SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Smofkabiven Peripheral emulsion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Smofkabiven Peripheral consists of a three-chamber bag system:

Amino acid solution with electrolytes
Glucose 13 %
Lipid emulsion

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Glucose 13 %
A clear, almost colourless solution and practically free from particles in a three-chamber bag.

Aminoven 10 % with electrolytes
A clear solution, colourless to slightly yellow and practically free from particles, in a three- chamber bag.

Smoflipid 20 %
A white, homogeneous emulsion in a three-chamber bag.

Mixed three-chamber bag
A white emulsion in an open/mixed three chamber bag.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Parenteral nutrition for adults and children aged 2 years and above when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Posology and method of administration

The appearance of SMOFKABIVEN PERIPHERAL after mixing the 3 chambers is a white emulsion.

The patient's ability to eliminate lipids and metabolise nitrogen and glucose, and the nutritional requirements should govern the dosage and infusion rate, see section 4.4.

The dose should be individualised to the patient's clinical condition, body weight (bw), nutritional and energy requirements, adjusting dosage based upon additional oral/enteral intake.

The nitrogen requirements for maintenance of body protein mass depend on the patient's condition (e.g. nutritional state and degree of catabolic stress or anabolism).

Adults

The requirements are 0,6 to 0,9 g amino acids/kg bw/day (0,10 to 0,15 g nitrogen/kg bw/day) in the normal nutritional state or in conditions with mild catabolic stress. In patients with moderate to high metabolic stress with or without malnutrition, the requirements are in the range of 0,9 to 1,6 g amino acids/kg bw/day (0,15 to 0,25 g nitrogen/kg bw/day). In some very special conditions (e.g. burns or marked anabolism) the need for nitrogen may be even higher.

Dosage

The dosage range of 20 to 40 ml SMOFKABIVEN PERIPHERAL/kg bw/day will provide 0,6 to 1,3 g amino acids/kg bw/day (corresponds to 0,10 to 0,20 g nitrogen/kg bw/day) and 14 to 28 kcal/kg bw/day of total energy (11 to 22 kcal/kg bw/day of non-protein energy). This covers the needs of the majority of the patients. In obese patients the dose should be based on the estimated ideal weight.

Infusion rate

The maximum infusion rate for glucose is 0,25 g/kg bw/h, for amino acids 0,1 g/kg bw/h, and for lipids 0,15 g/kg bw/h.

The infusion rate should not exceed 3,0 ml/kg bw/h (corresponding to 0,10 g amino acids,

0,21 g glucose and 0,08 g lipids/kg bw/h). The recommended infusion period is 14 to 24 hours.

Maximum daily dose

The maximum daily dose varies with the clinical condition of the patient and may even change from day to day. The recommended maximum daily dose is 40 ml/kg bw/day.

The recommended maximum daily dose of 40 ml/kg bw/day will provide 1,3 g amino acids/kg bw/day (corresponding to 0,2 g nitrogen/kg bw/day), 2,8 g glucose/kg bw/day, 1,1 g lipids/kg bw/day and a total energy content of 28 kcal/kg bw/day (corresponding to 22 kcal/kg bw/day of non-protein energy).

Paediatric population

Children (2 to 11 years) Dosage

The dose up to 40 ml/kg bw/day should be regularly adjusted to the requirements of the paediatric patient that varies more than in adult patients.

Infusion rate

The recommended maximum infusion rate is 3,0 ml/kg bw/h (corresponding to 0.10 g amino acids/kg/h, 0,21 g/glucose/kg/h and 0,08 g lipids/kg/h). The recommended infusion period is 12 to 24 hours.

If using the recommended maximum daily dose, the dose should be infused during a period of at least 13 hours to not exceed the recommended maximum infusion rate, except in particular cases.

Maximum daily dose

The maximum daily dose varies with the clinical condition of the patient and may even change from day to day. The recommended maximum daily dose is 40 ml/kg bw/day. This recommended maximum daily dose of 40 ml/kg bw/day will provide 1,3 g amino acids/kg bw/day (corresponding to 0,2 g nitrogen/kg bw/day), 2,8 g glucose/kg bw/day, 1,1 g lipids/kg bw/day and a total energy content of 28 kcal/kg bw/day (corresponding to 22 kcal/kg bw/day of non-protein energy).

Adolescents (12 to 16/18 years)

In adolescents, SMOFKABIVEN PERIPHERAL can be used as in adults.

Method of administration

Intravenous use, infusion into a peripheral or central vein.

SMOFKABIVEN PERIPHERAL is available in three pack sizes intended for patients with moderately increased or basal nutritional requirements. To provide

total parenteral nutrition, trace elements, vitamins and possibly electrolytes (taking into account the electrolytes already present in SMOFKABIVEN PERIPHERAL) should be added to SMOFKABIVEN PERIPHERAL according to the patients need.
For instructions on preparation of SMOFKABIVEN PERIPHERAL before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to fish, egg, soya or peanut protein or to any of the active substances or excipients (listed in section 6.1)
- Severe hyperlipidaemia
- Severe liver insufficiency
- Severe blood coagulation disorders
- Congenital errors of amino acid metabolism
- Severe renal insufficiency without access to hemofiltration or dialysis
- Acute shock
- Uncontrolled hyperglycaemia
- Pathologically elevated serum levels of any of the included electrolytes
- General contraindications to infusion therapy: acute pulmonary oedema, hyperhydration, and decompensated cardiac insufficiency
- Hemophagocytotic syndrome
- Unstable conditions (e.g. severe post-traumatic conditions, uncompensated diabetes mellitus, acute myocardial infarction, stroke, embolism, metabolic acidosis, severe sepsis, hypotonic dehydration and hyperosmolar coma)
- Infants and children under 2 years of age

4.4 Special warnings and precautions for use

SMOFKABIVEN PERIPHERAL should not be given simultaneously with blood in the same infusion set due to the risk of pseudo-agglutination.

To avoid risks associated with too rapid infusion rates, it is recommended to use a continuous and well-controlled infusion, if possible, by using a volumetric pump.

Since an increased risk of infection is associated with the use of any peripheral vein, strict aseptic precautions should be taken to avoid any contamination during catheter insertion and manipulation.

Fat overload syndrome

The capacity to eliminate lipids is individual and should therefore be monitored. This is done by checking the triglyceride levels. The concentration of triglycerides in serum should not exceed 4 mmol/l during infusion. An overdose may lead to fat overload syndrome, see section 4.8. SMOFKABIVEN PERIPHERAL should be given with caution in conditions of impaired lipid metabolism, which may occur in patients with renal failure, diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism and sepsis.

Hypersensitivity reactions

SMOFKABIVEN PERIPHERAL contains soya-bean oil, fish oil and egg phospholipids, which may cause allergic reactions. Cross allergic reactions have been observed between soya-beans and peanuts.

Any sign or symptom of anaphylactic reaction (such as fever, shivering, rash or dyspnoea) should lead to immediate interruption of the infusion.

Electrolyte and fluid balance

Disturbances of the electrolyte and fluid balance (e.g. abnormally high or low serum levels of the electrolytes) should be corrected before starting the infusion.

SMOFKABIVEN PERIPHERAL should be given with caution to patients with a tendency towards electrolyte retention. Special clinical monitoring is required at the beginning of any intravenous infusion. Should any abnormal sign occur, the infusion must be stopped.

General precautions

Serum glucose, electrolytes and osmolarity as well as fluid balance, acidbase status and liver enzyme tests should be monitored.

Blood cells count and coagulation should be monitored when lipids are given for a longer period.

In patients with renal insufficiency, the phosphate and potassium intake should be carefully controlled to prevent hyperphosphatemia and hyperkalaemia. The amount of individual electrolytes to be added is governed by the clinical condition of the patient and by frequent monitoring of serum levels.

Parenteral nutrition should be given with caution in lactic acidosis, insufficient cellular oxygen supply and increased serum osmolarity.

The lipid content of SMOFKABIVEN PERIPHERAL may interfere with certain laboratory measurements (e.g. bilirubin, lactate dehydrogenase, oxygen saturation, haemoglobin) if blood is sampled before lipids have been adequately cleared from the bloodstream. Lipids are cleared after a lipidfree interval of 5 to 6 hours in most patients.

Intravenous infusion of amino acids is accompanied by increased urinary excretion of the trace elements, in particular copper and zinc. This should be considered in the dosing of trace elements, especially during long-term intravenous nutrition. The amounts of zinc administered with SMOFKABIVEN PERIPHERAL should be taken into account.

In malnourished patients, initiation of parenteral nutrition can precipitate fluid shifts resulting in pulmonary oedema and congestive heart failure as well as a decrease in the serum concentration of potassium, phosphorus, magnesium and water soluble vitamins. These changes can occur within 24 to 48 hours, therefore careful and slow initiation of parenteral nutrition is recommended in this patient group, together with close monitoring and appropriate adjustments of fluid, electrolytes, minerals and vitamins.

Excess of glucose infusion

In patients with hyperglycaemia, administration of exogenous insulin might be necessary. Thrombophlebitis may occur if peripheral veins are used for infusions. The catheter insertion site should be evaluated daily for local signs of thrombophlebitis.

Paediatric population

Due to composition of the amino acid solution in SMOFKABIVEN PERIPHERAL it is not suitable for the use in newborns or infants below 2 years of age. There is no clinical experience of the use of SMOFKABIVEN PERIPHERAL in children (age 2 to 16/18 years).

4.5 Interaction with other medicinal products and other forms of interaction

Some medicines, like insulin, may interfere with the body's lipase system. This kind of interaction seems, however, to be of limited clinical importance.

Heparin given in clinical doses causes a transient release of lipoprotein lipase into the circulation. This may result initially in increased plasma lipolysis followed by a transient decrease in triglyceride clearance.

Soya-bean oil has a natural content of vitamin K1. However, the concentration in SMOFKABIVEN PERIPHERAL is so low that it is not expected to significantly influence the coagulation process in patients treated with coumarin derivatives.

4.6 Pregnancy and lactation

Pregnancy and Breastfeeding

There are no data available on exposure of SMOFKABIVEN PERIPHERAL in pregnant or breastfeeding women.

Fertility
There are no studies available on reproductive toxicity in animals.

4.7 Effects on ability to drive and use machines
SMOFKABIVEN PERIPHERAL has no influence on the ability to drive and use machines.

4.8 Undesirable effects
a) Tabulated list of adverse reactions

	Frequent	Less frequent
Immune system disorders		Hypersensitivity reactions (e.g. anaphylactic or anaphylactoid reactions, skin rash, urticaria, flush, headache), heat or cold sensation, paleness, cyanosis, pain in the neck, back, bones, chest and loins
Cardiac disorders		Tachycardia
Respiratory, thoracic and mediastinal disorders		Dyspnoea
Gastrointestinal disorders		Lack of appetite, nausea, vomiting
Metabolism and nutrition disorders		Elevated plasma levels of liver enzymes
Vascular disorders	Thrombophlebitis	Hypotension, hypertension
General disorders and administration site conditions	Increase in body temperature	Chills, dizziness, headache

b) Description of selected adverse reactions
Should these side-effects occur the infusion of SMOFKABIVEN PERIPHERAL should be stopped or, if necessary, continued at a reduced dosage.

Fat overload syndrome

Impaired capacity to eliminate triglycerides can lead to “Fat overload syndrome” which may be caused by overdose. Possible signs of metabolic overload must be observed. The cause may be genetic (individually different metabolism) or the lipid metabolism may be affected by ongoing or previous illnesses. This syndrome may also appear during severe hypertriglyceridaemia, even at the recommended infusion rate, and in association with a sudden change in the patient’s clinical condition, such as renal function impairment or infection. The fat overload syndrome is characterised by hyperlipidaemia, fever, lipid infiltration, hepatomegaly with or without icterus, splenomegaly, anaemia, leukopenia, thrombocytopenia, coagulation disorder, haemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms are usually reversible if the infusion of the lipid emulsion is discontinued.

Excess of amino acid infusion

As with other amino acid solutions, the amino acid content in SMOFKABIVEN PERIPHERAL may cause undesirable effects when the recommended infusion rate is exceeded. These effects are nausea, vomiting, shivering and sweating. Amino acid infusion may also cause a rise in body temperature. With an impaired renal function, increased levels of nitrogen containing metabolites (e.g. creatinine, urea) may occur.

Excess of glucose infusion

If the glucose clearance capacity of the patient is exceeded, hyperglycaemia will develop.

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. Health care 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

See section 4.8 “Fat overload syndrome”, “Excess of amino acid infusion” and “Excess of glucose infusion”.

If symptoms of overdose of lipids or amino acids occur, the infusion should be slowed down or discontinued. There is no specific antidote for overdose.

Emergency procedures should be general supportive measures, with particular attention to respiratory and cardiovascular systems. Close biochemical monitoring would be essential and specific abnormalities treated appropriately.

If hyperglycaemia occurs, it should be treated according to the clinical situation either by appropriate insulin administration and/or adjustment of the infusion rate.
Additionally, overdose might cause fluid overload, electrolyte imbalances and hyperosmolality.
In some serious cases, haemodialysis, haemofiltration or haemodiafiltration may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parenteral nutrition. ATC code: B05BA10

Lipid emulsion
The lipid emulsion of SMOFKABIVEN PERIPHERAL is composed of Smoflipid and has a particle size and biological properties similar to those of endogenous chylomicrons. The constituents of Smoflipid: soya-bean oil, medium-chain triglycerides, olive oil and fish oil have except for their energy contents, their own pharmacodynamic properties.
Soya-bean oil has a high content of essential fatty acids. The omega-6 fatty acid linoleic acid is the most abundant (approximately 55 % to 60 %). Alphalinolenic acid, an omega-3 fatty acid, constitutes about 8 %. This part of SMOFKABIVEN PERIPHERAL provides the Page 10 of 16

necessary amount of essential fatty acids.
Medium-chain fatty acids are rapidly oxidised and provide the body with a form of immediately available energy.
Olive oil mainly provides energy in the form of mono-unsaturated fatty acids, which are much less prone to peroxidation than the corresponding amount of poly-unsaturated fatty acids.
Fish oil is characterised by a high content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA is an important structural component of cell membranes, whereas EPA is a precursor of eicosanoids as prostaglandins, thromboxanes and leucotrienes.

Amino acids and electrolytes
The amino acids, constituents of protein in ordinary food, are utilised for tissue protein synthesis and any surplus is channelled to a number of metabolic pathways. Studies have shown a thermogenic effect of amino acid infusion.

Glucose
Glucose should have no pharmacodynamic effects apart from contributing to maintain or replete the normal nutritional status.

5.2 Pharmacokinetic properties

Lipid emulsion
The individual triglycerides in Smoflipid have different clearance rate but Smoflipid as a mixture is eliminated faster than long chain triglycerides (LCT). Olive oil has the slowest clearance rate of the components (somewhat slower than LCT) and medium chain triglycerides (MCT) the fastest. Fish oil in a mixture with LCT has the same clearance rate as LCT alone.

Amino acids and electrolytes
The principal pharmacokinetic properties of the infused amino acids and electrolytes are essentially the same as for amino acids and electrolytes supplied by ordinary food.
However, the amino acids of dietary protein first enter the portal vein and then the systemic circulation, while intravenously infused amino acids reach the systemic circulation directly.

Glucose
The pharmacokinetic properties of infused glucose are essentially the same as those of glucose supplied by ordinary food.

5.3 Preclinical safety data

Preclinical safety studies with SmofKabiven Peripheral have not been performed. However, preclinical data for Smoflipid as well as for amino acid and glucose solutions of various concentrations and sodium glycerophosphate reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. No teratogenic effects or other embryotoxic injuries could be observed in rabbits with amino acid solutions and are not to be expected from lipid emulsions and sodium glycerophosphate when giving at the recommended doses as substitution therapy. Nutritional products (amino acid solutions, lipid emulsions, and sodium glycerophosphate) used in replacement therapy at physiological levels are not expected to be embryotoxic, teratogenic, or to influence reproductive performance or fertility. In a test on guinea pigs (maximisation test) fish oil emulsion showed moderate dermal sensitisation. A systemic antigenicity test gave no indication of evidence of anaphylactic potential of fish oil. In a local tolerance study in rabbits with Smoflipid a slight, transient inflammation after intra-arterial, paravenous or subcutaneous administration was observed. After intramuscular administration a moderate transient inflammation and tissue necrosis were seen in some animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose 13 %

- Water for injections

Aminoven 10 % with electrolytes

- Acetic acid glacial
- Water for injections

SMOFlipid 20 %

- all-rac-α-Tocopherol
- Purified egg phospholipids
- Glycerol (anhydrous)
- Sodium oleate • Sodium hydroxide.
- Water for injections

6.2 Incompatibilities

SMOFKABIVEN PERIPHERAL may only be mixed with other medicines for which compatibility has been documented.

6.3 Shelf life

Shelf life of the medicine as packaged for sale
24 months

Shelf life after mixing
Chemical and physical in-use stability of the mixed three chamber bag has been demonstrated for 36 hours at 25 ˚C. From a microbiological point of view SMOFKABIVEN PERIPHERAL 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 mixing has taken place in controlled and validated aseptic conditions.

Shelf life after mixing with additives
From a microbiological point of view, SMOFKABIVEN PERIPHERAL should be used immediately when additions have been made. If not used immediately, the in-use storage time and conditions prior to use are the responsibility of the user and should 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.

6.4 Special precautions for storage

Store at or below 25°C. Do not freeze. Store in overpouch.

Shelf life after mixing: See section 6.3.
Shelf life after mixing with additives: See section 6.3.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

SMOFKABIVEN PERIPHERAL is packed into a three-chamber inner bag made of Biofine, a high barrier overpouch and an oxygen absorber. The inner bags are filled with amino acid solution corresponding to Aminoven 10 %, Glucose 13 % and SMOFlipid 20 % in separate chambers divided by peelable seals.

Pack sizes:

1 x 1206 ml, 4 x 1206 ml
1 x 1448 ml, 4 x 1448 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Instructions for use

Do not use if package is damaged. Use only if the amino acid and glucose solutions are clear and colourless or slightly yellow and the lipid emulsion is white and homogenous. The contents of the three separate chambers have to be mixed before use, and before any additions are made via the additive port.

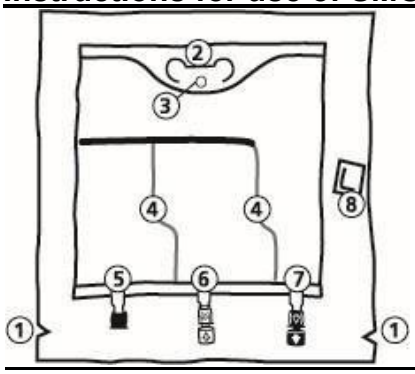
After separation of the peelable seals the bag should be inverted on a number of occasions to ensure a homogenous mixture, which does not show any evidence of phase separation.

Compatibility

Only medicines or nutrition solutions for which compatibility has been documented may be added to SMOFKABIVEN PERIPHERAL.
Compatibility for different additives and the storage time of the different admixtures will be available upon request. Addition should be made aseptically.

For single use only. Any mixture remaining after infusion must be discarded. Any unused medicine or waste material should be disposed in accordance with local requirement.

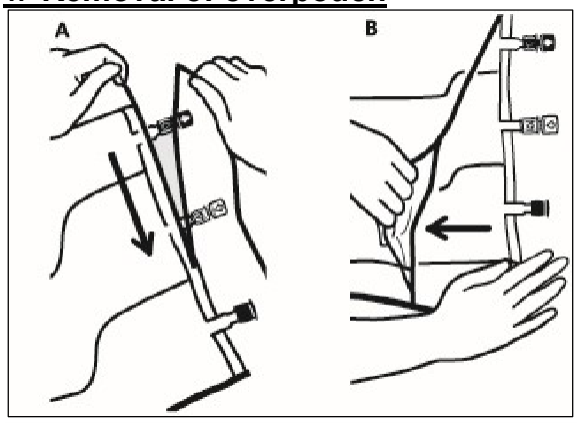
Instructions for use of SMOFKABIVEN PERIPHERAL The bag



1. Notches in the overpouch
2. Handle
3. Hole for hanging the bag
4. Peelable seals
5. Blind port (only used during manufacturing)
6. Additive port

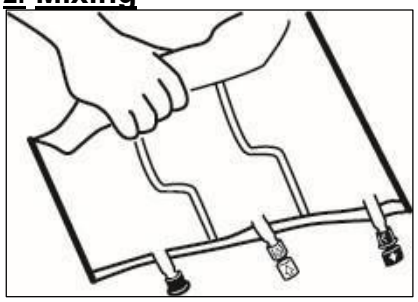
7. Infusion port
8. Oxygen absorber

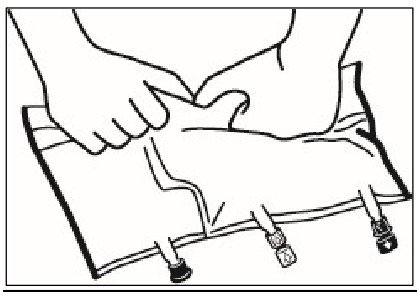
1. Removal of overpouch

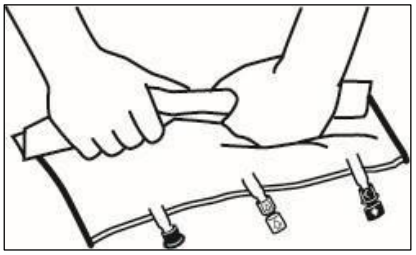


- To remove overpouch, hold the bag horizontally and tear from the notch close to the ports along the upper edge (A).
- Then simply tear the long side, pull off the overpouch and discard it along with the oxygen absorber (B).

2. Mixing



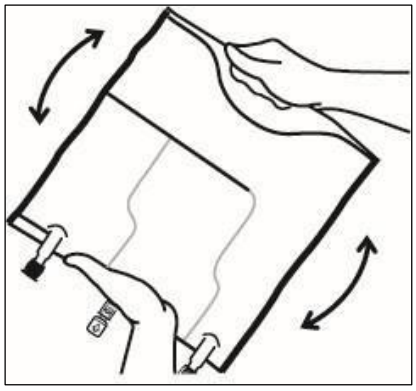




- Place the bag on a flat surface.

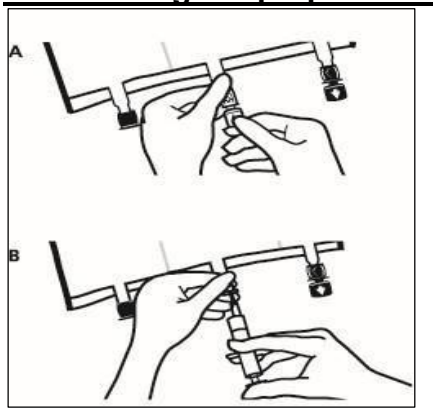
- Roll up the bag tightly from the handle side towards the ports, firstly with the right hand and then applying a constant pressure with the left hand until the vertical seals are broken. The vertical peel seals open due to the pressure of the fluid. The peel seals can also be opened before removing the overpouch.

Please note: The liquids mix easily although the horizontal seal remains closed.



- Mix the contents of the three chambers by inverting the bag three times until the components are thoroughly mixed.

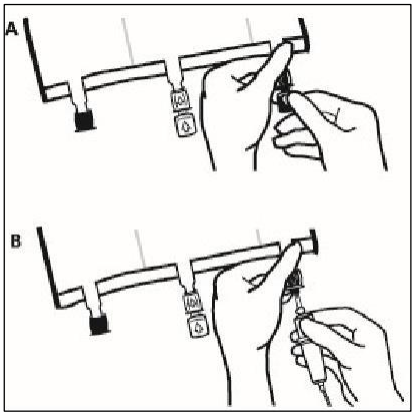
3. Finalising the preparation



- Place the bag on a flat surface again. Shortly before injecting the additives, break off the tamper-evident arrow flag from the white additive port (A).

Please note: The membrane in the additive port is sterile.

- Hold the base of the additive port. Insert the needle, inject the additives (with known compatibility) through the centre of the injection site (B).
- Mix thoroughly between each addition by inverting the bag three times. Use syringes with needles of 18 to 23 gauge and a length of max. 40 mm.



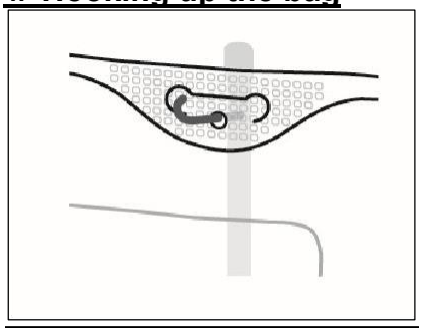
- Shortly before inserting the infusion set, break off the tamper evident arrow flag from the blue infusion port (A).

Please note: The membrane in the infusion port is sterile.

- Use a non-vented infusion set or close the air-inlet on a vented set.
- Hold the base of the infusion port.
- Push the spike through the infusion port. The spike should be fully inserted to secure it in place.

Please note: The inner part of the infusion port is sterile.

4. Hooking up the bag



- Hook the bag up by the hole below the handle.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

FRESENIUS KABI SOUTH AFRICA (PTY) LTD
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FDA/SD.255-020199

9. DATE OF FIRST AUTHORISATION OR RENEWAL

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10. DATE OF REVISION OF THE TEXT

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