PATIENT INFORMATION LEAFLET

POLINUTHREE EN-1000 Amino Acid Solution With Electrolytes, Glucose Solution And Lipid Emulsion

For intravenous administration bu perpheral and central route.

Sterile

- ***Active substances:*** When the compartments are mixed, each bag contains the following active substances:

Active substances	1000 mL	1500 mL	2000 mL
Refined olive oil (80%) + Refined soybean oil (20%)	40 g	60 g	80 g
L-alanine	8,28 g	12,42 g	16,56 g
L-arginine	4,6 g	6,9 g	9,2 g
Glycine	4,12 g	6,18 g	8,24 g
L-histidine	1,92 g	2,88 g	3,84 g
L-isoleucine	2,4 g	3,6 g	4,8 g
L-leucine	2,92 g	4,38 g	5,84 g
L-lysine (as L-lysine HCl)	2,32 g (2,9 g)	3,48 g (4,35 g)	4,64 g (5,8 g)
L-methionine	1,6 g	2,4 g	3,2 g
L-phenylalanine	2,24 g	3,36 g	4,48 g
L-proline	2,72 g	4,08 g	5,44 g
L-serine	2 g	3 g	4 g
L-threonine	1,68 g	2,52 g	3,36 g
L-tryptophan	0,72 g	1,08 g	1,44 g
L-tyrosine	0,16 g	0,24 g	0,32 g
L-valine	2,32 g	3,48 g	4,64 g
Sodium Acetate $3H_2O$	2,45 g	3,67 g	4,9 g
Sodium glycerophosphate $5H_2O$	2,14 g	3,22 g	4,29 g
Potassium chloride	1,79 g	2,68 g	3,58 g
Magnesium chloride $6H_2O$	0,45 g	0,67 g	0,9 g
Glucose	160 g	240 g	320 g
Calcium chloride $2H_2O$	0,3 g	0,44 g	0,59 g
Total calories (kcal)	1200	1800	2400
Non-protein calories (kcal)	1040	1560	2080

Excipients: Purified egg phosphatide (originated from chicken), glycerol, sodium oleate, sodium hydroxide, glacial acetic acid, hydrochloric acid and water for injection.

Read all of this PATIENT INFORMATION LEAFLET carefully before you start using this medicine because it contains important information for you.

- *Keep this **PATIENT INFORMATION LEAFLET.** You may need to read it again.*
- *If you have any additional questions, please contact your physician or pharmacist.*
- *This medicine has been prescribed personally for you. Do not pass it on to others.*
- *When you go to doctor or hospital while using this medicine, tell your doctor that you are using this medicine.*
- *Please completely follow the instructions in this information leaflet. Do not use **higher** or **lower** doses other than what is recommended to you.*

In this leaflet:

1. What is POLINUTHREE EN-1000 and what is it used for

Pharmacotherapeutic group: Parenteral nutrition solutions/combined products.

POLINUTHREE EN-1000 is a emulsion for infusion. It is marketed in a bag with three compartments. One of the compartments contains glucose solution with calcium, the second one contains lipid emulsion and the third one contains amino acid solution with electrolytes.

POLINUTHREE EN-1000 is marketed in three-compartment plastic bags of in 1000, 1500 and 2000 mililiters.

Before the contents of the three compartments are mixed, one compartment contains a homogeneous liquid (lipid emulsion) with a milky appearance, while the other two compartments contain a clear and colorless or light yellow solution (amino acid solution with electrolytes and glucose solution with calcium chloride) without visible particles.

When POLINUTHREE EN-1000 is mixed, it becomes a homogeneous and seems milky infusion emulsion. To prevent contact with oxygen in the air, the bag is packed with an oxygen barrier outer bag containing a chassis that absorbs oxygen.

POLINUTHREE EN-1000 is used to provide intravenous nutrition through a tube in cases where normal oral nutrition is not suitable for children older than two years and adults. POLINUHREE EN-1000 should be given only under medical supervision.

2. What you need to know before you use POLINUTHREE EN-1000

Do not use POLINUTHREE EN-1000 under the following circumstances.

- If the patient is a child under the age of 2, a infant or a premature newborn.
- If you are allergic to eggs, soybeans, peanut proteins or corn/corn products, or to the active ingredients or excipients contained in POLINUTHREE EN-1000.
- If there is a problem with the way your body uses amino acids.
- If the fat levels in your blood are particularly increased (hyperlipidemia).
- If your blood sugar level is too high (hyperglycemia).
- If there are situations when any of the substances called electrolytes (sodium, potassium, magnesium, calcium and/or phosphate) are abnormally high in your blood.

In any case, your doctor will decide whether you need to take this medication based on factors such as your age, weight, and medical condition, along with the test results.

Use POLINUTHREE EN-1000 with caution under the following circumstances.

Talk to your doctor or nurse before POLINUTHREE EN-1000 is given to you.

If intravenous total nutrition (total parenteral nutrition) solutions are given to you too quickly, this can lead to death.

If a symptom indicating an allergic reaction such as fever, chills, skin rash or breathing difficulties, excessive sweating, nausea and headache is observed, the administration of the drug will be discontinued immediately. This drug contains soybean oil and egg phospholipid proteins. Soybean and egg proteins may lead to hypersensitivity reactions (allergies). Cross-allergic reactions have been observed between soybean and peanut proteins.

POLINUTHREE EN-1000 contains glucose derived from corn, which may cause hypersensitivity reactions in patients who are allergic to corn or corn products.

Difficulty in breathing can also be a sign that small particles (pulmonary vascular deposits) have formed, which cause blockage of blood vessels located in the lungs. If you experience difficulty in breathing, tell your doctor or nurse. They will decide what needs to be done.

The antibiotic called ceftriaxone should not be mixed or given at the same time as calcium-containing solutions, including POLINUTHREE EN-1000, which are dripped into your vein. These drugs should not be given to you concomitantly, even through different infusion lines or different infusion sites. However, POLINUTHREE EN-1000 and ceftriaxone can be administered consecutively if infusion lines in different regions are used or infusion lines are changed, or if washed thoroughly with physiological saline to prevent precipitation between infusions.

Your doctor will check and monitor the levels of your triglycerides (a type of fat found in the blood).

Certain medications and diseases increase your risk of developing an infection (inflammation of a

tissue or organ in the body) or sepsis (the presence of bacteria in the blood). When a tube (intravenous catheter) is inserted into your vein, you are at risk of infection or sepsis. Your doctor will carefully monitor you for any signs of infection. In patients with a disease that needs to be fed through a vein (the delivery of food through a tube through your vein), the risk of infection is higher due to these conditions. The risk of infection can be reduced by using aseptic (sterile) techniques in catheter placement and care, as well as in the preparation of nutritional formulations (TPN).

Your doctor should be aware of:
- a severe kidney problem. You also must inform your doctor if you are on dialysis (a method of analysis or purification based on the removal of unwanted substances in body fluids from the body through a semi-permeable membrane) or if you have another form of blood cleaning treatment
- a severe liver problem
- a blood clotting problems
- adrenal glands that are not working properly (adrenal insufficiency). The adrenal glands are triangleshaped glands located on top of your kidneys.
- heart failure
- lung disease
- a build up of water in your body (hyperhydration)
- not enough water in your body (dehydration)
- high blood sugar (diabetes mellitus) that you are not being treated for
- a heart attack or shock due to a sudden heart failure,
- a severe metabolic acidosis (when the blood is too acid)
- a generalised infection (septicaemia)
- coma

If the patient is a child, the doctor will closely check their fluid status and/or blood values.

Fat overload syndrome has been reported with similar products. The reduced or limited ability of the body to remove the fats contained in POLINUTHREE EN-1000 may result in a "fat overload syndrome" (see section 4).

No additions should be made to the bag without first checking the compatibility. Formation of particles or a breaking down of the lipid emulsion could result. This can lead to blockage of the blood vessels.

If your blood sugar gets too high, your doctor should adjust the rate of POLINUTHREE EN-1000 delivery or give you insulin.

If you are severely malnourished such that you need to receive feedings by vein, it is recommended that parenteral nutrition is started slowly and carefully.

The balance of water and salt in your body and metabolic disorders will be corrected before starting the infusion. Your doctor will monitor your condition while you receive this medicine and may change the dosage or give you additional nutrients such as vitamins, electrolytes and trace elements if he/she feels they are appropriate.

To check the effectiveness and ongoing safety of the administration, your doctor will perform clinical and laboratory tests while you are receiving this medicine. If you are given this medicine for several weeks, your blood will be monitored on a regular basis. These tests are particularly required in case you suffer from certain conditions, such as a liver disorder, a kidney disorder, a disorder whereby amino acids cannot be processed by the body, a disorder in which the blood becomes too acidic, a disorder in which the level of fats and cholesterol is higher than normal, diabetes, or if you suffer from anaemia or difficulty to stop bleeding.

During the infusion if you notice pain, burning, stiffness, swelling or skin discoloration at the infusion site, or leakage of the infusion, tell your doctor or nurse. The administration will be stopped immediately and restarted in another vein.

Children
If the patient is a child, special care will be taken to give the correct dosage. Vitamin and trace element supplementation may be required depending on dose and duration. Increased precautions will also be taken because of the greater sensitivity of children to the risk of infection.

Other medicines and POLINUTHREE EN-1000
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

POLINUTHREE EN-1000 must not be administered together with blood through the same infusion tubing.

POLINUTHREE EN-1000 contains calcium. It should not be given together or through the same tube with the antibiotic ceftriaxone because particles may form. If the same device is used to give you successively these medicines, it should be thoroughly rinsed.

The olive and soybean oils present in POLINUTHREE EN-1000 contain vitamin K. This does not normally affect blood thinning medicines (anticoagulants) like coumarin. However, if you take anticoagulant medicines you should tell your doctor.

The lipids contained in this emulsion may interfere with the results of certain laboratory tests if the blood sample is taken before the lipids have been eliminated (these are generally eliminated after a period of 5 to 6 hours without receiving lipids).

POLINUTHREE EN-1000 with electrolytes contains potassium. Special care should be taken in patients taking diuretics, ACE inhibitors or angiotensin II receptor antagonists (drugs for high blood pressure) or immunosuppressants. These types of drugs may increase potassium levels in your blood.

POLINUTHREE EN-1000 with food and beverages

POLINUTHREE EN-1000 is administered intravenously; there is no interaction with food and drinks in terms of its route of administration.

Pregnancy

Please consult your physician or pharmacist before taking the drug.

Do not use POLINTHREE EN-1000 during pregnancy unless deemed particularly appropriate by your doctor. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before this medicine is given to you.

If you realize that you are pregnant during your treatment, immediately consult your physician or pharmacist.

Breast-feeding

Please consult your physician or pharmacist before taking the drug.

If you are breastfeeding ask your doctor for advice before this medicine is given to you.

Driving and using machines

There is no study about the effect of POLINUTHREE EN-1000 on ability in driving and using machine.

POLINUTHREE EN-1000 contains excipients

POLINUTHREE EN-1000 contains soybean oil. Do not use this medicinal product if you are allergic to peanuts or soy.

This medicinal product contains 32 mmol (about 704 mg) of sodium in each 1000 ml of it. This should be taken into account for patients who are on a controlled sodium diet.

It contains 160 g of glucose in each 1000 ml of it. This should be taken into account in patients with sugar (diabetes mellitus).

3. How you will be given POLINUTHREE EN-1000

Instructions regarding correct use and dosage/administration frequency:

POLINUTHREE EN-1000 should only be given in adults and children greater than 2 years of age.

The prescription may be continued for as long as it is needed, depending upon your clinical condition.

POLINUTHREE EN-1000 is for single use only.

Route and method of administration:

POLINUTHREE EN-1000 is administered through a plastic tube inserted into a vein in your arm or a large vein in your chest.

Different age groups:

Dosage - Adults

Your doctor will decide the amount you are given depending on your individual needs and clinical condition.

The maximum daily dose is 33 mL of emulsion / kg of body weight. For example: if you weigh 70 kg, the maximum daily dose should not exceed 2,310 mL of emulsion (33 mL of emulsion times 70 kg).

Dosage - Children greater than two years of age

Your doctor will decide the dose the child will need and for how long it will be given. This will depend on age, weight, height, clinical condition, daily fluid volume, energy and nitrogen requirements.

Special use

Kidney failure

It should be given with caution in those with renal insufficiency, especially if there is an increase in potassium in the blood.

Liver failure:

It should be given with caution in patients with hepatic insufficiency due to the risk of the development and worsening of neurological diseases associated with the height of ammonia in the blood.

Use in children:

It should not be used in children under 2 years of age.

Use in the elderly:

There is no additional information about this population.

If you have the impression that the effect of POLINUTHREE EN-1000 is too strong or weak, talk to your doctor or pharmacist.

If you are given more POLINUTHREE EN-1000 than you should

If the dose given is too high or the infusion too fast, the amino acid content may make your blood too acid and you may have too much fluid in the circulation. The glucose content may increase the glucose in your blood and urine or the lipid content may increase the triglycerides in your blood. Giving a volume of POLINUTHREE EN-1000 that is too large may cause nausea, vomiting, chills, chest pain, headache, cardiac arrhythmia or tachycardia and electrolyte disturbances, in such situations the infusion should be stopped immediately.

In some severe cases, your doctor may have to give you temporary renal dialysis to help your kidneys eliminate the excess product.

To prevent these events occurring, your doctor will regularly monitor your condition and test your blood parameters.

If you have any further questions on the use of this product, ask your doctor.

If you have used POLINUTHREE EN-1000 more than you should have or more than prescribed, consult a physician or a pharmacist.

If you forget to take POLINUTHREE EN-1000
Do not double-dose to make up for forgotten doses.

Possible effects once POLINUTHREE EN-1000 treatment is concluded
None

4. Possible side effects

Like all medicines, POLINUTHREE EN-1000 can cause side effects, although not everybody gets them. If you notice any changes in the way you feel during or after the treatment, tell your doctor or nurse right away.

The tests your doctor will perform while you are taking the medicine are meant to minimise side effects.

If one of the following develops, the infusion should be stopped, consult your doctor immediately or contact the emergency department of the nearest hospital:

- raised body temperature,
- chills,
- skin rashes
- breathing difficulties,
- excessive sweating,
- nauseas
- headache

These all are very serious side effects. If you have one of these, you may need immediate medical response.

The side effects are listed as defined by following categories:
Very common : may affect at least 1 in 10 patients;
Common : may affect up to 1 in 10 patients but more than one of 100 patients;
Uncommon : may affect in less than one of 100 patients but more than one of 1000 patients;
Rare : may affect in at least one in 1000 patients;
Very rare : may affect up to 1 in 10,000 people;
Not known : cannot be estimated from the available data.

Uncommon

- Allergic reactions

Frequency not known

- Constriction of the airway, breathing with whistling sound and/or cough (bronchospasm as part of allergic reaction)
- Fever, chills, inflammation
- Tremor (hand tremors)
- Pain in the limbs (extremities), muscle spasm
- Diarrhea, vomiting, nausea
- Abnormal flushing of the skin (erythema)
- Excessive sweating
- Extravasation, which may result in swelling/edema, pain, irritation and inflammation in the vein, redness/paresthesias, regional tissue damage, tissue death or blisters at the infusion site
- Thrombophlebitis (blood clot in a vein which causes pain, swelling and redness) when a hypertonic solution is infused
- The reduced or limited ability to remove the lipids contained in POLINUTHREE EN-1000 may result in a "fat overload syndrome". This may be caused by overdose but may also occur at the start of an infusion, even if the product is administered according to instructions. It is associated with a sudden deterioration in the patient's clinical condition. It is characterised by high level of fats in your blood (hyperlipidemia), fever, liver fatty infiltration (high level of fat in your liver), and/or an increase of your liver volume (hepatomegaly), an anaemia (reduction in red blood cells which can make the skin pale and cause weakness or breathlessness), a fall in white blood cells (leucocits) and blood platelets (trombosit), problem with your blood clotting and/or coma may also occur. The syndrome is usually reversible when the infusion of the lipid emulsion is stopped.

The following side effects have been reported with similar products:
Frequency not known

- Formation of small particles which may lead to blockage of blood vessels in the lungs (pulmonary vascular precipitates) resulting in pulmonary vascular embolism and difficulty breathing (respiratory distress).
- Decrease in the number of platelets (decrease in the number of cells responsible for blood clotting and bleeding, such as nosebleeds).
- Problems in the elimination of bile (cholestasis), an increase in liver volume, jaundice (yellowing of the skin or whites of the eyes due to a liver or blood problem)
- Hypersensitivity
- Increase in hepatic enzymes, fat levels in the blood (blood triglyceride levels), blood bilirubin levels
- Increased nitrogen level in the blood (azotemia)
- Fall in white blood cells and blood platelets have been reported in children.

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store POLINUTHREE EN-1000

Keep POLINUTHREE EN-1000 out of the sight and reach of children, and in its original packaging.

Store at room temperature below 25°C. Do not freeze.

Do not use this medicine after the expiry date which is stated on the container and the outer packaging after EXP. This expiry date refers to the last day of that month.

It should be stored in protective outer packaging. In order to protect the product from light, keep the product in its packaging and in a protective cardboard box.

For single use only. Partially used medicine should not be stored; it should be disposed of in accordance with the medical waste procedures of the health institution where the administration is made.

Use in compliance with the expiry date.

Do not use POLINUTHREE EN-1000 after the expiration date printed on its packaging.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

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This leaflet has been approved on 07.10.2022.

The Following Information Is Intended For Healthcare Professionals Only

1. Quantitative composition

After the contents of the 3 compartments have been mixed, the appearance of the mixture is a homogenous milk-like emulsion. The mixed emulsion for each of the different bag presentations provides the following:

Per bag	**1000 mL**	**1500 mL**	**2000 mL**
Nitrogen (g)	6,6	9,9	13,2
Amino acids (g)	40	60	80
Glucose (g)	160	240	320
Lipids (g)	40	60	80
Total calories (kcal)	1200	1800	2400
Non-protein calories (kcal)	1040	1560	2080
Glucose calories (kcal)	640	960	1280
Lipid calories (kcal)	400	600	800
Non-protein calorie/nitrogen ratio (kcal/g N)	158	158	158
Sodiuum (mmol)	32	48	64
Potassium (mmol)	24	36	48
Magnesium (mmol)	2,2	3,3	4,4
Calcium (mmol)	2	3	4
Phosphate (mmol)**	10	15	20
Acetate (mmol)	57	86	114
Chloride (mmol)	48	72	96
pH	6	6	6
Osmolarity (mOsm/L)	1450	1450	1450

** Including phosphates provided by the lipid emulsion

2. Posology and method of administration

The dosage depends on the patient's energy expenditure, clinical status, body weight, and the ability to metabolize the constituents of POLINUTHREE EN-1000, as well as additional energy or proteins provided orally/enterally; therefore, the bag size should be chosen accordingly.

The administration may be continued for as long as is required by the patient's clinical conditions.

The maximum daily dose should not be exceeded in adult and pediatric patients. Due to the static composition of the multi-chamber bag, the ability to simultaneously meet all nutrient needs of the patient may not be possible. Clinical situations may exist where patients require amounts of nutrients varying from the composition of the static bag.

As a general rule do not exceed doses of 3g/kg/day amino acids and /or 17 g/kg/day glucose and/or 3 g/kg/day lipids and/or 100ml/kg/day fluid, except in particular cases.

POLINUTHREE EN-1000 is for single use only.

The recommended duration of the parenteral nutrition infusion is between 12 and 24 hours.

Dosage and infusion rate– Adults

Average nitrogen requirements are 0.16 to 0.35 g/kg/day (approximately 1 to 2 g amino acids/kg/day). Energy requirements vary depending on the patient's nutritional state and level of catabolism. On average these are 20 to 40 kcal/kg/day.

Maximum daily dose:

The maximum daily dose is 33 ml/kg body weight (equivalent to 1.32 g amino acids, 5.28 g glucose, 1.32 g lipids, 1.06 mmol of sodium and 0.79 mmol potassium / kg), i.e. 2310 ml of the emulsion for infusion for a patient weighing 70 kg.

Maximum infusion rate:

As a general rule do not exceed infusion rates of 0.10 g/kg/hour amino acids and/or 0.25 g/kg/hour glucose and/or 0.15 g/kg/hour lipids, except in particular cases.

As a general rule, do not exceed 1.5 ml/kg/hour of the emulsion for infusion, i.e. 0.06 g amino acids, 0.24 g glucose and 0.06 g lipids / kg body weight / hour.

Dosage and infusion rate – Adolescents and children greater than 2 years of age

There have been no studies performed in the pediatric population.

The dosage is based on fluid intake and daily nitrogen requirements.

These intakes should be adjusted to take account of the child's hydration status.

Daily fluid, nitrogen and energy requirements are constantly decreasing with age.

The following is the guideline information for the maximum recommended hourly infusion rate and daily volume for pediatric patients:

For POLINUTHREE EN-1000

Maximum daily dose

Component	**Children 2-11 years of age**		**Children 12-18 years of age**	
	Recommended Maximum Daily Dose[a]	**POLİNUTHREE EN-1000 Maximum Daily Dose[b]**	**Recommended Maximum Daily Dose[a]**	**POLİNUTHREE EN-1000 Maximum Daily Dose[b]**
Fluid (mL/kg/day)	60 - 120	45	50-80	36
Amino acids (g/kg/day)	1 - 2 (up to 2,5)	1,8	1 - 2	1,4
Glucose (g/kg/day)	1,4-8,6	7,2	0,7-5,8	5,8
Lipids (g/kg/day)	0,5-3	1,8	0,5 - 2 (up to 3)	1,4
Total energy (kcal/kg/day)	30-75	54,0	20-55	43,2
Sodium (mmol/kg/day)	1-3	1,4	1-3	1,2
Potassium (mmol/kg/day)	1-3	1,1	1-3	0,9

[a]: The recommended values at the 2018 ESPGHAN/ESPEN/ESPR guidelines.

[b]: The concentration of magnesium is the limiting factor for the maximum daily dose in both age groups.

Maximum infusion rate

Component	Children 2-11 years of age		Children 12-18 years of age	
	Recommended Maximum Infusion Rate[a]	POLİNUTHREE EN-1000 Maximum Infusion Rate[b]	Recommended Maximum Infusion Rate[a]	POLİNUTHREE EN-1000 Maximum Infusion Rate[b]
Fluid (mL/kg/hour)	N/A	2,2	N/A	1,5
Amino acids (g/kg/hour)	0,20	0,09	0,12	0,06
Glucose (g/kg/hour)	0,36	0,35	0,24	0,24
Lipids (g/kg/hour)	0,13	0,09	0,13	0,06

[a]: The recommended values at the 2018 ESPGHAN/ESPEN/ESPR guidelines.

[b]: The concentration of glucose is the limiting factor for the maximum infusion rate in both age groups.

Route of administration

POLINUTHREE EN-1000 must be administered intravenously through a central or peripheral vein.

The administration flow rate should be adjusted to take account of the dose being administered, the characteristics of the final mixture being infused, the daily volume intake and the duration of the infusion.

3. Special warnings and precautions for use

- An excessively fast administration of total parenteral nutrition (TPN) solutions, including POLINUTHREE EN-1000, may result in severe or fatal consequences.

- The infusion must be stopped immediately if any abnormal signs or symptoms of an allergic reaction (such as sweating, fever, chills, headache, skin rashes, dyspnoea or bronchospasm) develop. This medicinal product contains soybean oil and egg phosphatide. Soybean and egg proteins may cause hypersensitivity reactions. Cross-allergic reactions between soybean and peanut proteins have been observed.

- POLINUTHREE EN-1000 contains glucose derived from corn, which can cause hypersensitivity reactions in patients allergic to corn or corn products.

- Severe water and electrolyte equilibration disorders, severe fluid overload states, and severe metabolic disorders must be corrected before starting the infusion.

- Specific clinical monitoring is required when an intravenous infusion is started.

- Ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions even via different infusion lines or different infusion sites. Cefriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If

use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion, considering the advice to flush infusion lines between solutions (see section4).

- Pulmonary vascular precipitates causing pulmonary vascular embolism and respiratory distress have been reported in patients receiving parenteral nutrition. In some cases, fatal outcomes have occurred. Excessive addition of calcium and phosphate increases the risk of the formation of calcium phosphate precipitates (see section 4, “Incompatibilities”).

- Do not add other medicinal products or substances to any components of the bag or to the reconstituted emulsion without first confirming their compatibility and the stability of the resulting preparation (in particular the stability of the lipid emulsion). Formation of precipitates or destabilization of the lipid emulsion could result in vascular occlusion.

- Vascular access infection and sepsis are complications that may occur in patients receiving parenteral nutrition, particularly in case of poor maintenance of catheters, immunosuppressive effects of illness or drugs. Careful monitoring of signs, symptoms, and laboratory tests for fever/chills, leukocytosis, technical complications with the access device and hyperglycaemia can help recognize early infections. Patients who require parenteral nutrition are often predisposed to infectious complications due to malnutrition and/or their underlying disease state. The occurrence of septic complications can be decreased with heightened emphasis on aseptic techniques in catheter placement, maintenance, as well as aseptic techniques in the preparation of the nutritional formula

- Monitor water and electrolyte balance, serum osmolarity, serum triglycerides, acid-base balance, blood glucose, liver and kidney function, and blood count, including platelets and coagulation parameters throughout treatment.

- Metabolic complications may occur if the nutrient intake is not adapted to the patient's requirements, or the metabolic capacity of any given dietary component is not accurately assessed. Adverse metabolic effects may arise from administration of inadequate or excessive nutrients or from inappropriate composition of an admixture for a particular patient's needs.

- Serum triglyceride concentrations and the ability of the body to remove lipids must be checked regularly.

- Serum triglyceride concentrations must not exceed 3 mmol/l during the infusion. These concentrations should not be determined before a minimum of a 3-hour period of continuous infusion.

- If a lipid metabolism abnormality is suspected, it is recommended that tests be performed daily by measuring serum triglycerides after a period of 5 to 6 hours without administering lipids. In adults, the serum must be clear in less than 6 hours after stopping the infusion containing the lipid emulsion. The next infusion should only be administered when the serum triglyceride concentrations have returned to normal values.

- Fat overload syndrome has been reported with similar products. The reduced or limited ability to metabolize the lipids contained in POLINUTHREE EN-1000 may result in a "fat overload syndrome" which may be caused by overdose; however the signs and symptoms of this syndrome

may also occur when the product is administered according to instructions.

- In the event of hyperglycaemia, the infusion rate of POLINUTHREE EN-1000 must be adjusted and/or insulin administered.

- While POLINUTHREE EN-1000 may be administered through a peripheral vein, thrombophlebitis may develop. The catheter insertion site must be monitored daily for local signs of thrombophlebitis.

- When making additions, the final osmolarity of the mixture must be measured before administration. The mixture obtained should be administered through a central or peripheral venous line depending on its final osmolarity. If the final mixture administered is hypertonic, it may cause irritation of the vein when administered into a peripheral vein.

- Although there is a natural content of trace elements and vitamins in the product, the levels are insufficient to meet body requirements and these should be added to prevent deficiencies from developing. See instructions for making additions to this product.

- Caution should be exercised in administering POLINUTHREE EN-1000 to patients with increased osmolarity, adrenal insufficiency, heart failure or pulmonary dysfunction

- Refeeding severely undernourished patients may result in the refeeding syndrome that is characterized by the shift of potassium, phosphorus, and magnesium intracellularly as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. Careful monitoring and slowly increasing nutrient intakes while avoiding overfeeding can prevent these complications. This syndrome has been reported with similar products.

- Do not connect bags in series in order to avoid air embolism due to residual air contained in the primary bag.

Hepatic Insufficiency

Use with caution in patients with hepatic insufficiency because of the risk of developing or worsening neurological disorders associated with hyperammonaemia. Regular clinical and laboratory tests are required particularly controlling liver function parameters, blood glucose, electrolytes and triglycerides.

Renal Insufficiency

Use with caution in patients with renal insufficiency, particularly if hyperkalaemia is present, because of the risk of developing or worsening metabolic acidosis and hyperazotemia if extra-renal waste removal is not being performed. Fluid triglycerides and electrolyte status should be closely monitored in these patients.

Hematologic

Use with caution in patients with coagulation disorders and anaemia. Blood count and coagulation parameters should be closely monitored.

Endocrine and Metabolism

Use with caution in patients with:

- Metabolic acidosis. Administration of carbohydrates is not recommended in the presence of lactic acidosis. Regular clinical and laboratory tests are required.
- Diabetes mellitus. Monitor glucose concentrations, glucosuria, ketonuria and, where applicable adjust insulin dosages.
- Hyperlipidaemia due to the presence of lipids in the emulsion for infusion. Regular clinical and laboratory tests are required.
- Amino acid metabolism disorders

Extravasation

Catheter site should be monitored regularly to identify signs of extravasation. If extravasation occurs, the administration should be stopped immediately, keeping the inserted catheter or cannula in place for immediate management of the patient. If possible, aspiration should be performed through the inserted cathter/ cannula, in order to reduce the amount of fluid present in the tissues before removing the catheter/ cannula. When involving an extremity, the concerned limb should be elevated.

Depending on the extravasated product (including the product(s) being mixed with POLINUTHREE EN-1000, if applicable) and the stage/extent of any injury, appropriate specific measures should be taken. Options for management may include non-pharmacologic, pharmacologic and/or surgical intervention. If there is any deterioration of the affected area (continued pain, necrosis, ulceration, suspected compartment syndrome), surgery should be consulted immediately.

The extravasation site should be monitored at least every 4 hours during the 24 first hours, then once daily.

The infusion should not be restarted in the same peripheral or central vein.

Special precautions in paediatrics

When administered to children greater than 2 years old, it is essential to use a bag which has a volume corresponding to the daily dosage.

Vitamin and trace element supplementation is always required. Paediatric formulations should be used.

4. Practical information on preparation and handling

Only use POLINUTHREE EN-1000 if:

- the bag is undamaged,

- the non-permanent seals are intact,

- the glucose and amino acid solutions are clear, colourless or slightly yellow, practically free of visible particles

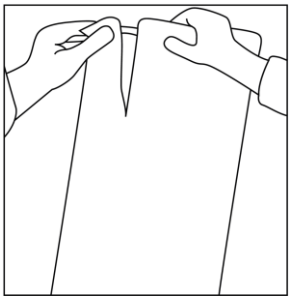
- the lipid emulsion is homogeneous and milk-like.

POLINUTHREE EN-1000 should be at room temperature before use.

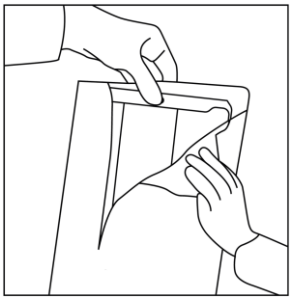
Only administer the product after the non-permanent seals between the 3 compartments have

been broken and the contents of the 3 compartments have been mixed as shown below.

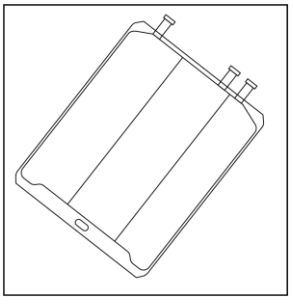
Ensure that the final emulsion for infusion does not show any evidence of phase separation.



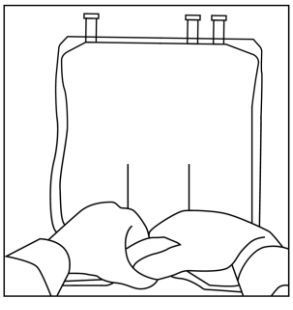
1. Tear from the top to open the overpouch.



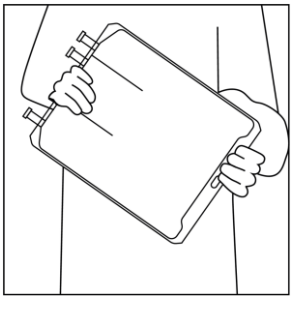
2. Peel the front of the overpouch to reveal the POLINUTHREE EN-1000 bag. Discard the overpouch and oxygen absorber sachet.



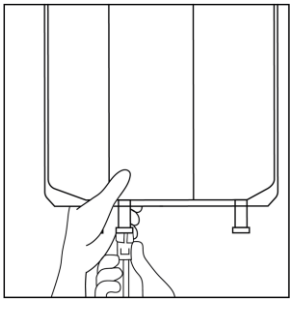
3. Place the bag flat on a horizontal and clean surface with handle in front of you.



4. Lift the hanger area to remove solution from the upper bag. Firmly roll the upper bag until peal seal is fully open (approximately half way).



5. Mix by turning the bag upside-down at least 3 times. Ensure a homogenous mixture, with no evidence of phase separation.



6. Hang the bag. Twist off the protector from the administration outlet. Firmly plug the spike connector.

After opening the bag, the content must be used immediately. The opened bag must never be stored for a subsequent infusion.

Do not reconnect any partially used bag.

Do not connect bags in series in order to avoid the possibility of air embolism due to air contained in the primary bag.

For single use only. Any unused product or waste material and all necessary devices must be discarded.

Do not store any partially used bags and discard all devices after use.

Supplementation

Do not add other medicinal products or substances to any components of the bag or to the reconstituted emulsion without first confirming their compatibility and the stability of the resulting preparation (in particular stability of the lipid emulsion).

However, POLINUTHREE EN-1000 can be used as such or after supplementation with electrolytes, trace elements or vitamins, when required.

The capacity of the bag is sufficient to enable additions such as, vitamins, electrolytes, and trace elements. Any additions (including vitamins) may be made into the reconstituted mixture (after the non-permanent seals have been opened and the contents of the three compartments have been mixed).

Vitamins may also be added into the glucose compartment before the mixture has been reconstituted (before opening the non-permanent seals and before mixing the solutions and the emulsion).

When making additions to the formulation, the final osmolarity of the mixture should be measured before administration via a peripheral vein.

POLINUTHREE EN-1000 may be supplemented with:

- Electrolytes: electrolytes already present in the bag should be taken into account: stability has been demonstrated up to a total quantity of 150 mmol of sodium, 150 mmol of potassium, 5.6 mmol of magnesium and 5 mmol of calcium per litre of the ternary mixture.

- Organic phosphate: stability has been demonstrated for additions of up to 15 mmol per bag.

Trace elements and vitamins: Stability has been demonstrated with commercially available preparations of vitamins and trace elements (containing up to 1 mg of iron). Compatibility for other additives is available upon request.

Additions must be performed by qualified personnel under aseptic conditions.

These additions are made into the injection site using a needle:

- Prepare the injection site,

- Puncture the injection site and inject,

- Mix the contents of the bag and the additives.

When making additions, the final osmolarity of the mixture must be measured before administration. The mixture obtained should be administered through a central or peripheral venous line depending on its final osmolarity. If administered peripherally a hypertonic emulsion, it may cause irritation of the vein.

Interactions

No interaction studies have been performed with POLINUTHREE EN-1000.

POLINUTHREE EN-1000 contains vitamin K, naturally present in lipid emulsions. The amount of Vitamin K in recommended doses of POLINUTHREE EN-1000 are not expected to influence effects of coumarin derivatives.

Ceftriaxone must not be mixed or administered simultaneously with intravenous calcium-

containing solutions, including POLINUTHREE EN-1000, because of the risk of precipitation of ceftriaxone-calcium salt.

Ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation.

If the same infusion line is used for sequential administration, the line must be thoroughly flushed between infusions with a compatible fluid (e.g. physiological salt solution) to avoid precipitation.

Due to the potassium content of POLINUTHREE EN-1000, special care should be taken in patients treated with potassium sparing diuretics (e.g, amiloride, spironolactone, triamterene) angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists or the immunosuppressants tacrolimus and cyclosporine in view of the risk of hyperkalemia.

The lipids contained in this emulsion may interfere with the results of certain laboratory tests (for example, bilirubin, lactate dehydrogenase, oxygen saturation, blood haemoglobin) if the blood sample is taken before the lipids have been eliminated (these are generally eliminated after a period of 5 to 6 hours without receiving lipids).

Incompatibilities

This emulsion for infusion must not be administered simultaneously with blood through the same infusion tubing.

POLINUTHREE EN-1000 contains calcium ions which pose additional risk of coagulation precipitates in citrate anticoagulated/preserved blood or components.

Incompatibilities may be produced for example by excessive acidity (low pH) or inappropriate content of divalent cations (Ca^{2+} and Mg^{2+}), which may de-stabilise the lipid emulsion.

As with any parenteral nutrition admixture, calcium and phosphate ratios must be considered. Excess addition of calcium and phosphate, especially in the form of mineral salts, may result in formation of calcium phosphate precipitates.

Check compatibility with solutions administered simultaneously through the same giving set, catheter or cannula.

Ceftriaxone must not be mixed or administered simultaneously with intravenous calcium-containing solutions, including POLINUTHREE EN-1000, because of the risk of precipitation of ceftriaxone-calcium salt (see section Interactions).

5. Shelf life

2 years if the overwrap is not damaged.

It is recommended that the product is used immediately after the non-permanent seals between the 3 compartments have been opened. The reconstituted emulsion has, however, been shown to be stable for a maximum of 7 days at between +2 and +8 °C followed by a maximum of 48 h at temperatures not exceeding + 25 °C.

After supplementation (electrolytes, trace elements, vitamins) of reconstituted POLINUTHREE

EN-1000, (see previous section), chemical and physical in-use stability has been demonstrated for 7 days at 2 to 8°C followed by 48 hours below 25 °C. From a microbiological point of view, any admixture should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless addition of supplements has taken place in controlled and validated aseptic conditions.