PROFESSIONAL INFORMATION

SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

NUMETA G13E emulsion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NUMETA G13E 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
300 ml	80 ml	160 ml	60 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 NUMETA G13E after mixing of the two (amino acids and glucose, 2 chamber bag, 240 ml solution) or three (amino acids, glucose and lipid, 3 chamber bag, 300 ml emulsion) chambers are provided in the following table.

Composition		
Active Substance	**Activated 2CB (240 ml)**	**Activated 3CB (300 ml)**
Amino Acid Chamber		
Alanine	0,75 g	0,75 g
Arginine	0,78 g	0,78 g
Aspartic acid	0,56 g	0,56 g
Cysteine	0,18 g	0,18 g
Glutamic acid	0,93 g	0,93 g
Glycine	0,37 g	0,37 g
Histidine	0,35 g	0,35 g
Isoleucine	0,62 g	0,62 g
Leucine	0,93 g	0,93 g
Lysine monohydrate (equivalent to Lysine)	1,15 g (1,03 g)	1,15 g (1,03 g)
Methionine	0,22 g	0,22 g
Ornithine hydrochloride (equivalent to Ornithine)	0,30 g (0,23 g)	0,30 g (0,23 g)
Phenylalanine	0,39 g	0,39 g
Proline	0,28 g	0,28 g
Serine	0,37 g	0,37 g
Taurine	0,06 g	0,06 g
Threonine	0,35 g	0,35 g
Tryptophan	0,19 g	0,19 g
Tyrosine	0,07 g	0,07 g
Valine	0,71 g	0,71 g

Composition		
Active Substance	**Activated 2CB (240 ml)**	**Activated 3CB (300 ml)**
Potassium acetate	0,61 g	0,61 g
Calcium chloride dihydrate	0,55 g	0,55 g
Magnesium acetate tetrahydrate	0,10 g	0,10 g
Sodium glycerophosphate hydrated	0,98 g	0,98 g
Glucose Chamber		
Glucose monohydrate (equivalent to glucose anhydrous)	44,00 g (40,00 g)	44,00 g (40,00 g)
Lipid Chamber		
Refined olive oil (approximately 80 %) + Refined soya bean oil (approximately 20 %)	-	7,5 g

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

For the full list of excipients, see section 6.1.

Contains sugar (glucose).

The reconstituted solution/emulsion provides the following:

Composition				
	Activated 2CB		Activated 3CB	
Per volume unit (ml)	**240**	**100**	**300**	**100**
Nitrogen (g)	1,4	0,59	1,4	0,47
Amino acids (g)	9,4	3,9	9,4	3,1
Glucose (g)	40,0	16,7	40,0	13,3
Lipids (g)	0	0	7,5	2,5
Energy				
Total calories (kcal)	198	82	273	91
Non-protein calories (kcal)	160	67	235	78
Glucose calories (kcal)	160	67	160	53
Lipid calories [a] (kcal)	0	0	75	25
Non-prot calories / nitrogen (kcal/g N)	113	113	165	165
Lipid calories (% non-protein calories)	N/A	N/A	32	32
Lipid calories (% total calories)	N/A	N/A	28	28
Electrolytes				
Sodium (mmol)	6,4	2,7	6,6	2,2
Potassium (mmol)	6,2	2,6	6,2	2,1
Magnesium (mmol)	0,47	0,20	0,47	0,16
Calcium (mmol)	3,8	1,6	3,8	1,3
Phosphate [b] (mmol)	3,2	1,3	3,8	1,3
Acetate (mmol)	7,2	3,0	7,2	2,4
Malate (mmol)	3,2	1,3	3,2	1,1
Chloride (mmol)	9,3	3,9	9,3	3,1
pH (approx.)	5,5	5,5	5,5	5,5

Osmolarity approx. (mOsm/l)	1400	1400	1150	1150

[a] Includes calories from egg phosphatide

[b] Includes phosphate from egg phosphatide 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, practically free from particles.
- The lipid emulsion is homogeneous and milky-white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NUMETA G13E is indicated for parenteral nutrition in preterm newborn infants 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 metabolise the constituents of NUMETA G13E, 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 static composition.

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 (240 ml)	**Activated 3CB (300 ml)**
Maximal rate of infusion in ml/kg/h	5,1	6,4
Corresponding to:		
Amino acid in g/kg/h	0,20[a]	0,20[a]
Glucose in g/kg/h	0,85	0,85
Lipids in g/kg/h	0	0,16
Maximal amount in ml/kg/day	102,3	127,9
Corresponding to:		
Amino acid in g/kg/d	4,0[a]	4,0[a]
Glucose in g/kg/d	17,1	17,1
Lipids in g/kg/d	0	3,2

[a] Limiting parameter according to ESPEN-ESPGHAN guidelines

NUMETA G13E may not be appropriate for some preterm infants, as the clinical condition of the patient may require administration of individualised formulations to meet the specific needs of the patient as assessed by the clinician.

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).

Due to its high osmolarity, undiluted NUMETA G13E can only be administered through a central vein; however, sufficient dilution of NUMETA G13E with water for injection lowers the osmolarity and allows peripheral infusion. The formula below indicates how the dilution impacts osmolarity of the bags:

$$\text{Final osmolarity} = \frac{\text{Volume of bag} * \text{Initial osmolarity}}{\text{Water added} + \text{Volume of bag}}$$

The table below shows examples of osmolarity for activated 2CB and activated 3CB admixtures after addition of water for injection:

	Amino Acids and Glucose (Activated 2CB)	**Amino Acids, Glucose, and Lipids (Activated 3CB)**
Initial volume in the bag (ml)	240	300
Initial osmolarity (mOsm/l approximately)	1400	1150
Volume of water added (ml)	240	300
Final volume after addition (ml)	480	600
Osmolarity after addition (mOsm/l approximately)	700	575

The flow rate should be increased gradually during the first hour. Upon discontinuation of NUMETA G13E, 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.

In preterm newborn infants, continuous parenteral administration over 24 hours is usually recommended; however, 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.

NUMETA G13E contains electrolytes and may be further supplemented using commercial electrolyte preparations according to the doctor's judgment and the clinical needs of the patient, see section 6.6.

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

4.3 Contraindications

The general contraindications for administering NUMETA G13E 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.
- Concomitant treatment with ceftriaxone, even if separate infusion lines are used. See sections 4.4, 4.5 and 6.2.
- Severe hyperglycaemia

The addition of lipids (administering NUMETA G13E 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 characterised 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 dyspnoea) develop.

NUMETA G13E contains glucose produced from cornstarch. Therefore, NUMETA G13E should be used with caution in patients with known allergy to corn or corn products.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature new-borns have been described. In preterm newborn infants, concomitant treatment with ceftriaxone is contraindicated (see section 4.3).

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 destabilisation 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 medicines, may promote infection and sepsis. Careful symptomatic and laboratory monitoring for fever/chills, leukocytosis, technical complications with the access device, and hyperglycaemia can help recognise 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 metabolise the lipids contained in NUMETA G13E, 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 characterised 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 G13E 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 G13E 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).

Light exposure of solutions for intravenous total parenteral nutrition after admixture may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. NUMETA G13E should be protected from light from the point of admixture through administration (see section 6.6).

Routinely monitor water and electrolyte balance, including magnesium, 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 G13E should be monitored and adjusted to meet the clinical needs of the patient.

There are limited data on the administration of NUMETA G13E in preterm infants less than 28 weeks gestational age.

Cardiovascular

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

Renal

Use with caution in patients with renal insufficiency. Fluid and electrolyte status, including magnesium, 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 metabolise 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 G13E must be adjusted and/or insulin administered, see section 4.9.

Haematologic

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

Special precaution relating to excipients

Contains glucose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

No pharmacodynamic interaction studies have been performed with NUMETA G13E.

NUMETA G13E must not be administered simultaneously with blood through the same infusion tubing because of the risk of pseudoagglutination.

As for other calcium-containing infusion solutions concomitant treatment with ceftriaxone and NUMETA G13E is contraindicated in preterm newborn infants (see sections 4.3, 4.4 and 6.2).

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 G13E special care should be taken in patients simultaneously treated with potassium sparing diuretics (e.g., amiloride, spironolactone, triamterene) or with ACE inhibitors, angiotensin II receptor antagonists, or the immunosuppressants tacrolimus and cyclosporine in view of the risk of hyperkalaemia.

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 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Not applicable since the product is intended for preterm newborn infants.

Breastfeeding

Not applicable since the product is intended for preterm newborn infants.

Fertility

The product contains glucose, a paediatrics amino acids solution, electrolytes, and a lipid emulsion; effects on fertility are unlikely.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse Reactions from Clinical Trials and Post-marketing experience

The safety and administration of NUMETA G13E was assessed in a single phase III study. One hundred and fifty-nine (159) paediatric patients were included in the study and received NUMETA products (113 preterm infants received NUMETA G13E, 28 full-term infants to toddlers up to 2 year of age (full-term infants and toddlers) received NUMETA G16E) and 18 children and adolescents (children/adolescents) up to 16 years of age received NUMETA G19E).

The pooled data from clinical trials and the post-marketing experience indicate the following undesirable effects 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]	Common
	Hyperglycaemia[a]	Common
	Hypercalcaemia[a]	Common
	Hypertriglyceridaemia[a]	Common
	Hyperlipidaemia[a]	Uncommon
	Hyponatraemia[a]	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 (≥1/1000 - <1/100), Rare (≥1/10000 - <1/1000), Very Rare (<1/10000), Not known (cannot be estimated based on available data).

[c] These undesirable effects have been reported only for NUMETA G13E and G16E when peripherally administered with insufficient dilution (see Section 4.4)

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 NUMETA G13E is administered according to instructions. The reduced or limited ability to metabolise the lipids contained in NUMETA G13E 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 characterised by findings such as hyperlipidaemia, fever, liver fatty infiltration (hepatomegaly), deteriorating liver function, anaemia, 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 emboli and pulmonary distress) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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 metabolise 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, haemodialysis, haemofiltration, or haemodiafiltration may be necessary. Severe cases of fat overload syndrome treated with exchange transfusions have been reported in the literature.

The reduced or limited ability to metabolise 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.

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, haemodialysis, haemofiltration, or haemodiafiltration may be necessary.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.25 Special foods

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 G13E 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 G13E 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 and lipids) are distributed, metabolised and eliminated in the same way as if they had been administered individually. NUMETA G13E is given intravenously and is thus 100 % bioavailable and the constituents are distributed to and metabolised 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 G13E (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	-
Purified egg phosphatide	-	-	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, NUMETA G13E 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.

As for other calcium-containing infusion solutions, concomitant treatment with ceftriaxone and NUMETA G13E is contraindicated in preterm newborn infants (see sections 4.3, 4.4 and 4.5).

Due to the risk of precipitation, NUMETA G13E should not be administered through the same infusion line together with ampicillin, fosphenytoin or frusemide.

NUMETA G13E must not be administered simultaneously with blood through the same infusion tubing, see section 4.5.

NUMETA G13E contains calcium ions which pose additional risk of coagulation precipitated in citrate anticoagulated/preserved blood or components.

6.3 Shelf life

18 months

Shelf life after reconstitution

It is recommended that NUMETA G13E 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 a maximum of 48 hours at or below 30 °C.

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

For specific admixtures physical stability of the NUMETA G13E formulation has been demonstrated for 7 days between 2 °C and 8 °C followed by a maximum of 48 hours at or below 30 °C. Information on these additions is specified in section 6.6.

From a microbiological point of view, NUMETA G13E 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 °C to 8 °C, unless reconstitution / dilution / supplementation has taken place in controlled and validated aseptic conditions.

Please also refer to section 4.2 and section 6.6.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze.

Store in over-pouch.

Keep out of reach of children.

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 over-pouch that contains an oxygen absorber sachet and an oxygen indicator.

Available pack sizes:

300 ml bags: 10 units per cardboard box

1 bag of 300 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.

Before opening the over-pouch, 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 NUMETA G13E if the colour of the oxygen indicator does not correspond to the reference colour printed next to the OK symbol.

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

Figure 1

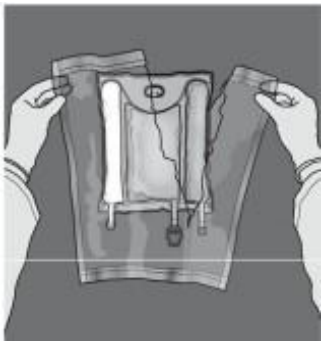


Figure 2

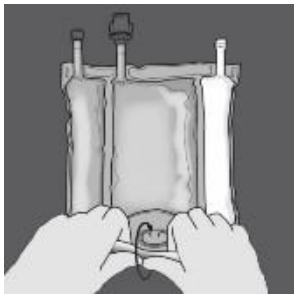
Preparation of the mixed emulsion:

Ensure that NUMETA G13E is at room temperature when breaking the non-permanent seals.

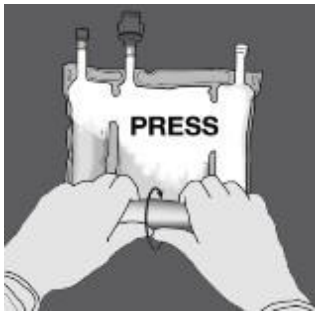
Place bag onto a flat clean surface.

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.



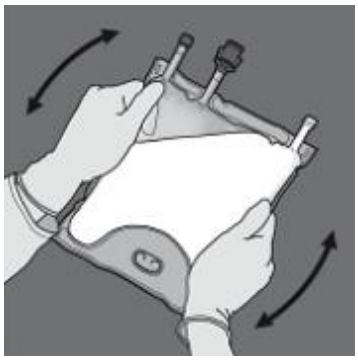
Step 3: Change direction by rolling the bag towards the D-hanger.

Continue until the seal is completely opened.

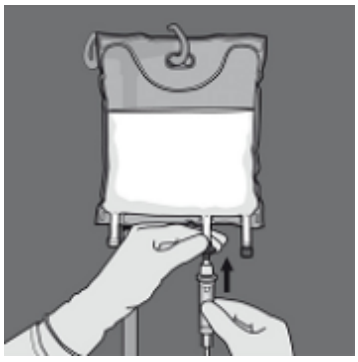
Proceed the same way to complete the opening of the second peel seal.

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.



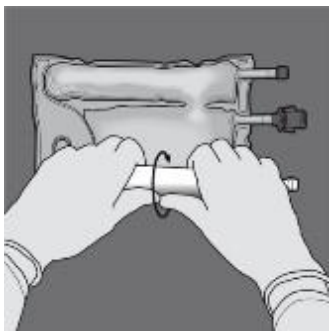
Step 5: Remove the protective cap from the administration site and insert the IV administration set.



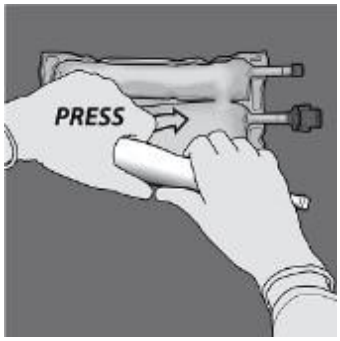
Activation of the 2CB (breaking the non-permanent seal between the Amino acid and Glucose chambers)

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

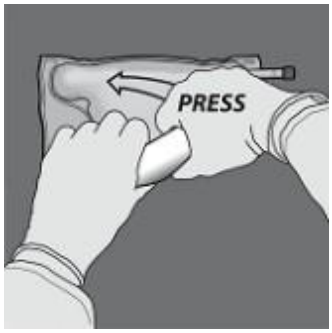
Step 2: Place the bag such that the lipid emulsion compartment is nearest to the operator and roll the bag while protecting the lipid emulsion compartment in the palms of the hands.



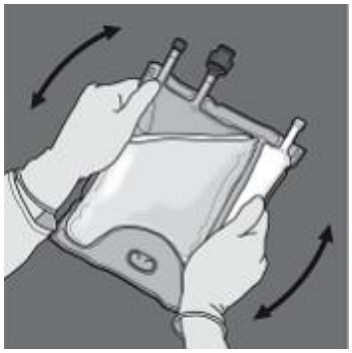
Step 3: With one hand, apply pressure by rolling the bag towards the tubes.



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, colourless 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 and TE4), vitamins (identified as lyophilizate V1 and emulsion V2), and electrolytes in defined quantities are shown in Tables 1-4.

1. Compatibility with TE4, V1 and V2

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

Per 300 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)	6,6	5,0	11,6	6,6	5,0	11,6
Potassium (mmol)	6,2	4,2	10,4	6,2	4,2	10,4

Magnesium (mmol)	0,47	0,83	1,3	0,47	0,83	1,3
Calcium (mmol)	3,8	3,5	7,3	3,8	3,5	7,3
Phosphate* (mmol)	3,8	2,5	6,3	3,8	2,5	6,3
Trace elements & vitamins	-	15 ml (1,5 vial) TE4 + 1,5 vial V1 + 25 ml (2,5 vials) V2	15 ml (1,5 vial) TE4 + 1,5 vial V1 + 25 ml (2,5 vials) V2	-	15 ml (1,5 vial) TE4 + 1,5 vial V1 + 25 ml (2,5 vials) V2	15 ml (1,5 vial) TE4 + 1,5 vial V1 + 25 ml (2,5 vials) V2
Water for Injection	-	-	-	-	300 ml	300 ml

* Organic phosphate

Table 2: Compatibility of 2-in-1 (Activated 2CB) with and without dilution with water

Per 240 ml (2 in 1 admixture without 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)	6,4	17,6	24	6,4	0,0	6,4
Potassium (mmol)	6,2	17,8	24	6,2	0,0	6,2

Magnesium (mmol)	0,47	2,13	2,6	0,47	0,0	0,47
Calcium (mmol)	3,8	3,5	7,3	3,8	0,0	3,8
Phosphate* (mmol)	3,2	4,0	7,2	3,2	0,0	3,2
Trace elements & vitamins	-	2,5 ml (¼ vial) TE4 + ¼ vial V1	2,5 ml (¼ vial) TE4 + ¼ vial V1	-	2,5 ml (¼ vial) TE4 + ¼ vial V1	2,5 ml (¼ vial) TE4 + ¼ vial V1
Water for Injection	-	-	-	-	240 ml	240 ml

* Organic phosphate

2. Compatibility with TE1, V1 and V2

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

Per 300 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)	6,6	5,0	11,6	6,6	0,0	6,6
Potassium (mmol)	6,2	4,2	10,4	6,2	0,0	6,2
Magnesium	0,47	0,83	1,3	0,47	0,0	0,47

(mmol)						
Calcium (mmol)	3,8	1,9	5,7	3,8	0,0	3,8
Phosphate* (mmol)	3,8	2,5	6,3	3,8	0,0	3,8
Trace elements & vitamins	-	2,5 ml (¼ vial) TE1 + ¼ vial V1 + 2,5 ml (¼ vial) V2	2,5 ml (¼ vial) TE1 + ¼ vial V1 + 2,5 ml (¼ vial) V2	-	2,5 ml (¼ vial) TE1 + ¼ vial V1 + 2,5 ml (¼ vial) V2	2,5 ml (¼ vial) TE1 + ¼ vial V1 + 2,5 ml (¼ vial) V2
Water for Injection	-	-	-	-	300 ml	300 ml

* Organic phosphate

Table 4: Compatibility of 2-in-1 (Activated 2CB) with and without dilution with water

Per 240 ml (2 in 1 admixture without 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)	6,4	17,6	24	6,4	0,0	6,4
Potassium (mmol)	6,2	17,8	24	6,2	0,0	6,2
Magnesium (mmol)	0,47	2,13	2,6	0,47	0,0	0,47

Calcium (mmol)	3,8	3,5	7,3	3,8	0,0	3,8
Phosphate* (mmol)	3,2	4,0	7,2	3,2	0,0	3,2
Trace elements & vitamins	-	2,5 ml (¼ vial) TE1 + ¼ vial V1	2,5 ml (¼ vial) TE1 + ¼ vial V1	-	2,5 ml (¼ vial) TE1 + ¼ vial V1	2,5 ml (¼ vial) TE1 + ¼ vial V1
Water for Injection	-	-	-	-	240 ml	240 ml

* Organic phosphate

The composition of vitamins and trace elements preparations are illustrated in Tables 5 and 6.

Table 5: Composition of the commercial trace elements preparation used:

Composition per vial	**TE1 (10 ml)**	**TE4 (10 ml)**
Zinc	38,2 µmol or 2,5 mg	15,3 µmol or 1 mg
Selenium	0,253 µmol or 0,02 mg	0,253 µmol or 0,02 mg
Copper	3,15 µmol or 0,2 mg	3,15 µmol or 0,2 mg
Iodine	0,0788 µmol or 0,01 mg	0,079 µmol or 0,01 mg
Fluorine	30 µmol or 0,57 mg	-
Manganese	0,182 µmol or 0,01 mg	0,091 µmol or 0,005 mg

Table 6: Composition of the commercial vitamin preparations used:

Composition per vial	**V1**	**V2**

Vitamin B1	2,5 mg	-
Vitamin B2	3,6 mg	-
Nicotinamide	40 mg	-
Vitamin B6	4,0 mg	-
Pantothenic acid	15,0 mg	-
Biotin	60 µg	-
Folic acid	400 µg	-
Vitamin B12	5,0 µg	-
Vitamin C	100 mg	-
Vitamin A	-	2300 IU
Vitamin D	-	400 IU
Vitamin E	-	7 IU
Vitamin K	-	200 µg

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 NUMETA G13E 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 G13E 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 NUMETA G13E or waste material and all necessary disposable devices must be properly discarded in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Baxter Healthcare South Africa (Pty) Ltd

The Campus – Eden Gardens

57 Sloane & Cnr Main Rd

Bryanston

2021

South Africa

8. REGISTRATION NUMBER

52/25/0739

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 September 2022

10. DATE OF REVISION OF THE TEXT

23 July 2025