment.

Table 1 shows the adverse events reported in these clinical studies regardless of causality, occurring in $\geq 5\%$ of patients and more common on EXTRANEAL than control.

Table 1 – Adverse Experiences in $\geq 5\%$ of Patients and More Common on EXTRANEAL

| | EXTRANEAL | Control |
|-----------------------------|------------------|----------------|
| | N = 493 | N = 347 |
| Peritonitis | 26% | 25% |
| Upper respiratory infection | 15% | 13% |

| | | |
|-------------------|-----|----|
| Hypertension | 13% | 8% |
| Rash | 10% | 5% |
| Headache | 9% | 7% |
| Abdominal Pain | 8% | 6% |
| Flu syndrome | 7% | 6% |
| Nausea | 7% | 5% |
| Cough increase | 7% | 4% |
| Edema | 6% | 5% |
| Accidental injury | 6% | 4% |
| Chest pain | 5% | 4% |
| Dyspepsia | 5% | 4% |
| Hyperglycemia | 5% | 4% |

Adverse events related to EXTRANEAL use or in conjunction with performing the peritoneal dialysis procedure include:

Reported with an incidence of > 5% and at least as common on dextrose control included asthenia, exit site infection, infection, back pain, hypotension, diarrhea, vomiting, anemia, peripheral edema, hypokalemia, hyperphosphatemia, hypoproteinemia, hypervolemia, arthralgia, dizziness, dyspnea, pruritis.

Reported with an incidence of < 5%: pain on infusion, abdominal enlargement, cloudy effluent, ultrafiltration decrease, postural hypotension, heart failure, hyponatremia, hypochloremia, hypercalcemia, hypoglycemia, alkaline phosphatase increase, SGPT increase, SGOT increase, cramping, confusion, lung edema, facial edema, exfoliative dermatitis, eczema, vesicobullous rash, maculopapular rash, erythema multiforme.

EXTRANEAL was additionally studied in a subpopulation of 92 high average/high transporter APD patients in a two-week controlled clinical trial where patients received a single daily exchange of EXTRANEAL (n=47) or dextrose control (n=45) for the long dwell (14 ± 2 hours). Consistent with the data reported in the original trials of EXTRANEAL, rash was the most frequently occurring event.

Clinical Laboratory Findings

An increase in mean serum alkaline phosphatase has been observed in clinical studies of ESRD patients receiving EXTRANEAL. No associated increases in other liver chemistry tests were observed. Serum alkaline phosphatase levels did not show progressive increase over a 12-month study period. Levels returned to normal approximately two weeks after discontinuation of EXTRANEAL.

Decreases in serum sodium and chloride have been observed in patients using EXTRANEAL. The mean change in serum sodium from baseline to the last study visit was -2.8 mmol/L for patients on EXTRANEAL and -0.3 mmol/L for patients on control solution. Four EXTRANEAL patients and two control patients developed serum sodium < 125 mmol/L. The mean change in serum chloride from baseline to last study visit was -2 mmol/L for EXTRANEAL patients and + 0.6 mmol/L for control patients. Similar changes in serum chemistries were observed in an additional clinical study in a subpopulation of high average/high transporter patients. The declines in serum sodium and chloride may be related to dilution resulting from the presence of icodextrin metabolites in plasma.

An apparent decrease in serum amylase activity has been observed in patients administered EXTRANEAL. Investigations indicate that icodextrin and its metabolites interfere with enzymatic-based amylase assays, resulting in inaccurately low values. This should be taken into account when evaluating serum amylase levels for diagnosis or monitoring of pancreatitis in patients using EXTRANEAL.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of EXTRANEAL, or in conjunction with performing the peritoneal dialysis procedure. Because these reactions are reported voluntarily from a

population of uncertain size, it is not possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Thrombocytopenia, Leukopenia, Leukocytosis

IMMUNE SYSTEM DISORDERS: Vasculitis, Serum sickness, Hypersensitivity

METABOLISM AND NUTRITION DISORDERS: Hypoglycemic shock, Dehydration

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, Ileus, Ascites, Inguinal hernia

SKIN AND SUBCUTANEOUS DISORDERS: Toxic epidermal necrolysis, Angioedema, Urticaria generalized, Prurigo, Dermatitis (including bullous, allergic and contact), Erythema, Onychomadesis, Dry skin, Skin chapped, Blister

MUSCULOSKELETAL, CONNECTIVE TISSUE DISORDERS: Musculoskeletal pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: Penile edema, Scrotal edema

GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS: Pyrexia, Chills, Malaise, Catheter site erythema, Catheter site inflammation, Infusion related reaction (including Infusion site pain, Instillation site pain)

INVESTIGATIONS: Liver function test abnormal, Urine output decreased

7. DRUG INTERACTIONS

As with other dialysis solutions, blood concentrations of dialyzable drugs may be reduced by dialysis. Dosage adjustment of concomitant medications may be necessary. In patients using cardiac glycosides (digoxin and others), plasma levels of calcium, potassium and magnesium must be carefully monitored [*see Warnings and Precautions (5.7)*].

Insulin: Patients with insulin-dependent diabetes may require modification of insulin dosage following initiation of treatment with EXTRANEAL. Monitor blood glucose and adjust insulin, if needed [*see Boxed Warning*].

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with EXTRANEAL or icodextrin. It is also not known whether EXTRANEAL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

8.3 Nursing Mothers

It is not known whether icodextrin or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when EXTRANEAL is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

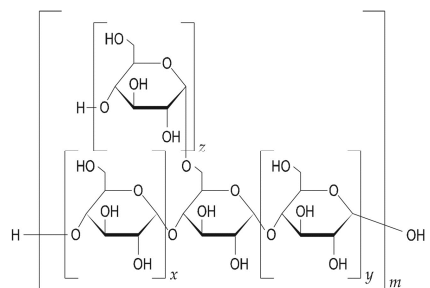
No formal studies were specifically carried out in the geriatric population. However, 140 of the patients in clinical studies of EXTRANEAL were age 65 or older, with 28 of the patients age 75 or older. No overall differences in safety or effectiveness were observed between these patients and patients under age 65. Although clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

10. OVERDOSAGE

No clinical trial data are available on experiences of overdosage with EXTRANEAL. Overdosage of EXTRANEAL would be expected to result in higher levels of serum icodextrin and metabolites, but it is not known what signs or symptoms might be caused by exposure in excess of the exposures used in clinical trials. An increase in plasma osmolality or clinical manifestations of hypovolemia may occur. In the event of overdosage with EXTRANEAL, continued peritoneal dialysis with glucose-based solutions should be provided.

11. DESCRIPTION

EXTRANEAL (icodextrin) Peritoneal Dialysis Solution is a solution intended for intraperitoneal administration that contains the colloid osmotic agent icodextrin. Icodextrin is a starch-derived, water-soluble glucose polymer linked by alpha (1-4) and less than 10% alpha (1-6) glucosidic bonds with a weight-average molecular weight between 13,000 and 19,000 Daltons and a number average molecular weight between 5,000 and 6,500 Daltons. The representative structural formula of icodextrin is:



Each 100 mL of EXTRANEAL contains:

| | |
|----------------------|--------|
| Icodextrin | 7.5 g |
| Sodium Chloride, USP | 535 mg |

| | |
|-------------------------|---------|
| Sodium Lactate | 448 mg |
| Calcium Chloride, USP | 25.7 mg |
| Magnesium Chloride, USP | 5.08 mg |

Electrolyte content per liter:

| | |
|-----------|-----------|
| Sodium | 132 mEq/L |
| Calcium | 3.5 mEq/L |
| Magnesium | 0.5 mEq/L |
| Chloride | 96 mEq/L |
| Lactate | 40 mEq/L |

Water for Injection, USP qs

HCl/NaOH may have been used to adjust pH.

EXTRANEAL contains no bacteriostatic or antimicrobial agents.

Calculated osmolarity: 282-286 mOsm/L; pH=5.0-6.0

EXTRANEAL is a sterile, nonpyrogenic, clear solution packaged in AMBU-FLEX II and ULTRABAG containers. The container systems are composed of polyvinyl chloride.

Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million; however, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

EXTRANEAL is an isosmotic peritoneal dialysis solution containing glucose polymers (icodextrin) as the primary osmotic agent. Icodextrin functions as a colloid osmotic agent to achieve ultrafiltration during long peritoneal dialysis dwells. Icodextrin acts in the peritoneal cavity by exerting osmotic pressure across small intercellular pores resulting in transcapillary ultrafiltration throughout the dwell. Like other peritoneal dialysis solutions, EXTRANEAL also contains electrolytes to help normalize electrolyte balance and lactate to help normalize acid-base status.

12.2 Pharmacodynamics

EXTRANEAL results in a reduction in the absorbed caloric (carbohydrate) load compared to 4.25% hyperosmolar glucose solutions. Additionally, EXTRANEAL results in an increased ultrafiltration volume per gram of absorbed carbohydrate compared to hyperosmolar glucose solutions.

12.3 Pharmacokinetics

Absorption

Absorption of icodextrin from the peritoneal cavity follows zero-order kinetics consistent with convective transport via peritoneal lymphatic pathways. In a single-dose pharmacokinetic study using EXTRANEAL, a median of 40% (60 g) of the instilled icodextrin was absorbed from the peritoneal solution during a 12-hour dwell. Plasma levels of icodextrin rose during the dwell and declined after the dwell was drained. Peak plasma levels of icodextrin plus its metabolites (median C_{peak} 2.2 g/L) were observed at the end of the long dwell exchange (median T_{max} = 13 hours).

At steady-state, the mean plasma level of icodextrin plus its metabolites was about 5 g/L. In multi-dose studies, steady-state levels of icodextrin were achieved within one week. Plasma levels of icodextrin and metabolites return to baseline values within approximately two weeks following cessation of icodextrin administration.

Metabolism

Icodextrin is metabolized by alpha-amylase into oligosaccharides with a lower degree of polymerization (DP), including maltose (DP2), maltotriose (DP3), maltotetraose (DP4), and higher molecular weight species. In a single dose study, DP2, DP3 and DP4 showed a progressive rise in plasma concentrations with a profile similar to that for total icodextrin, with peak values reached by the end of the dwell and declining thereafter. Only very small increases in blood levels of larger polymers were observed. Steady-state plasma levels of icodextrin metabolites were achieved within one week and stable plasma levels were observed during long-term administration.

Some degree of metabolism of icodextrin occurs intraperitoneally with a progressive rise in the concentration of the smaller polymers in the dialysate during the 12-hour dwell.

Elimination

Icodextrin undergoes renal elimination in direct proportion to the level of residual renal function. Diffusion of the smaller icodextrin metabolites from plasma into the peritoneal cavity is also possible after systemic absorption and metabolism of icodextrin.

Special Populations

Geriatrics

The influence of age on the pharmacokinetics of icodextrin and its metabolites was not assessed.

Gender and Race

The influence of gender and race on the pharmacokinetics of icodextrin and its metabolites was not assessed.

Drug Interactions

Insulin

A clinical study in 6 insulin-dependent diabetic patients demonstrated no effect of EXTRANEAL on insulin absorption from the peritoneal cavity or on insulin's ability to control blood glucose when insulin was administered intraperitoneally with EXTRANEAL. However, appropriate monitoring of blood glucose should be performed when initiating EXTRANEAL in diabetic patients and insulin dosage should be adjusted if needed [see *Drug Interactions (7)*].

Heparin

In vitro studies demonstrated no evidence of incompatibility of heparin with EXTRANEAL.

Antibiotics

Compatibility has been demonstrated with vancomycin, cefazolin, ceftazidime, gentamicin, and netilmicin. However, aminoglycosides should not be mixed with penicillins due to chemical incompatibility.

Minimum Inhibitory Concentration (MIC)

No formal clinical drug 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/fluoxacillin, ceftazidime, gentamicin, and amphotericin.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Icodextrin did not demonstrate evidence of genotoxicity potential in *in vitro* bacterial cell reverse mutation assay (Ames test); *in vitro* mammalian cell chromosomal aberration assay (CHO cell assay); and in the *in vivo*

micronucleus assay in mice. Long-term animal studies to evaluate the carcinogenic potential of EXTRANEAL or icodextrin have not been conducted. Icodextrin is derived from maltodextrin, a common food ingredient.

A fertility study in rats where males and females were treated for four and two weeks, respectively, prior to mating and until day 17 of gestation at up to 1.5 g/kg/day (1/3 the human exposure on a mg/m² basis) revealed slightly low epididymal weights in parental males in the high dose group as compared to Control. Toxicological significance of this finding was not evident as no other reproductive organs were affected and all males were of proven fertility. The study demonstrated no effects of treatment with icodextrin on mating performance, fertility, litter response, embryo-fetal survival, or fetal growth and development.

14. CLINICAL STUDIES

EXTRANEAL has demonstrated efficacy as a peritoneal dialysis solution in clinical trials of approximately 480 patients studied with end-stage renal disease (ESRD).

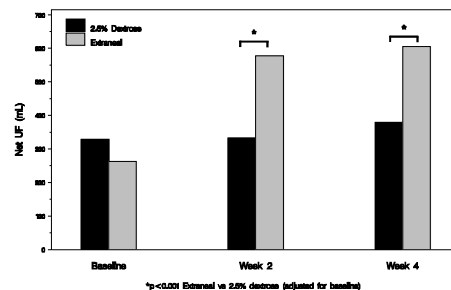
14.1 Ultrafiltration, Urea and Creatinine Clearance

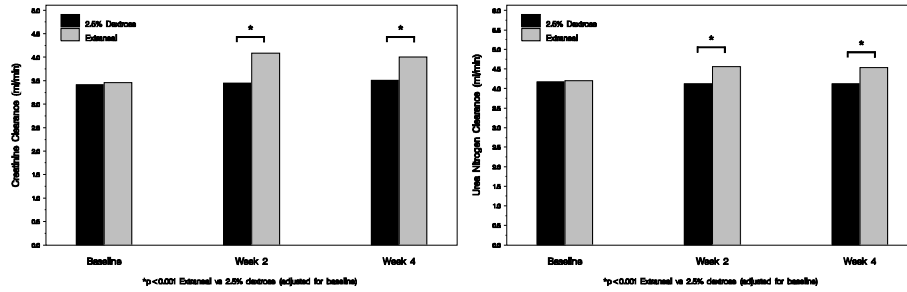
In the active-controlled trials of one to six months in duration, described below, EXTRANEAL used once-daily for the long dwell in either continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) therapy resulted in higher net ultrafiltration than 1.5% and 2.5% dextrose solutions, and higher creatinine and urea nitrogen clearances than 2.5% dextrose. Net ultrafiltration was similar to 4.25% dextrose across all patients in these studies. Effects were generally similar in CAPD and APD.

In an additional randomized, multicenter, active-controlled two-week study in high average/high transporter APD patients, EXTRANEAL used once daily for the long dwell produced higher net ultrafiltration compared to 4.25% dextrose. Mean creatinine and urea nitrogen clearances were also greater with EXTRANEAL and ultrafiltration efficiency was improved.

In 175 CAPD patients randomized to EXTRANEAL (N=90) or 2.5% dextrose solution (N=85) for the 8-15 hour overnight dwell for one month, mean net ultrafiltration for the overnight dwell was significantly greater in the EXTRANEAL group at weeks 2 and 4 (Figure 1). Mean creatinine and urea nitrogen clearances were also greater with EXTRANEAL (Figure1).

Figure 1 - Mean Net Ultrafiltration, Mean Creatinine and Urea Nitrogen Clearance for the Overnight Dwell



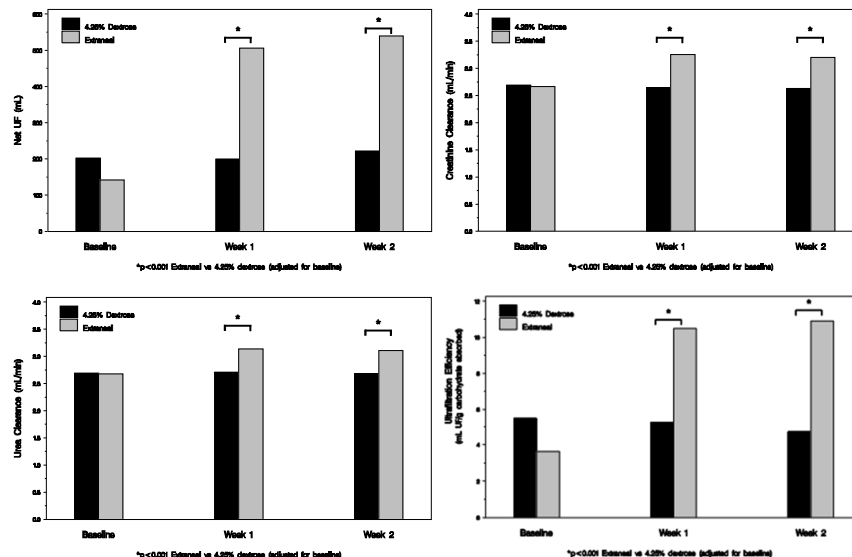


In another study of 39 APD patients randomized to EXTRANEAL or 2.5% dextrose solution for the long, daytime dwell (10-17 hours) for three months, the net ultrafiltration reported during the treatment period was (mean ± SD) 278 ± 192 mL for the EXTRANEAL group and -138 ± 352 mL for the dextrose group (p<0.001). Mean creatinine and urea nitrogen clearances were significantly greater for EXTRANEAL than 2.5% dextrose at weeks 6 and 12 (p<0.001).

In a six-month study in CAPD patients comparing EXTRANEAL (n=28) with 4.25% dextrose (n=31), net ultrafiltration achieved during an 8-hour dwell averaged 510 mL for EXTRANEAL and 556 mL for 4.25% dextrose. For 12-hour dwells, net ultrafiltration averaged 575 mL for EXTRANEAL (n=29) and 476 mL for 4.25% dextrose (n=31). There was no significant difference between the two groups with respect to ultrafiltration.

In a two week study in high average/high transporter APD patients (4-hour D/P creatinine ratio >0.70 and a 4-hour D/D₀ ratio <0.34, as defined by the peritoneal equilibration test (PET)), comparing EXTRANEAL (n=47) to 4.25% dextrose (n=45), after adjusting for baseline, the mean net ultrafiltration achieved during a 14 ± 2 hour dwell was significantly greater in the EXTRANEAL group than the 4.25% dextrose group at weeks 1 and 2 (p<0.001, see Figure 2). Consistent with increases in net ultrafiltration, there were also significantly greater creatinine and urea nitrogen clearances and ultrafiltration efficiency in the EXTRANEAL group (p<0.001, see Figure 2).

Figure 2 – Mean Net Ultrafiltration, Creatinine and Urea Nitrogen Clearances and Ultrafiltration Efficiency for the Long Dwell in High Average/High Transporter Patients



14.2 Peritoneal Membrane Transport Characteristics

After one year of treatment with EXTRANEAL during the long dwell exchange, there were no differences in membrane transport characteristics for urea and creatinine. The mass transfer area coefficients (MTAC) for urea,

creatinine, and glucose at one year were not different in patients receiving treatment with EXTRANEAL or 2.5% dextrose solution for the long dwell.

16. HOW SUPPLIED/STORAGE AND HANDLING

EXTRANEAL (icodextrin) Peritoneal Dialysis Solution is available in the following containers and fill volumes:

| Container | Fill Volume | NDC |
|--------------|-------------|------------------|
| ULTRABAG | 2 L | NDC 0941-0679-52 |
| ULTRABAG | 2.5 L | NDC 0941-0679-53 |
| AMBU-FLEX II | 2 L | NDC 0941-0679-06 |
| AMBU-FLEX II | 2.5 L | NDC 0941-0679-05 |

Each 100 mL of EXTRANEAL contains 7.5 grams of icodextrin in an electrolyte solution with 40 mEq/L lactate.

Store at 20–25°C (68–77°F). Excursions permitted to 15–30°C (59–86°F) [See USP Controlled Room Temperature]. Protect from freezing.

Store in moisture barrier overwrap and in carton until ready to use.

17. PATIENT COUNSELING INFORMATION

See Medication Guide. A Patient Medication Guide is provided in each carton of EXTRANEAL.

Inform patients of the following:

- Only use glucose-specific monitors and test strips [*see Boxed Warning*]. Use of non-specific blood glucose monitors and test strips has resulted in falsely elevated blood glucose readings due to the presence of maltose. Falsely elevated blood glucose readings have led patients or health care providers to withhold treatment of hypoglycemia or to administer insulin inappropriately. Both of these situations have resulted in unrecognized hypoglycemia, which has led to loss of consciousness, coma, neurological damage, and death.
- Serious allergic reactions have been observed in patients using EXTRANEAL. Patients should call their doctor or get medical help if they experience any of these symptoms during treatment with EXTRANEAL: swelling of the face, eyes, lips, tongue, or mouth; trouble swallowing or breathing; skin rash, hives, sores in the mouth, on eyelids, or in the eyes; or, if skin blisters or peels.
- Peritonitis is a common side effect of patients on peritoneal dialysis. Symptoms of peritonitis may include cloudy peritoneal effluent, pain, erythema or drainage at the exit site, or fever.

Because patients self-administer EXTRANEAL at home, patients should also be instructed to:

- Bring their EXTRANEAL Patient Kit with them when receiving care outside of the dialysis clinic to inform health care providers of their EXTRANEAL use so that only glucose-specific monitors and test strips are used. An EXTRANEAL Patient Kit will be shipped to the patient's home once EXTRANEAL is added to their prescription, following training by the dialysis clinic.
- Follow the peritoneal dialysis (PD) training instructions given by the health care provider. Use aseptic technique throughout their entire PD procedure. Discard any unused EXTRANEAL solution [*see Dosage and Administration (2.2)*].

- Check the appearance of EXTRANEAL solution prior to use. Do not use EXTRANEAL if solution appears cloudy, discolored, contain visible particulate matter, or if there is evidence of leaking containers.
- Regularly check fluid balance and body weight to avoid over-hydration or dehydration and associated side effects.
- Inform their physicians about any changes in prescription or over-the-counter medications and supplements.
- Have periodic laboratory tests and routinely follow up with their health care provider.
- In case of damage, the container should be discarded.

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