SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Numeta G19%E emulsion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This medicinal product is presented in the form of a three chamber bag. Each bag contains a sterile non-pyrogenic combination of a glucose solution, a paediatric amino acids solution, with electrolytes, and a lipid emulsion, as described below.

Container size	50% glucose solution	5.9% amino acids solution with electrolytes	12.5% lipid emulsion
1000 mL	383 mL	392 mL	225 mL

If lipid administration is undesirable, the design of the bag allows the possibility to activate only the peel seal between the amino acids/electrolytes and glucose chambers, leaving the peel seal between the amino acids and lipid chambers intact. The content of the bag can subsequently be infused with or without lipids. The composition of the drug product after mixing of the two (amino acids and glucose 2 chamber bag, 775 mL solution) or three (amino acids, glucose and lipid 3 chamber bag, 1000 mL emulsion) chambers are provided in the following table.

Composition		
Active Substance	**Activated 2CB (775 mL)**	**Activated 3CB (1000 mL)**
Amino Acid Chamber		
Alanine	1.83 g	1.83 g
Arginine	1.92 g	1.92 g
Aspartic acid	1.37 g	1.37 g
Cysteine	0.43 g	0.43 g
Glutamic acid	2.29 g	2.29 g
Glycine	0.91 g	0.91 g
Histidine	0.87 g	0.87 g
Isoleucine	1.53 g	1.53 g
Leucine	2.29 g	2.29 g
Lysine monohydrate (equivalent to Lysine)	2.82 g (2.51 g)	2.82 g (2.51 g)
Methionine	0.55 g	0.55 g
Ornithine hydrochloride (equivalent to Ornithine)	0.73 g (0.57 g)	0.73 g (0.57 g)
Phenylalanine	0.96 g	0.96 g
Proline	0.69 g	0.69 g
Serine	0.91 g	0.91 g
Taurine	0.14 g	0.14 g
Threonine	0.85 g	0.85 g
Tryptophan	0.46 g	0.46 g
Tyrosine	0.18 g	0.18 g
Valine	1.74 g	1.74 g
Sodium chloride	1.79 g	1.79 g
Potassium acetate	3.14 g	3.14 g
Calcium chloride dihydrate	0.56 g	0.56 g
Magnesium acetate tetrahydrate	0.55 g	0.55 g
Sodium glycerophosphate hydrated	2.21 g	2.21 g
Glucose Chamber		
Glucose monohydrate (equivalent to glucose anhydrous)	210.65 g (191.50 g)	210.65 g (191.50 g)
Lipid Chamber		
Refined olive oil (approximately 80%) + Refined soya bean oil (approximately 20%)	-	28.1 g

2CB=two chamber bag, 3CB= three chamber bag

For the full list of excipients, see section 6.1.

The reconstituted solution/emulsion provides the following:

Composition				
	Activated 2CB		**Activated 3CB**	
Per volume unit (mL)	**775**	**100**	**1000**	**100**
Nitrogen (g)	3.5	0.45	3.5	0.35
Amino acids (g)	23.0	3.0	23.0	2.3
Glucose (g)	192	24.7	192	19.2
Lipids (g)	0	0	28.1	2.8
Energy				
Total calories (kcal)	858	111	1139	114
Non-protein calories (kcal)	766	99	1047	105
Glucose calories (kcal)	766	99	766	77
Lipid calories (kcal) [a]	0	0	281	28
Non-prot calories / nitrogen (kcal/g N)	220	220	301	301
Lipid calories / non-protein calories (%)	NA	N/A	27	27
Lipid calories / total calories (%)	NA	N/A	25	25
Electrolytes				
Sodium (mmol)	45.1	5.8	45.8	4.6
Potassium (mmol)	32.0	4.1	32.0	3.2
Magnesium (mmol)	2.6	0.33	2.6	0.26
Calcium (mmol)	3.8	0.50	3.8	0.38
Phosphate (mmol) [b]	7.2	0.93	9.4	0.93
Acetate (mmol)	37.1	4.8	37.1	3.71
Malate (mmol)	8.8	1.1	8.8	0.88
Chloride (mmol)	42.6	5.5	42.6	4.3
pH (approx.)	5.5	5.5	5.5	5.5
Osmolarity approx. (mOsm/L)	1835	1835	1460	1460

a Includes calories from egg phospholipids for injection,
b Includes phosphate from egg phospholipids for injection component of the lipid emulsion

3. PHARMACEUTICAL FORM

Emulsion for infusion.

Appearance before reconstitution:

- The solutions in the amino acids and glucose chambers are clear, colourless or slightly yellow
- The lipid emulsion is homogeneous and milky-white

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Numeta G19%E is indicated for parenteral nutrition in children older than 2 years and adolescents 16-18 years old when oral or enteral nutrition is not possible, insufficient or contraindicated.

4.2 Posology and method of administration

Posology

The dosage depends on energy expenditure, the patient's weight, age, clinical status, and on the ability to metabolize the constituents of Numeta G19%E, as well as on additional energy or proteins given orally/enterally. Total electrolyte and macronutrient composition is dependent on the number of activated chambers (See section 2).

The maximum daily dose should not be exceeded. 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.

The maximal recommended hourly rate of infusion and volume per day depend on the constituent. The first of these limits to be reached sets the maximum daily dose. The guidelines for maximal recommended hourly rate of infusion and volume per day are:

	Activated 2CB (775 mL)	**Activated 3CB (1000 mL)**
Maximal rate of infusion in mL/kg/h	4.7	4.6
Corresponding to:		
Amino acid in g/kg/h	0.14[a]	0.11
Glucose in g/kg/h	1.17	0.89
Lipids in g/kg/h	0	0.13[a]

Maximal amount in mL/kg/day	64.8	83.6
Corresponding to:		
Amino acid in g/kg/d	1.9	1.9
Glucose in g/kg/d	16.0[a]	16.0[a]
Lipids in g/kg/d	0	2.3

[a] Limiting parameter according to ESPEN-ESPGHAN guidelines

Method of administration

For instructions for preparation, and handling of the solution/emulsion for infusion, see section 6.6.

The solution (in bags and administration sets) should be protected from light exposure from point of admixture through administration (see section 4.4 and 6.6).

Use of a 1.2 micron filter is recommended for administration of Numeta G19%E.

Due to its high osmolarity, undiluted Numeta G19%E can only be administered through a central vein. However, sufficient dilution of Numeta G19%E with water for injection lowers the osmolarity and allows peripheral infusion.

The table below indicates the minimum volume of water for injection to be added to the activated bag in order to achieve the target osmolarity for peripheral

administration. It should be noted that any other addition made to the activated bag will modify the final osmolarity.

	Target Osmolarity (mOsm/L)	**Minimum addition of water for injection to achieve target osmolarity (mL)**
Numeta G19%E[a] after 3-in-1 activation	< 900	690
	< 850	800
	< 800	920

[a]The dilution of Numeta G19%E 2-in-1 admixture for peripheral administration for children and adolescents up to 18 years is not appropriate because the volume of water which would be required to be added exceeds bag capacity and may exceed patients' daily fluid requirements.

The flow rate should be increased gradually during the first hour. Upon discontinuation of Numeta G19%E, the flow rate should be decreased gradually during the last hour. The administration flow rate must be adjusted taking into account the dose being administered, the daily volume intake, and the duration of the infusion, see section 4.9.

The same bag should not be activated, hung and infused longer than 24 hours. Cyclic infusions should be managed according to the patient's metabolic tolerance.

Treatment with parenteral nutrition may be continued for as long as is required by the patient's clinical conditions.

This product contains electrolytes and may be further supplemented using commercial electrolyte preparations according to the physician's judgment and the clinical needs of the patient, see section 6.6.

Vitamins and trace elements can be added according to the physician's judgment and the clinical needs of the patient, see section 6.6.

4.3 Contraindications

The general contraindications for administering Numeta G19%E as an activated 2 chamber bag for intravenous infusion are as follows:

- Hypersensitivity to egg, soy or peanut proteins, or to any of the active substances, excipients listed in section 6.1, or components of the container
- Congenital abnormality of the amino acid metabolism
- Pathologically elevated plasma concentrations of sodium, potassium, magnesium, calcium and/or phosphorus
- Severe hyperglycaemia

The addition of lipids (administering Numeta G19%E as an activated 3 chamber bag for intravenous emulsion) is contraindicated in the following additional clinical situations:

- Severe hyperlipidaemia, or severe disorders of lipid metabolism characterized by hypertriglyceridemia

4.4 Special warnings and precautions for use

The infusion must be stopped immediately if any signs or symptoms of an allergic reaction (such as fever, sweating, shivering, headache, skin rashes, or dyspnea) develop.

Numeta G19%E contains glucose produced from cornstarch. Therefore, Numeta G19%E should be used with caution in patients with known allergy to corn or corn products.

In patients of any age (including adults), ceftriaxone must not be mixed or administered simultaneously with any intravenous calcium-containing solutions, including Numeta G19%E, even via different infusion lines or at different infusion sites because of the risk of precipitation of ceftriaxone-calcium salt.

However, in patients older than 28 days of age 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.

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 6.2). Suspected precipitate formation in the blood stream have also been reported.

In addition to inspection of the solution, the infusion set and catheter should also periodically be checked for precipitates.

If signs of respiratory distress occur, the infusion should be stopped and medical evaluation initiated.

No additions to the bag should be made without first checking the compatibility, as formation of precipitates or destabilization of the lipid emulsion could result in vascular occlusion, see sections 6.2 and 6.6.

Infection and sepsis may occur as a result of the use of intravenous catheters to administer parenteral formulations, or poor maintenance of catheters. Immunosuppressive effects of illness, or drugs, may promote infection and sepsis. Careful symptomatic and laboratory monitoring 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 technique in catheter placement, maintenance, as well as aseptic technique in nutritional formula preparation.

Fat overload syndrome has been reported with other parenteral nutrition products. A reduced or limited ability to metabolize the lipids contained in Numeta, or an overdose, may result in a “fat overload syndrome” (see section 4.8 and 4.9).

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 and slow initiation of parenteral nutrition is recommended, with close monitoring of fluids, electrolytes, trace elements and vitamins.

Numeta must only be administered through a central vein, except if appropriate dilution is performed (see section 4.2). When making additions to the formulation, the final osmolarity of the mixture must be calculated before administration via peripheral vein to avoid vein irritation or tissue damage in the case of extravasation of the solution. Peripheral administration of Numeta has resulted in extravasation leading to soft tissue injury and skin necrosis. Do not connect bags in series in order to avoid air embolism due to possible residual gas contained in the primary bag.

Lipids, vitamins, additional electrolytes and trace elements should be administered as required.

PRECAUTIONS

Do not add other medicinal products or substances to one of the three chambers of the bag or to the reconstituted solution/emulsion without first confirming their compatibility and the stability of the resulting preparation (in particular, stability of the lipid emulsion) (see sections 6.2 and 6.6).

Numeta G19%E should be protected from light from the point of admixture through administration (see section 6.6).

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

In case of unstable conditions (for example, following severe post-traumatic conditions, uncompensated diabetes mellitus, acute phase of circulatory shock, acute myocardial infarction, severe metabolic acidosis, severe sepsis and hyperosmolar coma) delivery of Numeta G19%E should be monitored and adjusted to meet the clinical needs of the patient.

Cardiovascular

Use with caution in patients with pulmonary edema or heart failure. Fluid status should be closely monitored.

Renal

Use with caution in patients with renal insufficiency. Fluid and electrolyte status should be closely monitored in these patients.

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

Hepatic/Gastrointestinal

Use with caution in patients with severe liver insufficiency, including cholestasis, or elevated liver enzymes. Liver function parameters should be closely monitored.

Endocrine and Metabolism

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 metabolize lipids must be checked regularly. If a lipid metabolism abnormality is suspected, monitoring of serum triglycerides is recommended as clinically necessary.

In the event of hyperglycemia, the infusion rate of Numeta G19%E must be adjusted and/or insulin administered, see section 4.9.

Hematologic

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

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacodynamic interaction studies have been performed with Numeta G19%E.

Numeta G19%E must not be administered simultaneously with blood through the same infusion tubing because of the risk of pseudoagglutination.

In patients of any age (including adults), ceftriaxone must not be mixed or administered simultaneously with intravenous calcium-containing solutions, including Numeta G19%E, even via different infusion lines or at different infusion sites because of the risk of precipitation of ceftriaxone-calcium salt (see section 4.4).

However, in patients older than 28 days of age 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.

Olive and soybean oil have a natural content of vitamin K1 that may counteract the anticoagulant activity of coumarin (or coumarin derivatives including warfarin).

Due to the potassium content of Numeta G19%E special care should be taken in patients simultaneously treated with potassium sparing diuretics (amiloride, spironolactone, triamterene) or with 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 hemoglobin) if the blood sample is taken before the lipids are eliminated. Lipids are generally eliminated after a period of 5 to 6 hours when no additional lipids are administered.

Please also refer to section 6.2 “Incompatibilities”.

4.6 Fertility, pregnancy and lactation

There are no data from the use of Numeta G19%E in pregnant or lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing Numeta G19%E.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

4.8.1 Adverse Reactions from Clinical Trials and Post-marketing experience

The safety and administration of Numeta was assessed in a single phase III study. One hundred and fifty nine (159) paediatric patients were included in the study and received Numeta.

The pooled data from clinical trials and the postmarketing experience indicate the following adverse drug reactions (ADRs) related to Numeta:

Clinical Trial and Post-marketing experience Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency[b]**
METABOLISM AND NUTRITION DISORDERS	Hypophosphataemia[a] Hyperglycaemia[a] Hypercalcaemia[a] Hypertriglyceridaemia[a] Hyperlipidaemia Hyponatraemia[a]	Common Common Common Common Uncommon Common
HEPATOBILIARY DISORDERS	Cholestasis	Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Skin necrosis [c]	Not known
	Soft tissue injury [c]	Not known
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITION	Extravasation [c]	Not known

[a] Blood samples drawn during the infusion (without fasting conditions).
[b] Frequency is based upon the following categories: 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 based on available data).
[c] These adverse reactions have been reported only for Numeta G13%E Preterm and G16%E when peripherally administered with insufficient dilution (see Section 4.4)

4.8.2 Other (Class) Reactions

The following adverse reactions have been reported with other parenteral nutrition admixtures:

- Fat overload syndrome: may be caused by inappropriate administration (e.g. overdose and/or infusion rate higher than recommended, see section 4.9); however the signs and symptoms of this syndrome may also occur when the product is administered according to instructions. The reduced or limited ability to metabolize the lipids contained in Numeta G19%E accompanied by

prolonged plasma clearance may result in a "fat overload syndrome". This syndrome is associated with a sudden deterioration in the patient's clinical condition and is characterized by findings such as hyperlipidemia, fever, liver fatty infiltration (hepatomegaly), deteriorating liver function, anemia, leukopenia, thrombocytopenia, coagulation disorders, acute respiratory distress, metabolic acidosis, and central nervous system manifestations (e.g. coma). The syndrome is usually reversible when the infusion of the lipid emulsion is stopped

- Pulmonary vascular precipitates (pulmonary vascular embolism and respiratory distress) (see section 4.4).

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

In the event of inappropriate administration (overdose, and/or infusion rate higher than recommended), nausea, vomiting, shivering, electrolyte disturbances and signs of hypervolemia or acidosis may occur and result in fatal consequences. In such situations, the infusion must be stopped immediately. If medically appropriate, further intervention may be indicated.

Hyperglycaemia, glucosuria, and hyperosmolar syndrome may develop if the glucose infusion rate exceeds clearance.

An overdose or reduced or limited ability to metabolize lipids may result in fat overload syndrome, the results of which are usually reversible after infusion of the lipid emulsion is stopped, see section 4.8. In neonates and infants, the fat overload syndrome has been associated with metabolic acidosis and respiratory distress.

There is no specific antidote for overdose. Emergency procedures should be general supportive measures, with particular attention to respiratory and cardiovascular systems. In some serious cases, hemodialysis, hemofiltration, or hemodiafiltration may be necessary. Severe cases of fat overload syndrome treated with exchange transfusions have been reported in the literature.

Close biochemical monitoring is essential and specific abnormalities should be treated appropriately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parenteral nutrition/combination

ATC Code: B05 BA10

The content of nitrogen (20 L-series amino acids, including 8 essential amino acids) in Numeta G19%E and energy (glucose and triglycerides) enables maintenance of an adequate nitrogen/energy balance. Nitrogen and energy are required for normal functioning of all cells in the body, and are important for protein synthesis, growth, wound healing, immune function, muscle function, and many other cellular activities.

This formulation also contains electrolytes.

The amino acids profile is as follows:

- Essential amino acids/total amino acids: 47.5%
- Branched-chain amino acids/total amino acids: 24.0%

The lipid emulsion included in Numeta G19%E is a mixture of refined olive oil and refined soybean oil (ratio 80/20 approximately), with the following relative distribution of fatty acids:

- 15% saturated fatty acids (SFA)
- 65% monounsaturated fatty acids (MUFA)
- 20% polyunsaturated fatty acids (PUFA)

The phospholipid/triglyceride ratio is 0.06. The moderate essential fatty acid (EFA) content improves the status of their upper derivatives while correcting EFA deficiency.

Olive oil contains significant amounts of alpha-tocopherol which, when combined with a moderate PUFA intake, contributes to vitamin E status and is important for limiting lipid peroxidation.

The carbohydrate source is glucose. Glucose is a primary source of energy in the body.

5.2 Pharmacokinetic properties

The ingredients of the emulsion for infusion (amino acids, electrolytes, glucose, lipids) are distributed, metabolized and eliminated in the same way as if they had been

administered individually. The product is given intravenously and is thus 100% bioavailable and the constituents are distributed to and metabolized by all cells in the body.

5.3 Preclinical safety data

Preclinical studies performed on the components of the triple chamber bag have revealed no additional risks to those already mentioned in other sections of the SmPC.

Animal studies with Numeta G19%E (double or triple chamber combinations) have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:	Amino acid Chamber	Glucose Chamber	Lipid Chamber
L-Malic acid [a]	X	-	-
Hydrochloric acid [a]	-	X	-
Egg phospholipids for injection	-	-	X
Glycerol	-	-	X
Sodium oleate	-	-	X
Sodium hydroxide [a]	-	-	X
Water for injections	X	X	X

[a] for pH adjustment

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, see Section 6.6.

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 the formation of calcium phosphate precipitates.

In patients of any age ceftriaxone must not be mixed or administered simultaneously with intravenous calcium-containing solutions, including Numeta, even via different infusion lines or at different infusion sites because of the risk of precipitation of ceftriaxone-calcium salt.

Due to the risk of precipitation, Numeta G19%E should not be administered through the same infusion line together with ampicillin, fosphenytoin or furosemide.

Numeta G19%E must not be administered simultaneously with blood through the same infusion tubing, see section 4.5.

Numeta G19%E contains calcium ions which pose additional risk of coagulation precipitates in citrate-anticoagulated/preserved blood or components.

6.3 Shelf life

24 months

Shelf life after reconstitution

It is recommended that the product be used immediately after the non-permanent seals between the two or three chambers have been opened. However, stability data of the reconstituted mixtures supports 7 days between 2°C and 8°C followed by 48 hours at 30°C.

Shelf life after supplementation (electrolytes, trace elements, vitamins, water):

For specific admixtures in-use stability of the Numeta formulation has been demonstrated for 7 days between 2°C and 8°C followed by 48 hours at 30°C.

From a microbiological point of view, the product 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 reconstitution /dilution /supplementation has taken place in controlled and validated aseptic conditions.

Please also refer to section 4.2 “Posology and method of administration” and section 6.6 “Special precautions for disposal and other handling”.

6.4 Special precautions for storage

Do not freeze.

Store in overpouch.

6.5 Nature and contents of container

The three-chamber full non-PVC bag consists of the following components:

- A multi-layer plastic sheeting.
- A port tube on the compartment containing the lipid emulsion. It is sealed off after filling to prevent additions to this chamber.

- Two port tubes on the amino acid solution and glucose solution chambers.
  - An injection site that closes the port tube of the glucose compartment.
  - An administration site that closes the port tube of the amino acid compartment.

All components are free of natural latex rubber.

To prevent air contact, the bag is packaged in an oxygen barrier overpouch that contains an oxygen absorber sachet and an oxygen indicator.

Available pack sizes:

1000 mL bags: 6 units per cardboard box

1 bag of 1000 mL

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

For single use only.

Do not use damaged bags.

Confirm the integrity of the bag and non-permanent seals.

Only use if the amino acid and glucose solutions are clear, colourless or slightly yellow and free from particles, and if the lipid emulsion is homogenous with a milky appearance.

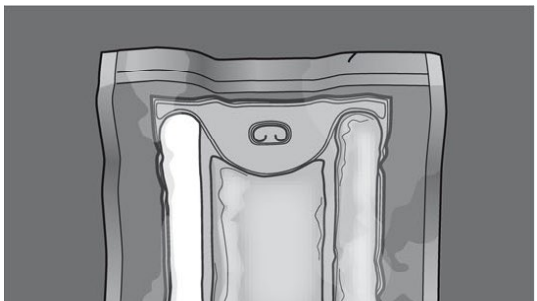
Use of a 1.2 micron filter is recommended for administration of Numeta G19E.

Before opening the overpouch, check the colour of the oxygen indicator.

- Compare it to the reference colour printed next to the OK symbol and shown in the printed area of the indicator label.

- Do not use the product if the colour of the oxygen indicator does not correspond to the reference color printed next to the OK symbol.

Figures 1 and 2 illustrate how to remove the protective overpouch. Discard the overpouch, oxygen indicator and oxygen absorber.



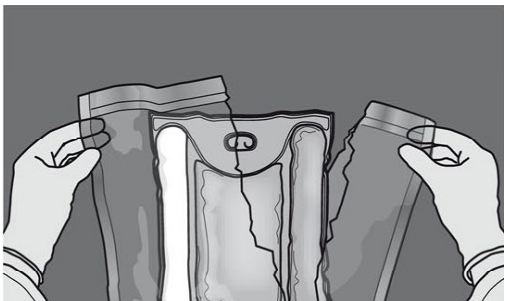


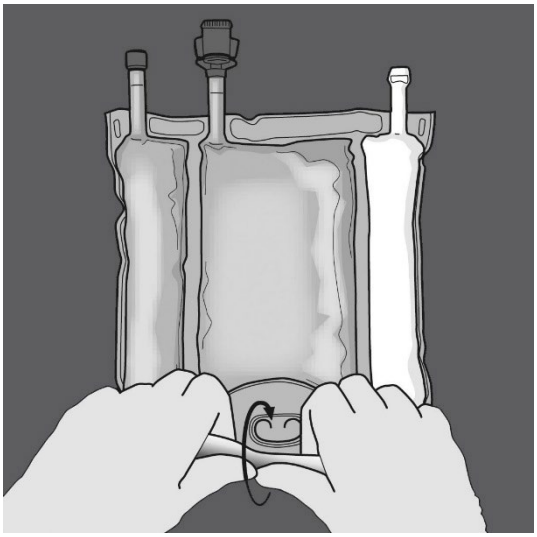
Figure 1 Figure 2

<u>Preparation of the mixed emulsion:</u>

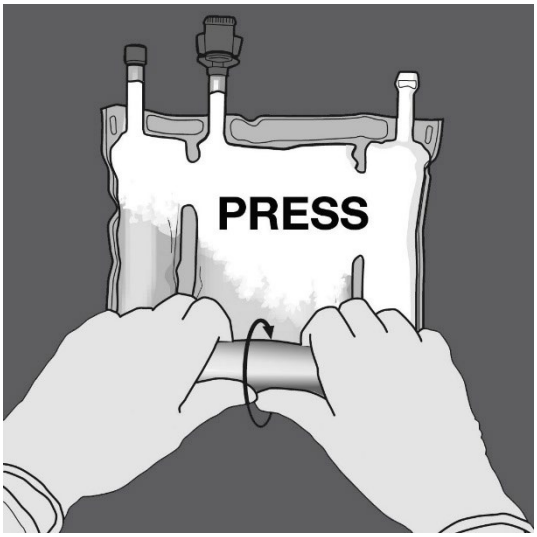
- Ensure that the product is at room temperature when breaking the non-permanent seals.
- Place bag onto a flat clean surface.

Activation of the 3CB (breaking two non-permanent seals)

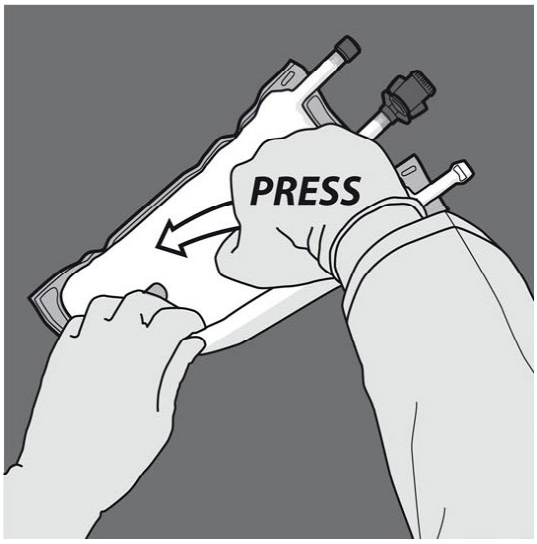
Step 1: Start rolling the bag from the D-hanger side.



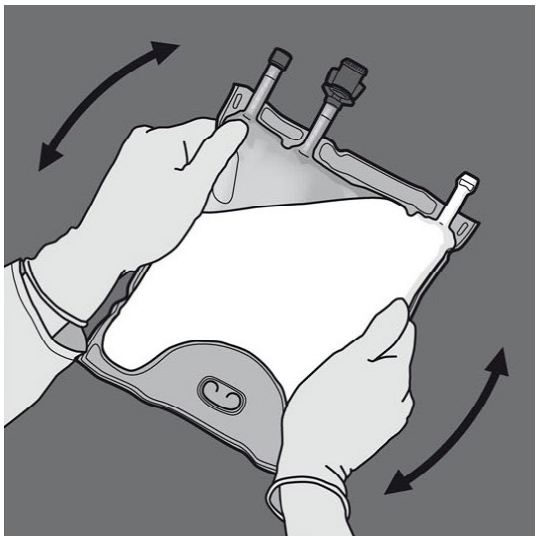
Step 2: Apply pressure until peal seals open.



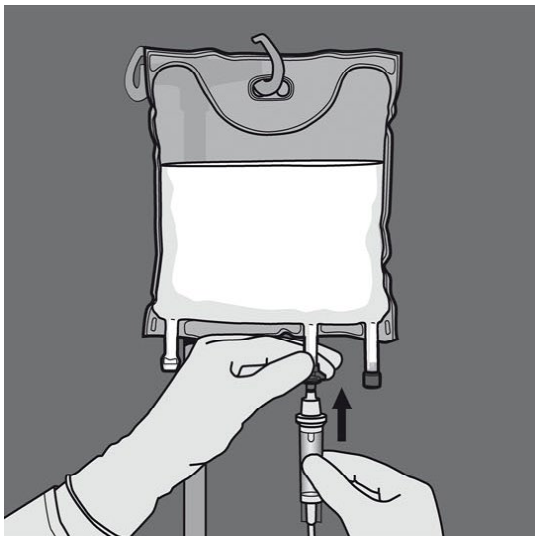
Step 3: Change direction by rolling the bag towards the D-hanger.
Continue until the seal is completely opened
Proceed the same way to complete the opening of the second peel seal.



Step 4: Turn the bag over at least three times to mix the contents thoroughly. The appearance of the mixed solution should be a milky-white emulsion.

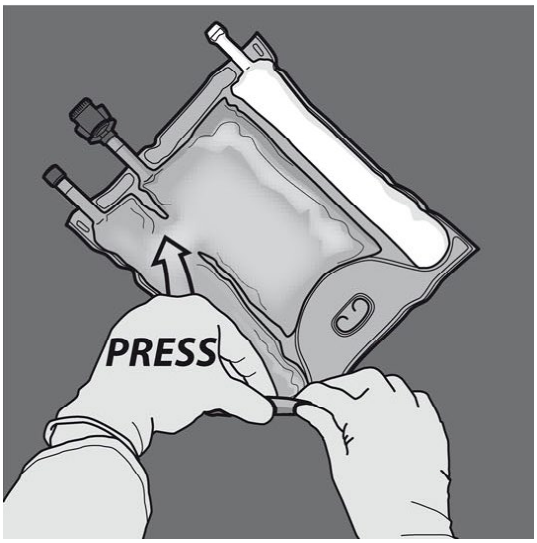


Step 5: Remove the protective cap from the administration site and insert the IV administration set.

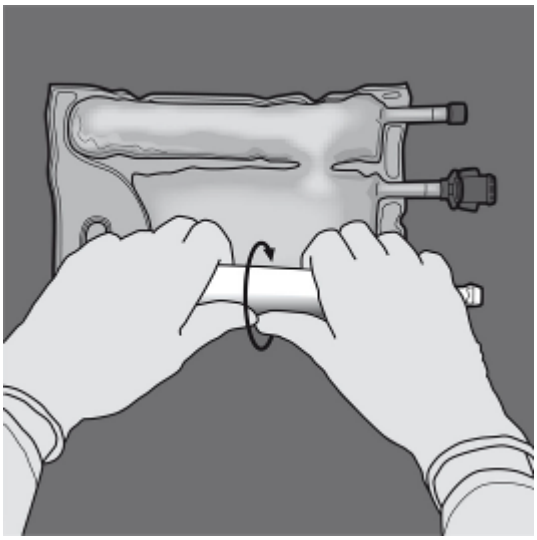


Activation of the 2CB (breaking the non-permanent seal between the Amino Acids and Glucose chambers)

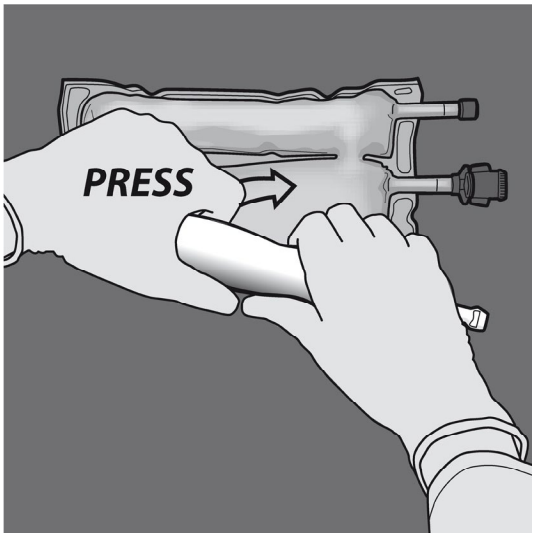
Step 1: To break only the amino acids/glucose peel seal, start rolling the bag from the D-hanger corner of the seal separating the amino acids and glucose chambers and apply pressure to open the seal separating the glucose and amino acids compartments.



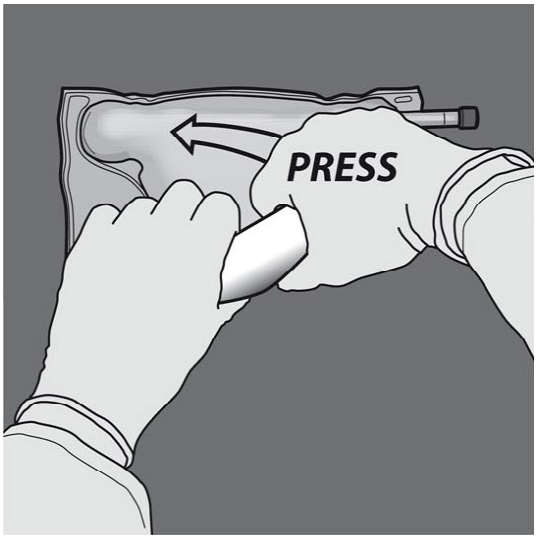
Step 2: Place the bag such that the lipid emulsion compartment is nearest to the operator and roll the bag while protecting the lipid emulsion compartment in the palms of the hands.



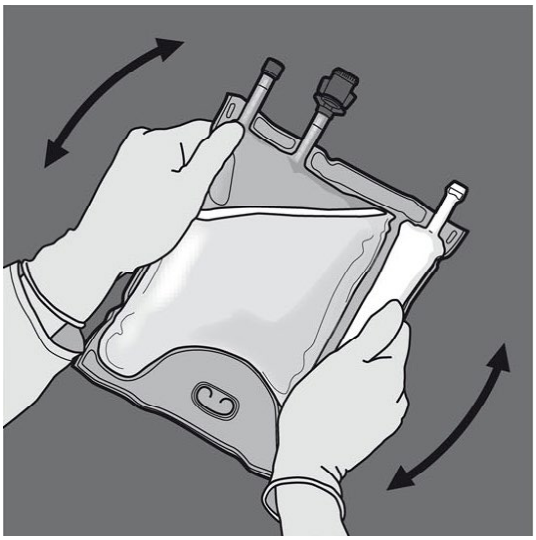
Step 3: With one hand, apply pressure by rolling the bag towards the tubes.



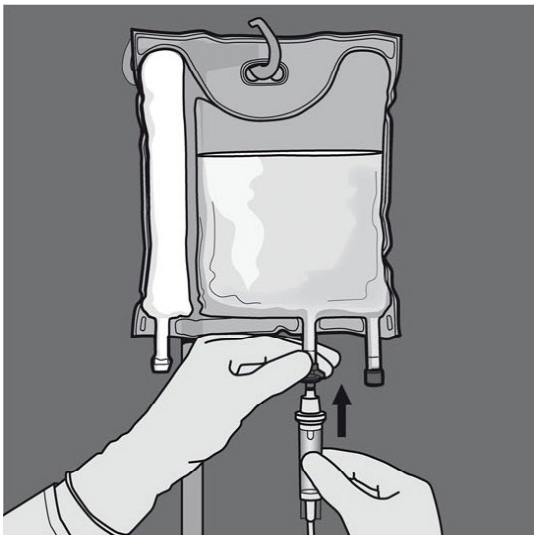
Step 4: Then change direction by rolling the bag towards the D-hanger, pressing with the other hand, continuing until the seal separating the amino acids and glucose solutions is completely opened.



Step 5: Turn the bag over at least three times to mix the content thoroughly. The appearance of the mixed solution should be clear, colorless or slightly yellow.



Step 6: Remove the protective cap from the administration site and insert the IV administration set.



Addition of additives

Admixtures including trace elements and vitamins should be protected from light, from the point of admixture through administration. Exposure to ambient light generates peroxides and other degradation products that can be reduced by photoprotection (see section 4.4).

Compatible additives may be added via the injection site into the reconstituted mixture (after the non-permanent seals have been opened and after the contents of the two or three chambers have been mixed).

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

Possible additions of commercially available trace element solutions (identified as TE1, TE2 and TE4), vitamins (identified as lyophilizate V1 and emulsion V2), and electrolytes in defined quantities are shown in Tables 1-6.

1. *Compatibility with TE4, V1 and V2*

Table 1: Compatibility of 3-in-1 (Activated 3CB) with and without dilution with water

Per 1000 mL (3 in 1 admixture with lipids)						
	Admixture without dilution			Admixture with dilution		
Additives	Included level	Maximum further addition	Maximum total level	Included level	Maximum further addition	Maximum total level
Sodium (mmol)	45.8	105	151	45.8	105	151
Potassium (mmol)	32.0	118	150	32.0	118	150
Magnesium (mmol)	2.6	7.8	10.4	2.6	7.8	10.4
Calcium (mmol)	3.8	20.5	24.3	3.8	20.5	24.3
Phosphate* (mmol)	9.4	14.6	24.0	9.4	14.6	24.0
Trace elements & vitamins	-	34 mL TE4 + 3.4 vials V1 + 38 mL V2	34 mL TE4 + 3.4 vials V1 + 38 mLV2	-	34 mL TE4 + 3.4 vials V1 + 38 mL V2	34 mL TE4 + 3.4 vials V1 + 38 mLV2
Water for Injection	-	-	-	-	1450 mL	1450 mL

* Organic phosphate

Table 2: Compatibility of 2-in-1 (Activated 2CB)

Per 775 mL (2 in 1 admixture without lipids)			
Additives	Included level	Maximum further addition	Maximum total level
Sodium (mmol)	45.1	32.0	77.1
Potassium (mmol)	32.0	45.6	77.6
Magnesium (mmol)	2.6	5.2	7.8
Calcium (mmol)	3.8	19.4	23.2
Phosphate* (mmol)	7.2	16.0	23.2
Trace elements & vitamins	-	10mL TE4 +1 vial V1	10mL TE4 +1 vial V1

* Organic phosphate

2. *Compatibility with TE1, V1 and V2*

Table 3: Compatibility of 3-in-1 (Activated 3CB)

Per 1000 mL (3 in 1 admixture with lipids)			
Additives	Included level	Maximum further addition	Maximum total level
Sodium (mmol)	45.8	0	45.8
Potassium (mmol)	32.0	0	32.0
Magnesium (mmol)	2.6	0	2.6
Calcium (mmol)	3.8	6.4	10.2
Phosphate* (mmol)	9.4	0	9.4
Trace elements & vitamins	-	15 mL TE1 + 1 vial V1 + 10 mL V2	15 mL TE1 + 1 vial V1 + 10 mL V2

* Organic phosphate

Table 4: Compatibility of 2-in-1 (Activated 2CB)

Per 775 mL (2 in 1 admixture without lipids)			
Additives	Included level	Maximum further addition	Maximum total level
Sodium (mmol)	45.1	32.0	77.1
Potassium (mmol)	32.0	45.6	77.6
Magnesium (mmol)	2.6	5.2	7.8
Calcium (mmol)	3.8	19.4	23.2
Phosphate* (mmol)	7.2	16.0	23.2
Trace elements & vitamins	-	10mL TE1 +1 vial V1	10mL TE1 +1 vial V1

* Organic phosphate

3. *Compatibility with TE2, V1 and V2*

Table 5: Compatibility of 2-in-1 (Activated 2CB)

Per 775 mL (2 in 1 admixture without lipids)			
Additives	Included level	Maximum further addition	Maximum total level
Sodium (mmol)	45.1	32.0	77.1
Potassium (mmol)	32.0	45.6	77.6
Magnesium (mmol)	2.6	5.2	7.8
Calcium (mmol)	3.8	19.4	23.2
Phosphate* (mmol)	7.2	16.0	23.2
Trace elements & vitamins	-	15mL TE2 + 1 vial V1	15mL TE2 + 1 vial V1

* Organic phosphate

Table 6: Compatibility of 3-in-1 (Activated 3CB)

Per 1000 mL (3 in 1 admixture with lipids)			
Additives	Included level	Maximum further addition	Maximum total level
Sodium (mmol)	45.8	0	45.8
Potassium (mmol)	32.0	0	32.0
Magnesium (mmol)	2.6	0	2.6
Calcium (mmol)	3.8	6.4	10.2
Phosphate* (mmol)	9.4	0	9.4
Trace elements & vitamins	-	15mL TE2 + 1 vial V1 + 10 mL V2	15mL TE2 + 1 vial V1 + 10 mL V2

* Organic phosphate

The composition of vitamins and trace elements preparations are illustrated in Tables 7 and 8.

Table 7: Composition of the commercial trace elements preparation used

Composition per 10mL	TE1	TE2	TE4
Iron	-	8.9µmol or 0.5mg	-
Zinc	38.2µmol or 2.5mg	15.3µmol or 1mg	15.3µmol or 1mg
Selenium	0.253µmol or 0.02mg	0.6µmol or 0.05mg	0.253µmol or 0.02mg
Copper	3.15µmol or 0.2mg	4.7µmol or 0.3mg	3.15µmol or 0.2mg
Iodine	0.0788µmol or 0.01mg	0.4µmol or 0.05mg	0.079µmol or 0.01mg
Fluorine	30µmol or 0.57mg	26.3µmol or 0.5mg	-
Molybdenum	-	0.5µmol or 0.05mg	-
Manganese	0.182µmol or 0.01mg	1.8µmol or 0.1mg	0.091µmol or 0.005mg
Chromium	-	0.4µmol or 0.02mg	-
Cobalt	-	2.5µmol or 0.15mg	-

Table 8: Composition of the commercial vitamin preparations used:

Composition per vial	**V1**	**V2**
Vitamin B1	2.5mg	-
Vitamin B2	3.6mg	-
Nicotinamide	40mg	-
Vitamin B6	4.0mg	-
Pantothenic acid	15.0mg	-
Biotin	60µg	-
Folic acid	400µg	-
Vitamin B12	5.0µg	-
Vitamin C	100mg	-
Vitamin A	-	2300IU
Vitamin D	-	400IU
Vitamin E	-	7IU
Vitamin K	-	200µg

To perform an addition:

- Aseptic conditions must be observed
- Prepare the injection site of the bag
- Puncture the injection site and inject the additives using an injection needle or a reconstitution device
- Mix content of the bag and the additives

Preparation of the infusion:

- Aseptic conditions must be observed
- Suspend the bag
- Remove the plastic protector from the administration outlet
- Firmly insert the infusion set spike into the administration outlet

Administration of the infusion:

- Only administer the product after the non-permanent seals between the two or three chambers have been opened and the contents of the two or three chambers have been mixed
- Ensure that the final activated 3CB emulsion for infusion does not show any evidence of phase separation or the final 2CB solution for infusion does not show any evidence of particles
- Immediate use once non-permanent seals are broken is recommended. Numeta G19%E should not be stored for subsequent infusion.
- Do not connect any partially used bag
- Do not connect in series in order to avoid the possibility of air embolism due to possible residual gas contained in the primary bag
- Any unused product or waste material and all necessary disposable devices must be properly discarded.

7. MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8. MARKETING AUTHORISATION NUMBER

PA2299/030/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th December 2011

Date of last renewal: 15th December 2020

10. DATE OF REVISION OF THE TEXT

12/05/2026