Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

EXTRANEAL Solution for peritoneal dialysis

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

A sterile peritoneal dial y sis fluid containing Ic odextri n at a concentration of 7 .5 % w/v in an electroly te solution.

Icodextrin	75	g/L
Sodium Chloride	5.4	g/L
Sodium S-Lactate	4.5	g/L
Calciu m Chloride	0.25 7	g/L
Magnesiu m Chloride	0.05 1	g/L

Theoretical osm o larity : 284 (m illiosm oles per litre)
Theoretical osm o lality : 301 (m illiosm oles per kg)

Electroly te so lution co ntent per 100 0 m l:

Sodium	133	mmol/L
Calciu m	1.75	mmol/L
Magnesiu m	0.25	mmol/L
Chloride	96	mmol/L
Lactate	40	mmol/L

pH = 5 to 6

For the full list of excipients, see se ction 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

Posology:

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

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

Adults

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

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 2.5L 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.

Older people

As for Adults.

Paediatric population

The safety and efficacy of Extraneal in children aged less than 18 years has not been established. No data are available.

Administration:

Precautions to be taken before handling or administering the medicinal product

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

• Peritoneal dialysis solutions may be warmed in the overpouch to 37°C to enhance patient comfort. However, only dry heat (for example, heating pad, warming plate) should be used. Solutions should not be heated in water or in a microwave oven due to the potential for patient injury or discomfort.

• Aseptic technique should be employed throughout the peritoneal dialysis procedure.

• 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 infection or aseptic peritonitis (see Section 4.4).

• For single use only

4.3 Contraindications

Extraneal should not be used in patients with:

• Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
• a known allergy to starch based polymers (e.g. maize starch) and/or icodextrin
• maltose or isomaltose intolerance
• glycogen storage disease
• pre-existing severe lactic acidocis
• 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

4.4 Special warnings and precautions for use

- 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 (GDO)-based methods should 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 hypoglycaemia, 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 hypoglycaemia 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, or GDH-FAD-based blood glucose monitors may be used in hospital settings, it is important that the health care providers of 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 patients to alert healthcare providers of this interaction whenever they are admitted to the hospital.

- Peritoneal dialysis should be done with caution in patients with: 1) abdominal conditions, including disruption of the peritoneal membrane and diaphragm by surgery, from congenital anomalies or trauma until healing is complete, abdominal tumours, abdominal wall infection, hernias, faecal fistula, colostomy or iliostomy, frequent episodes of diverticulitis, inflammatory or ischemic bowel disease, 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 recent aortic graft replacement and severe pulmonary disease.

- Ecapsulating 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 some patients using EXTRANEAL as part of their PD therapy. Infrequently, fatal outcomes have been reported with EXTRANEAL.

- Patients with conditions known to increase the risk of lactic acidocis [e.g., severe hypotension, sepsis, acute renal failure, inborn errors of metabolism, treatment with drugs such as metformin and nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)] should 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.

- Peritoneal reactions, including abdominal pain, cloudy effluents with or without bacteria (aseptic peritonitis) have been associated with Extraneal (see section 4.8). 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.

- 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), broadspectrum antibiotics may be indicated.

- Rarely, serious hypersensitivity reactions to Extraneal have been reported such as toxic epidermal necrolysis, angioedema, 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.

- Extraneal is not recommended in patients with acute renal failure.

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

- 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.

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

- Treatment of EXTRANEAL overinfusion is to release the EXTRANEAL from the peritoneal cavity by drainage of the EXTRANEAL volume contained within the peritoneal cavity.

- 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.

- 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.

- 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 serum alkaline phosphatase of approximately 20 IU/L was seen during clinical trials. There were individual cases where increased alkaline phosphatase was associated with elevated SGOT levels.

Paediatric population

- Extraneal is not recommended in children

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been conducted with EXTRANEAL. The blood concentrations of dialysable drugs may be reduced by dialysis. Corrective therapy should be instituted if necessary.

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 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. (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of Extraneal in pregnant women.
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
Extraneal is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding
It is unknown whether Extraneal metabolites are excreted in human milk.
A risk to the newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Extraneal therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
There are no clinical data on fertility.

4.7 Effects on ability to drive and use machines

End stage renal disease (ESRD) patients undergoing peritoneal dialysis may experience undesirable effects, which could affect the ability to drive or use machines.

4.8 Undesirable effects

Undesirable effects which occurred in patients treated with Extraneal from the clinical trials and post marketing are listed 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.

Frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100-<1/10), Uncommon (≥1/1,000-<1/100), Rare (≥1/10,000-<1/1,000), Very Rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class (SOC)	Preferred MedDRA Term	Frequency
INFECTIONS AND INFESTATIONS	Flu syndrome Furuncle	Uncommon Uncommon
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Anaemia Leukocytosis Eosinophilia Thrombocytopenia Leucopenia	Uncommon Uncommon Uncommon Not known Not known
IMMUNE SYSTEM DISORDERS	Vasculitis Hypersensitivity**	Not known Not known
METABOLISM AND NUTRITION DISORDERS	Dehydration Hypovolaemia Hypoglycaemia Hyponatraemia Hyperglycaemia Hypervolaemia Anorexia Hypochloraemia Hypomagnesaemia Hypoproteinaemia Shock hypoglycaemia Fluid imbalance	Common Common Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Not known Not known
PSYCHIATRIC DISORDERS	Thinking abnormal Anxiety Nervousness	Uncommon Uncommon Uncommon
NERVOUS SYSTEM DISORDERS	Dizziness Headache Hyperkinesia Paraesthesia Ageusia Hypoglycaemic coma Burning sensation	Common Common Uncommon Uncommon Uncommon Not known Not known
EYE DISORDERS	Vision blurred	Not known
EAR AND LABYRINTH DISORDERS	Tinnitus	Common
CARDIAC DISORDERS	Cardiovascular disorder Tachycardia	Uncommon Uncommon
VASCULAR DISORDERS	Hypotension Hypertension Orthostatic hypotension	Common Common Uncommon
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	Pulmonary oedema Dyspnoea Cough Hiccups Bronchospasm	Uncommon Uncommon Uncommon Uncommon Not known
GASTROINTESTINAL	Abdominal pain	Common

DISORDERS	Ileus	Uncommon
	Peritonitis	Uncommon
	Bloody peritoneal effluent	Uncommon
	Diarrhoea	Uncommon
	Gastric ulcer	Uncommon
	Gastritis	Uncommon
	Vomiting	Uncommon
	Constipation	Uncommon
	Dyspepsia	Uncommon
	Nausea	Uncommon
	Dry mouth	Uncommon
	Flatulence	Uncommon
	Ascites	Not known
	Inguinal hernia	Not known
	Abdominal discomfort	Not known
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash (including macular, papular, erythematous)	Common
	Pruritus	Common
	Skin exfoliation	Common
	Urticaria	Uncommon
	Dermatitis bullous	Uncommon
	Psoriasis	Uncommon
	Skin ulcer	Uncommon
	Eczema	Uncommon
	Nail disorder	Uncommon
	Dry skin	Uncommon
	Skin discolouration	Uncommon
	Toxic epidermal necrolysis	Not known
	Erythema multiform	Not known
	Angiodema	Not known
	Urticaria generalised	Not known
	Toxic skin eruption	Not known
	Periorbital oedema	Not known
	Dermatitis (including allergic and contact)	Not known
	Erythema	Not known
	Blister	Not known
MUSCULOSKELETAL ANDCONNECTIVE TISSUE DISORDERS	Bone pain	Uncommon
	Muscle spasms	Uncommon
	Myalgia	Uncommon
	Neck pain	Uncommon
	Arthralgia	Not known
	Back pain	Not known
	Musculoskeletal pain	Not known
RENAL AND URINARY DISORDERS	Renal pain	Uncommon
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS	Oedema peripheral	Common
	Asthenia	Common
	Chest pain	Uncommon
	Face oedema	Uncommon
	Oedema	Uncommon
	Pain	Uncommon
	Pyrexia	Not known
	Chills	Not known
	Malaise	Not known
	Catheter site erythema	Not known
	Catheter site inflammation	Not known

	Infusion related reaction (including infusion site pain, instillation site pain)	Not known
INVESTIGATIONS	Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Liver function test abnormal Weight decreased Weight increased	Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS	Device interaction*	Not known

*Icodextrin interferes with blood glucose measurement devices (see section 4.4).

** Hypersensitivity-type reactions have been reported in patients using Extraneal including bronchospasm, hypotension, rash, pruritus and urticaria

Other undesirable effects of peritoneal dialysis related to the procedure: fungal peritonitis, bacterial peritonitis, catheter site infection, catheter related infection and catheter related complication.

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

Hypoglycaemic episodes in diabetic patients (see section 4.4).

Increase in serum alkaline phosphatases (see section 4.4) and electrolyte disturbances (e.g. hypokalaemia, hypocalcaemia and hypercalcaemia).

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

Fatigue was often reported spontaneously and in literature as an undesirable effect related to the procedure.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

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

5.1 Pharmacodynamic properties

Code ATC: B05DA

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 2000mg/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

None Known.
Drug compatibility must be checked before admixture. In addition, the pH and salts of the solution must be taken into account.

6.3 Shelf life

2 years
12 months (for medicinal product manufactured at Alliston, Canada and North Cove, USA only).
The product, once removed from its overpouch, should be used immediately.

6.4 Special precautions for storage

Do not store below 4°C. Do not use unless the solution is clear and the container undamaged.

6.5 Nature and contents of container

Flexible PVC container holding 1.5, 2.0 or 2.5 litres.

1.5 L 8 units per box Single bag Sy II (luer connector)
1.5 L 8 units per box Single bag Sy III (spike connector)
1.5 L 8 units per box Twin bag Sy II (luer connector)
1.5 L 8 units per box Twin bag Sy III (spike connector)
1.5 L 6 units per box Single bag Sy II (luer connector)
1.5 L 6 units per box Single bag Sy III (spike connector)
1.5 L 6 units per box Twin bag Sy II (luer connector)
1.5 L 6 units per box Twin bag Sy III (spike connector)
2.0 L 8 units per box Single bag Sy II (luer connector)
2.0 L 8 units per box Single bag Sy III (spike connector)
2.0 L 8 units per box Twin bag Sy II (luer connector)
2.0 L 8 units per box Twin bag Sy III (spike connector)
2.0 L 6 units per box Single bag Sy II (luer connector)
2.0 L 6 units per box Single bag Sy III (spike connector)
2.0 L 6 units per box Twin bag Sy II (luer connector)
2.0 L 6 units per box Twin bag Sy III (spike connector)
2.0 L 5 units per box Single bag Sy II (luer connector)
2.0 L 5 units per box Single bag Sy III (spike connector)
2.0 L 5 units per box Twin bag Sy II (luer connector)
2.0 L 5 units per box Twin bag Sy III (spike connector)
2.5 L 5 units per box Single bag Sy II (luer connector)
2.5 L 5 units per box Single bag Sy III (spike connector)
2.5 L 5 units per box Twin bag Sy II (luer connector)
2.5 L 5 units per box Twin bag Sy III (spike connector)
2.5 L 4 units per box Single bag Sy II (luer connector)
2.5 L 4 units per box Single bag Sy III (spike connector)
2.5 L 4 units per box Twin bag Sy II (luer connector)
2.5 L 4 units per box Twin bag Sy III (spike connector)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For details see section 4.2
A range of antibiotics including vancomycin, cephazolin, ampicillin/flucloxacillin, ceftazidime, gentamycin, amphotericin and insulin have shown no evidence of incompatibility with Extraneal. However aminoglycosides should not be mixed with penicillins due to chemical incompatibility.
The product should be used immediately after adding any drug.
Discard any unused remaining solution.

7 MARKETING AUTHORISATION HOLDER

Vantive Belgium SRL
Boulevard D'Angleterre 2
Braine-L'Alleud
1420
Belgium

8 MARKETING AUTHORISATION NUMBER

PA25288/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 July 1997

Date of last renewal: 06 January 2012

10 DATE OF REVISION OF THE TEXT

November 2024