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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EXTRANEAL (Icodextrin 7.5%)
Solution for peritoneal dialysis.

2. Qualitative and Quantitative Composition

A sterile peritoneal dialysis fluid containing Icodextrin at a concentration of 7.5% w/v in an electrolyte solution.

Icodextrin	75	g/L
Sodium Chloride	5.4	g/L
Sodium Lactate	4.5	g/L
Calcium Chloride	0.257	g/L
Magnesium Chloride	0.051	g/L

Theoretical osmolarity 284 (milliosmoles per litre)

Theoretical osmolality 301 (milliosmoles per kg)

Electrolyte solution content per 1000 ml:

Sodium	133 mmol/L
Calcium	1.75 mmol/L
Magnesium	0.25 mmol/L
Chloride	96 mmol/L
Lactate	40 mmol/L

pH = 5 to 6.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for peritoneal dialysis.
Extraneal is a sterile, clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and Method of Administration

Extraneal is recommended for use during the longest dwell period, i.e. in CAPD usually overnight and in APD for the long daytime dwell.

Adults: by intraperitoneal administration limited to a single exchange in each 24 hour-period, as part of a CAPD or APD regimen.

Elderly: As for Adults.

Children: not recommended for use in children (less than 18 years).

The volume to be instilled should be given over a period of approximately 10 to 20 minutes at a rate which the patient finds comfortable. For adult patients of normal body size the instilled volume should not exceed 2.0 L.

For larger patients (more than 70-75 kg), a fill volume of 2.5 L may be used.

If the instilled volume causes discomfort due to abdominal tension the instilled volume should be reduced. The recommended dwell time is between 6 and 12 hours in CAPD and 14-16 hours in APD. Drainage of the fluid is by gravity 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 or aseptic peritonitis (see Section 4.4).

4.3 **Contra-indications**

Extraneal should not be used in patients with a known allergy to starch based polymers and in patients with maltose or isomaltose intolerance or patients with glycogen storage disease.

Extraneal is also contra-indicated in patients with a history of abdominal surgery in the month preceding commencement of therapy or in patients with abdominal fistulae, tumours, open wounds, herniae or other conditions which compromise the integrity of the abdominal wall, abdominal surface or intra-abdominal cavity.

4.4 **Special Warnings and Precautions for Use**

Extraneal is not recommended during pregnancy or lactation (see section 4.6), in children or in patients with acute renal failure.

In common with other peritoneal dialysis fluids, Icodextrin should be used with caution, after careful evaluation of its potential risks and benefits, in patients with conditions which preclude normal nutrition, with impaired respiratory function or with potassium deficiency.

Patients should be carefully monitored to avoid over or under hydration. Enhanced ultra-filtration, particularly in elderly patients, may lead to dehydration, resulting in hypotension and possibly neurological symptoms.

An accurate fluid balance record should be kept and the patient's body weight monitored.

Blood chemistry, haematology and plasma osmolality should be monitored at regular intervals.

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

Patients with diabetes mellitus often need additional insulin in order to maintain glycaemic control during Peritoneal Dialysis (PD). Transfer from glucose based PD solution to Extraneal may necessitate an adjustment of the usual insulin dosage.

Insulin can be administered intraperitoneally.

Blood glucose measurement must be done with a glucose specific method to prevent maltose interference. Glucose dehydrogenase pyrroloquinolinequinone (GDH PQQ) or glucose-dye-oxidoreductase-based methods should not be used. If GDH-PQQ or glucose-dye-oxidoreductase-based methods are used, using Extraneal may cause a falsely high glucose reading, which could result in the administration of more insulin than needed. This can cause hypoglycaemia, which can result in loss of consciousness, coma, neurological damage and death. Additionally, falsely elevated blood glucose measurements due to maltose interference may mask true hypoglycaemia and allow it to go untreated with similar consequences. It is recommended that reference is made to the relevant section of the glucose test kit product leaflet to ascertain that interference while using Icodextrin-based dialysis therapy or maltose / medicines metabolised to maltose is not described.

A decrease in the serum sodium and chloride level has been observed in some patients. Though these decreases have been regarded as clinically non-significant, it is recommended that serum electrolyte levels are monitored regularly.

A decrease in serum amylase levels has also been noticed as a common finding in PD patients on long term treatment. The decrease has not been reported to be accompanied with any side effects. However, it is not known whether subnormal amylase level may mask the rise in serum amylase, commonly seen during acute pancreatitis. An increase in mean serum alkaline phosphatase of approximately 20IU/L was seen during clinical trials. There were individual cases where increased alkaline phosphatase was associated with elevated SGOT levels.

Treatment should be initiated under the supervision of a physician experienced in the treatment of patients with renal failure.

Peritoneal reactions, including abdominal pain, cloudy effluents with or without bacteria (aseptic peritonitis) have been associated with Extraneal (see section 4.8.2). In case of peritoneal reactions, the patient should keep the icodextrin drained fluid bag along with its batch number, and contact the medical team for analysis of the drained fluid bag.

The drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of infection or aseptic peritonitis. Patients should be asked to inform their physician if this occurs and appropriate microbiological samples should be drawn. The initiation of antibiotic treatment should be a clinical decision based on whether or not infection is suspected. If other possible reasons for cloudy fluid have been excluded, Extraneal should be stopped and the result of this action evaluated. If Extraneal is stopped and the fluid becomes clear afterwards, Extraneal should not be reintroduced unless under close supervision. If by re-challenging with Extraneal, the cloudy fluid recurs then this patient should not be prescribed Extraneal again. Alternative peritoneal dialysis therapy should be initiated and the patient should be kept under close supervision.

4.5 **Interactions with other Medicinal Products and other forms of Interaction**

None known - however, the blood concentrations of dialysable drugs may be reduced by dialysis. Corrective therapy should be instituted if necessary. In patients using cardiac glycosides, plasma levels of potassium and calcium must be carefully checked. In the event of abnormal levels, appropriate actions should be taken.

Glucose dehydrogenase pyrroloquinolinequinone (GDH PQQ) or glucose-dye-oxidoreductase-based methods to measure glucose should not be used while using Extraneal (see section 4.4).

4.6 **Pregnancy and Lactation**

Animal studies on the effects of Icodextrin are insufficient with respect to effects on embryonal/foetal development and lactation.

There are no adequate data from the use of Extraneal in pregnant women.

Extraneal should not be used during pregnancy or while breast feeding unless clearly necessary.

Women of childbearing potential should be treated with Extraneal only when adequate contraceptive precautions have been taken.

4.7 Effects on Ability to Drive and Use Machines

None known.

4.8 Undesirable Effects

4.8.1 Undesirable effects which occurred in patients treated with Extraneal from the clinical trials are listed below. The adverse drug reactions listed in this section are given following the recommended frequency convention: very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; very rare: $< 0.01\%$.

MedRA Standard System Organ Class (SOC)	Undesirable effects Preferred term/High Level Term (PT)	Frequency
Metabolism and nutrition disorders	Dehydration Hypochloraemia Hyponatraemia Hypovolaemia	Common Common Common Common
Nervous system disorders	Dizziness Headache	Common Common
Vascular disorders	Hypertension Hypotension	Common Common
Gastrointestinal disorders	Abdominal pain	Common
Skin and subcutaneous disorders	Pruritus Rash Skin exfoliation	Common Common Common
General disorders and administration site conditions	Asthenia Oedema	Common Common
Investigations	Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphate increased Blood amylase decreased	Uncommon Uncommon Common Common

4.8.2 Some undesirable effects, probably related to Extraneal, are indicated below.

Extraneal associated skin reactions, including rash and pruritus, are generally mild or moderate in severity. Occasionally, these rashes have been associated with exfoliation. In the event of this occurring and depending on the severity, Extraneal should be withdrawn at least temporarily.

Enhanced ultrafiltration, particularly in the elderly patients, may lead to dehydration, resulting in hypotension, dizziness and possibly neurological symptoms (see section 4.4).

Hypoglycemic episodes in diabetic patients (see section 4.4).

Increase in serum alkaline phosphatases (see section 4.4).

Peritoneal reactions, including abdominal pain, cloudy effluents with or without bacteria, aseptic peritonitis (see section 4.4).

4.8.3 Other undesirable effects of peritoneal dialysis related to the procedure

The following undesirable effects are often reported spontaneously and in the literature.

-Those which are related to the procedure, include peritonitis (septic or aseptic) with or without abdominal pain, cloudy effluent and sometimes fever; bleeding, catheter blockage, infection around the catheter (signs of inflammation: redness and secretion), hypervolaemia, hypovolaemia, hypertension, hypotension, dehydration, oedema, constipation, hernia of the abdominal cavity, ileus, loss of appetite, dyspepsia, nausea and vomiting, dizziness, fatigue, headache, shoulder pain, pruritus and abnormal laboratory tests results.

-Those which are generally related to peritoneal dialysis solutions, are seen less frequently than those related to the procedure and include cloudy effluent/aseptic peritonitis, electrolyte disturbances (e.g. hypokalaemia, hypocalcaemia and hypercalcaemia), fainting, muscle cramping, respiratory symptoms associated with shortness of breath and weakness.

4.9 Overdose

No data are 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.

5. PHARMACOLOGICAL PROPERTIES

Code ATC: B05DA.

5.1 Pharmacodynamic Properties

Icodextrin is a starch-derived glucose polymer which acts as an osmotic agent when administered intraperitoneally for continuous ambulatory peritoneal dialysis. A 7.5% solution is approximately iso-osmolar to serum but produces sustained ultrafiltration over a period up to 12 hours in CAPD. There is a reduction in calorie load compared to hyperosmolar glucose solutions.

The volume of ultrafiltrate produced is comparable to that with 3.86% glucose when used in CAPD. Blood glucose and insulin levels remain unaffected.

Ultrafiltration is maintained during episodes of peritonitis.

The recommended posology is limited to a single exchange in each 24 hour-period, as part of a CAPD or APD regimen.

5.2 Pharmacokinetic Properties

Carbohydrate polymer levels in blood reach steady state after about 7-10 days when used on a daily basis for overnight dialysis. The polymer is hydrolysed by amylase to smaller fragments which are cleared by peritoneal dialysis. Steady state plasma levels of 1.8 mg/ml have been measured for oligomers of glucose units greater than 9 (G9) and there is a rise in serum maltose (G2) to 1.1 mg/ml but there is no significant change in serum osmolality. When used for the long day time dwell in APD maltose levels of 1.4 mg/ml have been measured but with no significant change in serum osmolality.

The long term effects of raised plasma levels of maltose and glucose polymer are unknown, but there is no reason to suppose these to be harmful.

5.3 Preclinical Safety Data

Acute toxicity

Acute i.v. and i.p. studies in mice and rats have demonstrated no effects at doses up to 2000 mg/kg.

Subchronic toxicity

Twice daily i.p. administration of 20% Icodextrin solution for 28 days to rats and dogs revealed no target organ or tissue toxicity. The major effect was upon the dynamics of fluid balance.

Mutagenic and tumorigenic potential

In vitro and in vivo studies on mutagenicity gave negative results. Carcinogenicity studies with the product are not feasible but carcinogenic effects are unlikely given the chemical nature of the molecule, its lack of pharmacological effect, lack of target organ toxicity and negative results in mutagenicity studies.

Reproductive toxicity

A reproduction toxicity study in rats demonstrated no effect on fertility or embryofetal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Water for Injections
Sodium Hydroxide or
Hydrochloric acid q.s. to required pH.

6.2 Incompatibilities

Drug compatibility must be checked before admixture. In addition, the pH and salts of the solution must be taken into account.

6.3 Special Precautions for Storage

Do not store above 30°C. Do not use unless the solution is clear and the container undamaged.

The product, once removed from its overpouch should be used immediately.

6.4 Presentation

Plastic bags of 2 and 2.5 liters.
Pouches of 2 and 2.5 liters.

6.5 Special Precautions for Disposal

Do not administer unless the solution is clear and the container undamaged.

Aseptic technique should be observed throughout the procedure.

To reduce discomfort on administration, the solution may be warmed in the oversealed bag to a temperature of 37°C prior to use.

This should be done using dry heat, ideally using a warming plate specially designed for the purpose. The bag should not be immersed in water to warm it to avoid contamination of connectors.

A range of antibiotics including vancomycin, cephazolin, ampicillin/flucloxacillin, ceftazidime, gentamycin, amphotericin and insulin have shown no evidence of incompatibility with Extraneal.

The product should be used immediately after any drug addition.
Discard any unused remaining solution.
For single use only.

7. **REGISTRATION NUMBER**

116 27 29763 00.

8. **MANUFACTURER**

Baxter Healthcare S.A., Ireland

9. **IMPORTER**

Teva Medical Marketing Ltd.,
Haorgim St. 2, Ashdod 77100