

PRODUCT INFORMATION

NAME OF MEDICINE

KABIVEN® G19%

KABIVEN is a three chamber bag of amino acid solution with electrolytes, glucose solution and lipid emulsion for intravenous infusion.

The active ingredients are:

AMINO ACIDS 3.3%: alanine (CAS No.:56-41-7), arginine (CAS No.:74-79-3), aspartic acid (CAS No.:6899-03-2), glutamic acid (CAS No.:56-86-0), glycine (CAS No.:56-40-6), histidine (CAS No.:71-00-1), isoleucine (CAS No.:73-32-5), leucine (CAS No.:61-90-5), lysine hydrochloride (CAS No.:657-27-2), methionine (CAS No.:63-68-3), phenylalanine (CAS No.:63-91-2), proline (CAS No.:147-85-3), serine (CAS No.:56-45-1), threonine (CAS No.:72-19-5), tryptophan (CAS No.:73-22-3), tyrosine (CAS No.:60-18-4) and valine (CAS No.:72-18-4).

LIPIDS 3.9%: soya oil (CAS No.:8001-22-7).

GLUCOSE 9.7%: glucose monohydrate (CAS No.:5996-10-1)

ELECTROLYTES 0.7%: calcium chloride dihydrate (CAS No.:10035-04-8), magnesium sulfate heptahydrate (CAS No.:10034-99-8), potassium chloride (CAS No.:7447-40-7), sodium acetate trihydrate (CAS No.:6131-90-4) and sodium glycerophosphate (CAS No.:1334-74-3).

DESCRIPTION

Kabiven G19% consists of a three chamber bag and an overpouch. An oxygen absorber is placed between the inner bag and the overpouch. The inner bag is separated into three chambers by seals which can be separated for mixing. The individual chambers contain glucose, amino acid solutions, and fat emulsion, respectively. The glucose and amino acid solutions are clear solutions while the fat emulsion is white.

Each bag contains the following different volumes depending on the four pack sizes.

	2566 mL	2053 mL	1540 mL	1026 mL
Glucose (19%)	1316 mL	1053 mL	790 mL	526 mL
Amino acids and electrolytes (<i>Vamin 18 Novum</i>)	750 mL	600 mL	450 mL	300 mL
Triglycerides (<i>Intralipid 20%</i>)	500 mL	400 mL	300 mL	200 mL

This corresponds to the following compositions.

Active Ingredients (g)	2566 mL	2053 mL	1540 mL	1026 mL
Soya Oil (g)	100	80	60	40
Glucose monohydrate	275	220	165	110
<i>Corresponding to Glucose (anhydrous)</i>	250	200	150	100

Alanine	12.0	9.6	7.2	4.8
Arginine	8.5	6.8	5.1	3.4
Aspartic acid	2.6	2.0	1.5	1.0
Glutamic acid	4.2	3.4	2.5	1.7
Glycine	5.9	4.7	3.6	2.4
Histidine	5.1	4.1	3.1	2.0
Isoleucine	4.2	3.4	2.5	1.7
Leucine	5.9	4.7	3.6	2.4
Lysine hydrochloride	8.5	6.8	5.1	3.4
<i>Corresponding to Lysine</i>	6.8	5.4	4.1	2.7
Methionine	4.2	3.4	2.5	1.7
Phenylalanine	5.9	4.7	3.6	2.4
Proline	5.1	4.1	3.1	2.0
Serine	3.4	2.7	2.0	1.4
Threonine	4.2	3.4	2.5	1.7
Tryptophan	1.4	1.1	0.86	0.57
Tyrosine	0.17	0.14	0.10	0.07
Valine	5.5	4.4	3.3	2.2

Active Ingredients (g)	2566 mL	2053 mL	1540 mL	1026 mL
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Calcium chloride dihydrate	0.74	0.59	0.44	0.29
<i>Corresponding to calcium chloride</i>	0.56	0.44	0.33	0.22
Potassium chloride	4.5	3.6	2.7	1.8
Magnesium sulfate heptahydrate	2.5	2.0	1.5	0.99
<i>Corresponding to magnesium sulfate</i>	1.2	0.96	0.72	0.48
Sodium acetate trihydrate	6.1	4.9	3.7	2.5
<i>Corresponding to sodium acetate</i>	3.7	2.9	2.2	1.5
Sodium glycerophosphate	3.8	3.0	2.3	1.5

	2566 mL	2053 mL	1540 mL	1026 mL
• Amino acids	85	68	51	34
• Nitrogen	13.5	10.8	8.1	5.4
• Triglycerides	100	80	60	40
• Carbohydrates - glucose (dextrose) equivalent to glucose anhydrous	250	200	150	100
• Energy content				
– Total kJ	9660	7980	5880	3780
– Total kcal	2300	1900	1400	900
– Non protein kJ	8400	6720	5040	3360
– Non protein kcal	2000	1600	1200	800
• Electrolytes (mmol)				
– sodium	80	64	48	32
– potassium	60	48	36	24
– magnesium	10	8	6	4
– calcium	5	4	3	2
– phosphate	25	20	15	10

– sulfate	10	8	6	4
– chloride	116	93	70	46
– acetate	97	78	58	39

- Osmolality Approx 1230 mOsm/kg water
- Osmolarity Approx. 1060 mOsm/L
- pH Approx 5.6

Excipients:

Egg lecithin
Glycerol
Sodium hydroxide
Glacial acetic acid
Water for injections

PHARMACOLOGY

Fat emulsion

Intralipid, the fat emulsion used in Kabiven G19% provides essential and non-essential long chain fatty acids for energy metabolism and the structural integrity of cell membranes.

Intralipid in the recommended dosage does not cause haemodynamic changes. No clinically significant changes in pulmonary function have been described when Intralipid is used properly. The transient increase in liver enzymes seen in some patients on parenteral nutrition is reversible and disappears when parenteral nutrition is discontinued. Similar changes are also seen in parenteral nutrition without fat emulsions.

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.

Pharmacokinetics

Fat emulsion

Intralipid has biological properties similar to those of endogenous chylomicrons. Unlike chylomicrons, Intralipid does not contain cholesterol esters or apolipoproteins, while its phospholipid content is significantly higher.

Intralipid is eliminated from the circulation via a pathway similar to that of endogenous chylomicrons, at least early on in the catabolism. The exogenous fat particle is primarily hydrolysed in the circulation and taken up by the LDL receptors peripherally and by the liver. The elimination rate is determined by the composition of the fat particles, the nutritional status, the disease and the rate of infusion. In healthy volunteers, the maximum clearance rate of Intralipid after fasting overnight is equivalent to 3.8 ± 1.5 g of triglyceride per kg body weight per 24 hours.

Both the elimination and the oxidation rates are dependent on the patient's clinical condition; elimination is faster and utilisation is increased in postoperative patients and in trauma, while patients with renal failure and hypertriglyceridaemia show lower utilisation of exogenous fat emulsions.

Amino acids and electrolytes

The 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. This difference results only in a marginal change of kinetics and does not change the bioavailability of the amino acids.

Glucose

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

CLINICAL TRIALS

Three open, randomised, comparative clinical studies comparing the safety/tolerance of Kabiven G19% with other intravenous TPN solutions have been conducted. A total of 120 patients requiring total parenteral nutrition were evaluated. In two studies Kabiven G19% was administered postoperatively at 25 to 30 mL/kg body weight/day (equivalent to 23 - 27 kcal/kg bw) to patients undergoing general surgery. The third study was performed in patients in need of long term parenteral nutrition (at least 4 weeks). Most of the patients were on Home Parenteral Nutrition and required at least 5 days parenteral nutrition/week. All episodes of adverse events in subjects with serious adverse events as well as all episodes of serious adverse events were assessed as unrelated to the trial medication. The evaluation of clinical and laboratory safety parameters demonstrated that Kabiven G19% and the comparative formulations were equally safe and well tolerated.

INDICATIONS

Parenteral nutrition for adult patients when oral or enteral nutrition is impossible or insufficient or contraindicated.

CONTRAINDICATIONS

- Hypersensitivity to egg-, soya- or peanut protein or to any of the ingredients.
- Severe hyperlipaemia
- Severe liver insufficiency
- Severe blood coagulation disorders
- Inborn errors of amino acid metabolism
- Severe renal insufficiency without access to haemofiltration or dialysis
- Acute shock
- Hyperglycaemia, which requires more than 6 units insulin/h
- Pathologically elevated serum levels of any of the included electrolytes
- General contraindications to infusion therapy: acute pulmonary oedema, hyperhydration, decompensated cardiac insufficiency and hypotonic dehydration
- Haemophagocytotic syndrome
- Unstable conditions (e.g. severe post-traumatic conditions, uncompensated diabetes, acute myocardial infarction, metabolic acidosis, severe sepsis and hyperosmolar coma)

- Due to composition, Kabiven G19% is not suitable for use in new-borns or infants under 2 years of age.

PRECAUTIONS

The ability to eliminate fat should be monitored. It is recommended that this is done by measuring serum triglycerides after a fat-free period of 5-6 hours.

The serum concentration of triglycerides should not exceed 3 mmol/L during infusion.

Kabiven G19% is designed for adult patients. Children may have greater demands of energy and protein than listed under "Dosage and Administration".

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.

Special clinical monitoring is required at the beginning of any intravenous infusion. Should any abnormal sign occur, the infusion must be stopped. Since an increased risk of infection is associated with the use of any central vein, strict aseptic precautions should be taken to avoid any contamination during catheter insertion and manipulation.

Kabiven G19% should be given with caution in conditions of impaired lipid metabolism, such as in renal insufficiency, uncompensated diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism (with hypertriglyceridaemia) and sepsis. If Kabiven G19% is given to patients with these conditions, close monitoring of serum triglycerides is mandatory.

Serum glucose, electrolytes and osmolarity as well as fluid balance, acid-base status and liver enzyme tests (alkaline phosphatase, ALT, AST) should be monitored.

Blood cell count and coagulation should be monitored when fat is given for a longer period.

In patients with renal insufficiency, the phosphate and potassium intake should be carefully controlled to prevent hyperphosphataemia 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 metabolic acidosis, lactic acidosis, insufficient cellular oxygen supply and increased serum osmolarity.

Kabiven G19% should be given with caution to patients with a tendency towards electrolyte retention.

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

Intravenous infusion of amino acids is accompanied by increased urinary excretion of the trace elements copper and, in particular, zinc. This should be considered in the dosing of trace elements, especially during long-term intravenous nutrition.

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 together with close monitoring and appropriate adjustments of fluid, electrolytes, minerals and vitamins.

Kabiven G19% should not be given simultaneously with blood in the same infusion set due to the risk of pseudoagglutination.

In patients with hyperglycaemia, administration of exogenous insulin might be necessary.

Kabiven G19% contains soya oil and egg lecithin which may rarely cause allergic reactions. Cross allergic reaction has been observed between soya-bean and peanut.

Use in pregnancy (Category : Exempt)

Reproduction studies in animals have not been conducted with Kabiven G19%. No clinical data are currently available to assess the safety of Kabiven G19% in pregnancy. The prescriber should consider the benefit/risk relationship before administering Kabiven G19% to pregnant women.

Use in lactation

No clinical data are currently available on the use of Kabiven G19% in breast-feeding women. Following intravenous infusion, most of the active ingredients contained in Kabiven G19% are expected to be excreted into human milk, and the safety to the breast-feeding infant has not been adequately established. The prescriber should consider the benefit/risk relationship before administering Kabiven G19% to breast-feeding women.

Carcinogenicity, mutagenicity, impairment of fertility

No study has been conducted to examine the carcinogenic or mutagenic potential of Kabiven G19%. The effects of Kabiven G19% have not been investigated in animal studies.

Interaction with other drugs

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.

Other drugs, like insulin, may influence lipase activity but there is no evidence to suggest that this adversely affects therapeutic value.

Soya oil has a natural content of vitamin K₁. This may interfere with the therapeutic effect of coumarin derivatives, which should be closely monitored in patients treated with such drugs.

There are no clinical data to show that any of the above listed interactions are of definite clinical relevance.

Effects on ability to drive and use machines

Not applicable

Effect on laboratory tests

The fat content of Kabiven G19% may interfere with certain laboratory measurements (e.g. bilirubin, lactate dehydrogenase, oxygen saturation, and haemoglobin) if blood is sampled before fat has been adequately cleared from the bloodstream. Fat is cleared after a fat-free interval of 5-6 hours in most patients.

ADVERSE EFFECTS

Intralipid may cause a rise in body temperature (incidence < 3%) and, less frequently, shivering, chills and nausea/vomiting (incidence < 1%). Transient increases in liver enzymes during intravenous nutrition have also been reported.

As with all hypertonic solutions for infusion, thrombophlebitis may occur if peripheral veins are used.

Reports of other undesirable effects in conjunction with Intralipid infusions are extremely rare; less than one adverse event per million infusions. Hypersensitivity reactions (anaphylactic reaction, skin rash, urticaria), respiratory symptoms (e.g. tachypnoea) and hyper/hypotension have been described. Haemolysis, reticulocytosis, abdominal pain, headache, tiredness and priapism have been reported.

Fat overload syndrome

An impaired capacity to eliminate fat may lead to the fat overload syndrome. This may occur as a result of overdosage, but also at recommended rates of infusion, in association with a sudden change in the patient's clinical condition resulting in severe renal or hepatic impairment.

The fat overload syndrome is characterised by hyperlipaemia, fever, fat infiltration, hepatomegaly, splenomegaly, anaemia, leucopenia, thrombocytopenia, blood coagulation disorders and coma. These changes are invariably reversible on discontinuation of the fat infusion.

DOSAGE AND ADMINISTRATION

The ability to eliminate fat and metabolise glucose should govern the dosage and infusion rate. See "PRECAUTIONS".

Dosage

The dose should be individualised and the choice of bag size should be made with regard to the patient's clinical condition, body weight and nutritional requirements.

The nitrogen requirements for maintenance of body protein mass depend on the patient's condition (e.g. nutritional state and degree of catabolic stress). The requirements are 0.10-0.15 nitrogen/kg body weight (b.w.)/day in the normal nutritional state or in conditions with mild metabolic stress. In patients with moderate to high metabolic stress with or without malnutrition, the requirements are in the range of 0.15-0.30 g nitrogen/kg b.w./day (1.0-2.0 g amino acid/kg b.w./day). The corresponding commonly accepted requirements are 2.0-6.0 g for glucose and 1.0-2.0 g for fat.

The dose range of 0.10-0.20 g nitrogen/kg b.w./day (0.7-1.3 g amino acid/kg b.w./day) which covers the need of the majority of the patients. This corresponds to 19 mL – 38 mL Kabiven G19%/kg b.w./day. For a 70 kg patient this is equivalent to 1330 mL to 2660 mL Kabiven G19% per day.

The total energy requirement depends on the patient's clinical condition and is most often between 25-35 kcal/kg b.w./day. In obese patients the dose should be based on the estimated ideal weight.

Kabiven G19% is produced in four sizes intended with high, moderately increased, basal, or low nutritional requirements. To provide total parenteral nutrition, trace elements and vitamins should be given additionally.

Infusion rate:

The maximum infusion rate for glucose is 0.25 g/kg/h.

Amino acid dosage should not exceed 0.1 g/kg/h.

Fat dosage should not provide more than 0.15 g/kg/h.

The infusion rate should not exceed 2.6 mL/kg b.w./hour (corresponding to 0.25 g glucose, 0.09 g amino acid and 0.1 g fat/kg b.w.). The recommended infusion period is 12-24 hours.

Maximum daily dose

40 mL/kg b.w./day. This is equal to one bag (largest size) to a 64 kg-patient and will provide 1.3 g amino acids/kg b.w./day (0.21 g N/kg b.w./day), 31 kcal/kg b.w./day non-protein energy (3.9 g glucose/kg b.w./day and 1.6 g fat/kg b.w./day).

The maximum daily dose varies with the clinical condition of the patient and may even change from day to day.

Method and duration of administration

Intravenous infusion only into a central vein. Infusion may be continued for as long as required by the patient's clinical condition. Kabiven G19% should be used within 24 hours of preparation.

Instructions for use

Use in one person on one occasion only. Contains no antimicrobial preservative. Discard any unused mixture.

Do not use if package is damaged. Kabiven G19% should only be mixed and used if the solutions are clear and colourless or slightly yellow and if the emulsion is white and homogenous.

The contents of the three separate chambers have to be mixed before use. Mixing of the solutions by opening the seals between the chambers results in the ready-to-use solution. For that purpose pressure must be exerted on one solution chamber by rolling up the bag from one of the side edges until the middle seal opens. After separation of the seals the bag should be inverted on a number of occasions to ensure a homogenous mixture, (please also refer to section "SPECIAL HANDLING INSTRUCTIONS").

Compatibility

Additives

Only medicinal or nutritional solutions for which compatibility has been documented may be added to Kabiven G19%.

Additions should be made aseptically.

The standard recommendation is given in the following table.

<u>Additions</u>	<u>2566 mL</u>	<u>2053 mL</u>	<u>1540 mL</u>	<u>1026 mL</u>
Soluvit N	1 vial	1 vial	1 vial	0.5 vial
Vitalipid N Adult	10 mL	10 mL	10 mL	5 mL
	Up to a total of:			
Sodium	385 mmol	308 mmol	231 mmol	154 mmol
Potassium	385 mmol	308 mmol	231 mmol	154 mmol
Magnesium	13 mmol	10 mmol	8 mmol	5 mmol
Calcium	13 mmol	10 mmol	8 mmol	5 mmol
Phosphate	38 mmol	31 mmol	23 mmol	15 mmol

Any mixture remaining after infusion must be discarded.

Incompatibilities

Kabiven G19% may only be mixed with other medicinal products for which compatibility has been documented. See "DOSAGE AND ADMINISTRATION - Compatibility".

OVERDOSAGE

See "Fat overload syndrome" under "ADVERSE REACTIONS".

Nausea, vomiting and sweating have been observed during infusion of amino acids at rates exceeding the recommended maximum rate.

If symptoms of overdose occur, the infusion should be slowed down or discontinued. Additionally, overdose might cause fluid overload, electrolyte imbalances, hyperglycaemia, and hyperosmolality.

In some rare serious cases, haemodialysis, haemofiltration or haemo-diafiltration may be necessary.

PRESENTATION AND STORAGE CONDITIONS

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

After breaking the seals, chemical and physical in-use stability of the mixed three chamber bag has been demonstrated for 24 hours at 25°C.

Aseptic technique must be used to inject additives and the product must be used within 24 hours.

The container consists of a multichamber inner bag and an overpouch. The inner bag is separated into three chambers by seals. An oxygen absorber is placed between the inner bag and the overpouch.

The inner bag is made of a multilayer polymer film, Biofine.

The **Biofine** inner bag film consists of poly(propylene-co-ethylene), synthetic rubber poly[styrene-block-(butylene-co-ethylene)] (SEBS) and synthetic rubber poly(styrene-block-isoprene)(SIS). The infusion and additive ports are made of polypropylene and synthetic rubber poly[styrene-block-(butylene-co-ethylene)] (SEBS) equipped with synthetic polyisoprene (latex-free) stoppers. The blind port, which is only used during

manufacturing, is made of polypropylene equipped with a synthetic polyisoprene (latex-free) stopper.

Pack sizes:

Biofine bags

1 x 1026ml, 4 x 1026ml	AUST R 97889
1 x 1540ml, 4 x 1540ml	AUST R 97890
1 x 2053ml, 4 x 2053ml	AUST R 97891
1 x 2566ml, 3 x 2566ml	AUST R 97892

NAME AND ADDRESS OF THE SPONSOR

Fresenius Kabi Australia Pty Limited
Level 2, 2 Woodland Way
Mount Kuring-gai NSW 2080
Australia
Telephone: (02) 9391 5555

Fresenius Kabi New Zealand Limited
60 Pavilion Drive
Airport Oaks, Auckland 2022
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Freecall: 0800 144 892

POISON SCHEDULE

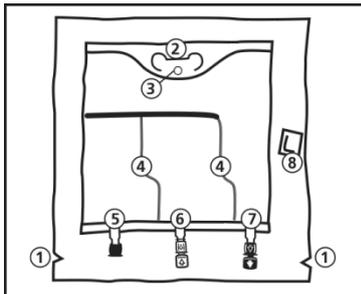
Australia: Not Scheduled
New Zealand: General Sale Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS: 20 July 2004

DATE OF MOST RECENT AMENDMENT: 11 April 2019

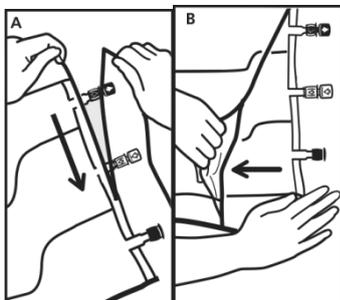
SPECIAL HANDLING INSTRUCTIONS

- (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).



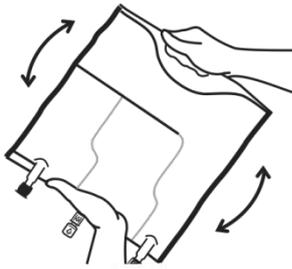
2. Mixing

- 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.

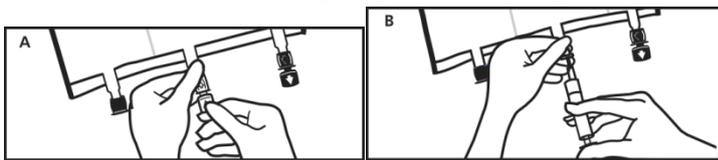


3. Finalising the preparation:

- 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 18-23 gauge and a length of max. 40 mm.

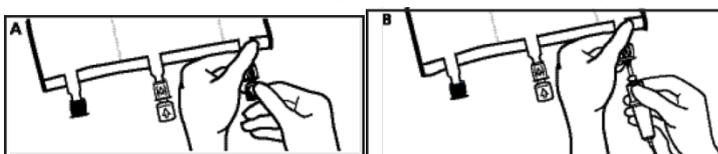


- Shortly before inserting the infusion set, break off the tamper evident arrow flag from the blue infusion port (A).

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. Hanging up the bag

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

