BFLUID® Infusion

Amino Acids and Glucose, Electrolytes and Vitamin B_1

DESCRIPTION

1. Composition

The upper chamber contains an amino acid solution with electrolytes and the lower chamber contains a glucose solution with electrolytes and vitamin B_1. This product contains the following ingredients.

(1) Upper chamber (amino acid solution with electrolytes)

Ingredients	150 mL	300 mL
L-Leucine	2.100 g	4.200 g
L-Isoleucine	1.200 g	2.400 g
L-Valine	1.200 g	2.400 g
L-Lysine Hydrochloride (L-Lysine equivalent)	1.965 g (1.573 g)	3.930 g (3.146 g)
L-Threonine	0.855 g	1.710 g
L-Tryptophan	0.300 g	0.600 g
L-Methionine	0.585 g	1.170 g
Acetylcysteine (L-Cysteine equivalent)	0.202 g (0.150 g)	0.404 g (0.300 g)
L-Phenylalanine	1.050 g	2.100 g
L-Tyrosine	0.075 g	0.150 g
L-Arginine	1.575 g	3.150 g
L-Histidine	0.750 g	1.500 g
L-Alanine	1.200 g	2.400 g
L-Proline	0.750 g	1.500 g
L-Serine	0.450 g	0.900 g
Glycine	0.885 g	1.770 g
L-Aspartic Acid	0.150 g	0.300 g
L-Glutamic Acid	0.150 g	0.300 g
Dibasic Potassium Phosphate	0.501 g*	1.002 g**
Dibasic Sodium Phosphate Hydrate	0.771 g	1.542 g
Sodium Citrate Hydrate	0.285 g	0.570 g
Sodium L-Lactate	1.145 g	2.290 g

* Contains 5.8 mEq of K^+ (38 mEq/L).

** Contains 11.5 mEq of K^+ (38 mEq/L).

Sodium Bisulfite 0.05 g/L is used as a stabilizer. Glacial Acetic Acid is used as a pH adjuster.

(2) Lower chamber (glucose solution with electrolytes and vitamin B_1)

Ingredients	350 mL	700 mL
Glucose	37.499 g	74.998 g
Potassium Chloride	0.317 g*	0.634 g**
Calcium Chloride Hydrate	0.184 g	0.368 g
Magnesium Sulfate Hydrate	0.308 g	0.616 g
Zinc Sulfate Hydrate	0.70 mg	1.40 mg
Thiamine Chloride Hydrochloride (Thiamine equivalent)	0.96 mg (0.75 mg)	1.92 mg (1.5 mg)

* Contains 4.3 mEq of K^+ (12 mEq/L).

** Contains 8.5 mEq of K^+ (12 mEq/L).

Hydrochloric Acid is used as a pH adjuster.

(3) After the two solutions are mixed

Ingredients	500 mL	1000 mL
Electrolytes		
Na^{+*}	17.5 mEq	35 mEq
K^{+}	10 mEq	20 mEq
Mg^{2+}	2.5 mEq	5 mEq
Ca^{2+}	2.5 mEq	5 mEq
Cl^{-*}	17.5 mEq	35 mEq
SO_4^{2-}	2.5 mEq	5 mEq
$Acetate^{-*}$	8 mEq	16 mEq
$L\text{-}Lactate^{-}$	10 mEq	20 mEq
$Citrate^{3-}$	3 mEq	6 mEq
P	5 mmol	10 mmol
Zn	2.5 μmol	5 μmol
Carbohydrate		
Glucose	37.50 g	75.00 g
Glucose concentration	7.5%	7.5%
Amino acids		
Total free amino acids	15.00 g	30.00 g
Total nitrogen	2.35 g	4.70 g
Essential/nonessential amino acids	1.44	1.44
Branched-chain amino acids	30% (w/w)	30% (w/w)
Vitamin		
Thiamine Chloride Hydrochloride (Thiamine equivalent)	0.96 mg (0.75 mg)	1.92 mg (1.5 mg)
Total calories	210 kcal	420 kcal
Nonprotein calories	150 kcal	300 kcal
Nonprotein calories/nitrogen	64	64

Zn concentrations are approximate values.
* Includes the amount derived from additives.

2. Product Description

Solutions in the upper and lower chambers are clear and colorless.

	pH		**Osmotic pressure ratio (relative to 0.9% saline solution)**
	Immediately after manufacture	**Specification**	
Upper chamber solution	Approx. 6.8	6.3–7.3	Approx. 4
Lower chamber solution	Approx. 4.0	3.5–4.5	Approx. 2.5
After mixing	Approx. 6.7	–	Approx. 3

INDICATIONS

Provision of amino acids, electrolytes, vitamin B_1, and water via a peripheral vein to patients with mild hypoproteinemia or malnutrition due to inadequate oral intake, and before and after gastrointestinal surgery.

DOSAGE AND ADMINISTRATION

The usual adult dosage is 500 mL per dose, infused via a peripheral vein. The usual infusion rate in adults is 500 mL administered over 120 minutes. The infusion rate should be reduced in the elderly and in critically ill patients. The dosage should be adjusted according to the patient's condition, body weight, and age. The maximum dosage is 2500 mL per day.

PRECAUTIONS

1. Careful Administration (BFLUID® Infusion should be administered with care in the following patients.)

(1) Patients with hepatic dysfunction
[Abnormalities in water and electrolyte metabolism may be exacerbated.]

(2) Patients with renal dysfunction
[Since these patients have impaired water and electrolyte metabolism, the solution should be administered with care.]

(3) Patients on dialysis or hemofiltration with serious renal disorder, azotemia, or oliguria
[The amounts of water and electrolytes may be excessive and urea and other amino acid metabolites may be retained.] (See (5) in section **2. Important Precautions.**)

(4) Patients with cardiovascular dysfunction
[An increase in the circulating blood volume may cause a burden on the heart, resulting in the patient's clinical condition to deteriorate.]

(5) Patients with acidosis
[The patient's clinical condition may deteriorate.]

(6) Patients with diabetes mellitus
[Impaired uptake of glucose into the tissues may result in hyperglycemia, which may cause the patient's clinical condition to deteriorate.]

(7) Patients with known hypersensitivity to drugs

2. Important Precautions

(1) BFLUID® Infusion contains 15 g of amino acids (2.35 g nitrogen) and 150 kcal (nonprotein calories) in 500 mL. However, daily caloric requirements cannot be met by administering this solution as the sole source of nutritional support. This solution should therefore be used only for short-term nutritional therapy.

(2) When used as a nutritional supplement in patients in whom oral intake is inadequate, the solution should be administered based on an overall assessment of the patient's nutritional requirements and oral intake.

(3) When this solution is used alone in postoperative patients, its use should be limited to 3–5 days and oral/enteral nutrition or other regimens should be instituted as soon as it is feasible to do so.

(4) BFLUID® Infusion contains 0.96 mg of thiamine chloride hydrochloride (vitamin B_1) as a vitamin source in 500 mL, and contains 1.92 mg of thiamine chloride hydrochloride (vitamin B_1) as a vitamin source in 1000 mL. Additional vitamin B_1 or other vitamins should be administered, depending on the patient's condition.

(5) The volume of water, electrolytes, or urea, etc. removed and accumulated in patients on dialysis or hemofiltration with serious renal disorder, azotemia, or oliguria varies depending on the dialysis method and patients' conditions. Initiation and continuation of administration should be determined after the patient's conditions are carefully checked based on assessment of blood biochemistry, acid-base equilibrium, and body-fluid balance, etc.

3. Adverse Reactions

Reported incidence rates are based on the results obtained for 50 patients who had undergone gastrointestinal surgery in a phase III clinical study. With regard to adverse events (clinically significant adverse reactions), a total of 8 patients (16.0%) experienced 11 adverse reactions, including vascular pain (3), phlebitis (4), and chest discomfort (1) in a total of 7 patients as subjective or objective manifestations and elevated serum AST (GOT) levels (1), elevated serum ALT (GPT) levels (1), and elevated serum ALP levels (1) in a total of 1 patient as abnormal changes in laboratory data. (These data were obtained at the time of drug approval in Japan, 2006.) Refer to the "CLINICAL STUDIES" section.

(1) Clinically significant adverse reactions

Shock (frequency unknown): Shock may occur. Patients should be closely monitored, and if any signs or symptoms such as decreased blood pressure, chest discomfort, or dyspnea occur, administration should be discontinued immediately and appropriate measures should be taken.
Note: Adverse reactions commonly associated with thiamine chloride hydrochloride injections.

(2) Other adverse reactions

If other adverse reactions are observed, take appropriate measures such as discontinuing administration.

Reactions	≥ 5%	0.1% to <5%	Frequency unknown
Hypersensitivity			[Rash etc.]
Gastrointestinal		[Nausea, vomiting]	
Cardiovascular		Chest discomfort	[Palpitations etc.]

Hepatic		Elevated AST (GOT), ALT (GPT), ALP, or [total Bilirubin Levels]	
Large dose and rapid administration			[Cerebral, pulmonary, and peripheral edema, hyperkalemia, water intoxication], [acidosis]
Other	Vascular pain, Phlebitis		[Chills, fever, sensation of warmth, headache]

4. Use in the Elderly

Since elderly patients often have reduced physiological function and associated hepatic, renal, or cardiac dysfunction, it is advisable to take measures such as reducing the dose by decreasing the infusion rate under careful supervision.

5. Use during Pregnancy, Delivery, or Lactation

(1) BFLUID® Infusion should be used in pregnant women and in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the potential risks associated with administration.
(The safety of this product in pregnant women has not been established.)

(2) It is advisable to avoid using this product in nursing mothers. If use of this product is judged to be essential, breast feeding should be discontinued during administration.
(The safety of this product in nursing mothers has not been established.)

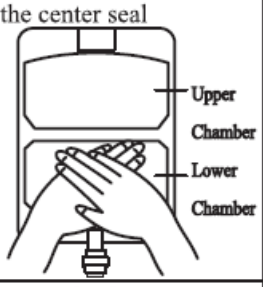
6. Pediatric Use

The safety of this product in children has not been established (no clinical experience).

7. Precautions Concerning Use

(1) Preparation: Open the outer wrap immediately before use, break the center seal between the two chambers and mix the two solutions thoroughly. The solution in one chamber should not be administered alone without mixing it with the solution in the other chamber.

Method of mixing two solutions (Never fail to mix two solutions).
Be sure to press the lower chamber to break the center seal between the two chambers.

To open the package	To break the center seal	To mix
		
Tear outer wrap at notch and remove solution container.	Press the lower chamber with both hands until the center seal breaks (admix other drugs, when needed, after mixing two solutions).	Press both chambers alternately to mix solutions thoroughly.

(2) Precautions at the time of preparation

1) Physicochemical changes in the solution, such as precipitation, may occur if this product is combined with the following drugs. The product should be carefully observed for such changes.
   a) Drugs that are stable under acidic or alkaline conditions

b) Drugs that are slightly soluble in water
c) Drugs that contain calcium salt or phosphate

2) Since the solution contains calcium salt, blood coagulation may occur if it is mixed with citrated blood.
3) After opening the outer wrap and mixing the two solutions, the mixed solution should be used promptly.

(3) Precautions before administration

1) Be sure to confirm that the center seal between the two chambers has been broken.
2) When administering BFLUID® Infusion, it is recommended that urine output be maintained at more than 500 mL per day or more than 20 mL per hr.
3) To minimize the risk of infection, perform all procedures under aseptic conditions (disinfection of patient's skin and devices).
4) Use the solution after warming it to near body temperature if it is to be used under cold environmental conditions.
5) After use, discard all unused solution.

(4) Precautions during administration

1) The usual adult dose is 500 mL administered over 120 min. The administration rate should be reduced in the elderly and in seriously ill patients.
2) If vascular pain occurs, use an alternate infusion site or discontinue administration.
3) Extravasation of the solution may result in skin necroses and ulceration. After confirming the clinical signs of extravasation (e.g., erythema, infiltration, or swelling) at the infusion site, immediately discontinue administration and institute appropriate treatment.
4) A light-resistant cover should be used or other appropriate measures should be taken to avoid photochemical decomposition of the vitamin B_1 in the solution, although such photochemical decomposition does not occur in a very short time.
When other vitamins are added, a light-resistant cover should also be used or other appropriate measures should be taken to avoid photochemical decomposition of vitamins.

CONTRAINDICATIONS (BFLUID® Infusion is contraindicated in the following patients.)

(1) Patients with hepatic coma or at risk of developing hepatic coma
[Due to impaired amino acid metabolism, the patient's clinical condition may deteriorate.]
(2) Patients with serious renal disorder or azotemia (for both, patient on dialysis or hemofiltration are excluded)
[The amounts of water and electrolytes may be excessive, causing the patient's clinical condition to deteriorate. Urea and other amino acid metabolites may be retained, which may cause the patient's clinical condition to deteriorate.]
(See (3) in section **1. Careful Administration** and (5) in section **2. Important Precautions.)**.
(3) Patients with oliguria (patients on dialysis or hemofiltration are excluded)
[The patient's clinical condition may deteriorate.] (See (5) in section **1. Careful Administration** and (5) in section **2. Important Precautions.)**
(4) Patients with congestive heart failure
[An increase in the circulating blood volume may cause a burden on the heart, resulting in the patient's clinical condition to deteriorate.]
(5) Patients with severe acidosis (hyperlactacidemia etc.)
[The patient's clinical condition may deteriorate.]
(6) Patients with hyperkalemia or Addison's disease
[The patient's clinical condition may deteriorate.]
(7) Patients with hyperphosphatemia or hypoparathyroidism
[The patient's clinical condition may deteriorate.]
(8) Patients with hypermagnesemia or hypothyroidism
[The patient's clinical condition may deteriorate.]
(9) Patients with hypercalcemia
[The patient's clinical condition may deteriorate.]
(10) Patients with reduced urine output due to obstructive uropathy
[Water and/or electrolyte overload may occur, causing the patient's clinical condition to deteriorate.]
(11) Patients with abnormal amino acid metabolism
[Since the infused amino acids are not adequately metabolized, the patient's clinical condition may deteriorate.]
(12) Patients with known hypersensitivity to thiamine chloride hydrochloride

PHARMACOKINETICS

(Reference data in rats)

BFLUID® Infusion containing ^{14}C-labeled glucose was administered intravenously to intact rats. The radioactivity was rapidly distributed throughout the body, with particularly high levels observed in the liver (which plays an active role in glucose metabolism) and in the brain (which utilizes a large amount of glucose). The main route of excretion of the administered radioactivity was in the expired air as $^{14}CO_2$, accounting for 62.8% of the administered dose up to 24 hr. Radioactivity was also excreted in the urine (4.9%). The glucose was utilized mainly as an energy source and expired in the breath.

CLINICAL STUDIES

A comparative clinical study of BFLUID® Infusion was conducted at 16 institutions in Japan. This study included a total of 110 patients who had undergone gastrointestinal surgery. The clinical effects were evaluated in 97 of the 110 patients (46 patients in the BFLUID® Infusion group and 51 patients in the control group).

Blood levels of vitamin B_1 were maintained in the BFLUID® Infusion group, in contrast to the decreased levels of vitamin B_1 observed in the control group. Levels of serum proteins (total protein, albumin, prealbumin, transferrin, and retinol-binding protein) showed similar trends in both groups. Safety was evaluated in 102 of the 110 patients (50 patients in the BFLUID® Infusion group and 52 patients in the control group). Adverse events were defined as findings related to signs and symptoms, abnormal changes in vital signs, abnormal changes in laboratory data, and metabolic acidosis. Adverse events for which a relationship to administration of the study drug could not be ruled out were defined as adverse reactions. For vital signs and laboratory data, adverse events were also defined as values outside the normal range (the standard range for healthy subjects at each facility) after the start of infusion in comparison with postoperative preinfusion values. In addition, if the Investigator or the Co-investigators noted any abnormal changes in outcome variables not specified in the protocol, the changes were handled as adverse events. A total of 17 (34.0%) of the 50 patients in the BFLUID® Infusion group experienced 32 adverse reactions, showing no statistically significant difference with the findings in the control group (17 of 52 subjects [32.7%], 36 adverse reactions).

Adverse events are also commonly observed after surgical procedures for gastrointestinal diseases, and their frequencies were comparable to the results for the control group. (Refer to the tables below.)

Vitamin B_1 deficiency was not observed in either the BFLUID® Infusion group or the control group during the 5-day infusion period.

Signs and symptoms

Vascular pain

		BFLUID® Infusion group (n=50)		Control group (n=52)	
	Grade	Freq.	Total No.	Freq.	Total No.
Pain at injection site	Mild[b)]	3	2	3	3
Discomfort in left upper extremity	Mild[b)]		1		0

Phlebitis

		BFLUID® Infusion group (n=50)		Control group (n=52)	
	Grade	Freq.	Total No.	Freq.	Total No.
Erythema at injection site	Mild[b)]	4*	2	4*	2
Swelling at injection site	Mild[b)]		3		3
	Moderate[b)]		1		0
Hemorrhage at injection site	Mild[b)]		1		0

Other

	Grade	BFLUID® Infusion group (n=50)	Control group (n=52)
Chest discomfort	Mild[b)]	1	0
Rash	Moderate[b)]	0	1

Abnormal laboratory values

Increase in serum AST (GOT) levels

Grade[a)]	Range (IU/L)	BFLUID® Infusion group (n=50)	Control group (n=52)
<1	<50	1	1
1	≥50, <100	0	3
2	≥100, <500	1**	1**

Increase in serum ALT (GPT) levels

Grade[a)]	Range (IU/L)	BFLUID® Infusion group (n=50)	Control group (n=52)
<1	<50	0	1
1	≥50, <100	0	3
2	≥100, <500	1**	2 1**

Increase in serum ALP levels

Grade[a)]	Range (IU/L)	BFLUID® Infusion group (n=50)	Control group (n=52)
<1	<1.25×N	0	1
1	≥1.25×N, <2.5×N	1 1**	1

N = upper limit of normal at the facility.

Increase in serum bilirubin levels

Grade[a)]	Range (mg/dL)	BFLUID® Infusion group (n=50)	Control group (n=52)
1	≥1.6, <3.0	1	1[c)]

Cholestasis

Grade	BFLUID® Infusion group (n=50)	Control group (n=52)
Mild (associated with elevated serum bilirubin levels of Grade 1) [c)]	0	1[c)]

Increase in blood urea nitrogen (BUN) levels

Grade[a)]	Range (mg/dL)	BFLUID® Infusion group (n=50)	Control group (n=52)
1	<25	2	0
2	≥25, <40	2	0

Decrease in serum creatinine levels

Grade	BFLUID® Infusion group (n=50)	Control group (n=52)
Mild [b] (0.90×N)	0	1

N = lower limit of normal at the facility (mg/dL).

Increase in serum glucose levels

Grade[a]	Range (mg/dL)	BFLUID® Infusion group (n=50)	Control group (n=52)
<1	<160	4	4
1	≥160, ≤200	1	0

Decrease in serum sodium levels

Grade[a]	Range (mEq/L)	BFLUID® Infusion group (n=50)	Control group (n=52)
<1	≥135	0	2
1	<135, ≥125	0	1

Decrease in serum chloride levels

Grade	Range (mEq/L)	BFLUID® Infusion group (n=50)	Control group (n=52)
Mild [b] (0.98×N)		0	1

N = lower limit of normal at the facility (mEq/L).

Increase in serum phosphorus levels

Grade		BFLUID® Infusion group (n=50)		Control group (n=52)	
		Freq.	Total No.	Freq.	Total No.
Mild [b]	1.02×N	1	5	0	2
	1.05×N	0		1	
	1.07×N	2		0	
	1.09×N	2		1	

N = upper limit of normal at the facility (mg/dL).

Decrease in serum zinc levels

Grade	BFLUID® Infusion group (n=50)	Control group (n=52)
Mild [b] (0.80×N)	1	0

N = lower limit of normal at the facility (μg/dL).

Summary

Grade	BFLUID® Infusion group (n=50)	Control group (n=52)
Total No. of adverse reactions	32	36
Total No. of patients experiencing adverse reactions (percentage)	17 (34.0%)	17 (32.7%)

[*] Some patients experienced multiple adverse reactions.

** Appropriate measures were taken for abnormal laboratory values.

a) The grades indicated for abnormal laboratory values are based on the "Standards for Classification of Serious Adverse Drug Reactions" (Ministry of Health, Labour and Welfare of Japan). The grades indicated for serum glucose levels are based on postprandial values.
b) For some items related to laboratory tests not specified in the standards above, the judgment of the Investigator or the Co-investigators was described together with the upper or lower limits of normal at the facility. Specifically, *mild*: no specific medical treatment was required, and the adverse event was easily tolerated by the subject; *moderate*: specific medical treatment was required; *severe*: discontinuation of administration of the investigational drug or specific medical treatment was required. The equations shown in parentheses indicate the cutoff value relative to the upper or lower limit of normal at the facility. The judgment of the Investigator or the Co-investigators concerning signs and symptoms was also described as specified above.
c) Cholestasis was determined as "mild" based on elevated serum bilirubin levels (Grade 1). Cholestasis and elevated serum bilirubin were observed in the same patient.
With special regard to the deviations of laboratory values shown in the tables above, all deviations cannot be judged to be "medically significant adverse reactions" because postoperative fluctuations in laboratory values were not taken into consideration. Therefore, an "abnormal value for which treatment was required" was defined as a "medically significant adverse reaction". A total of 8 (16.0%) of the 50 patients in the BFLUID® Infusion group experienced 11 medically significant adverse reactions, showing no statistically significant difference with the findings in the control group (8 of 52 patients [15.4%], 10 adverse reactions). (See the table below.)

Adverse reaction	Frequency	
	BFLUID® Infusion group (n=50)	**Control group (n=52)**
Vascular pain	3	3
Phlebitis	4	4
Chest discomfort	1	0
Rash	0	1
Increase in serum AST (GOT) levels	1	1
Increase in serum ALT (GPT) levels	1	1
Increase in serum ALP levels	1	0
Total No. of adverse reactions	11	10
Total No. of patients experiencing adverse reactions (percentage)	8 (16.0%)	8 (15.4%)

PHARMACOLOGY

BFLUID® Infusion was administered to intact rats and dogs and laparotomized vitamin B_1-starved rats, and its effects in the provision of vitamin B_1 and electrolytes and its nutritional effects were compared against those of AMINOFLUID® Infusion. In intact rats and dogs, blood levels of vitamin B_1 remained at preadministration levels in the BFLUID® Infusion group. In laparotomized vitamin B_1-starved rats, recovery of vitamin B_1 levels to the normal range was observed after BFLUID® Infusion. Therefore, it was concluded that BFLUID® Infusion is useful for the provision of vitamin B_1. BFLUID® Infusion and AMINOFLUID® Infusion were found to be comparable in terms of the provision of electrolytes and nutrition.

PRECAUTIONS FOR HANDLING

1. An oxygen absorbent is enclosed between the bag and the outer wrap to maintain stability of the product. Do not remove the outer wrap until immediately before use.
2. A crystalline precipitate may form in the upper chamber solution (amino acid solution with electrolytes) due to changes in environmental temperature. Shake the solution at a temperature of 15°C–25°C to dissolve all precipitate before use.
3. Do not use the solution if the outer wrap covering the product has been damaged, the solution is discolored, or a precipitate that cannot be dissolved by shaking has formed.
4. If the two solutions contained in the chambers have already been mixed together for any reason or if the center seal between the two chambers appears white in color (the seal appears white if it is not intact), do not use the product.
5. Puncture the rubber stopper vertically with a needle in the marked circle. If the stopper is not pierced vertically, the needle may pass through the neck of the container, resulting in leakage of the contents.

6. Soft bag products may not be infused in tandem using a connection tube.
7. If droplets of water are noted inside the outer wrap or if the solution is cloudy, do not use the solution.
8. The volume markings on the container may not be accurate. Use them only as a rough guide.

STORAGE
Store below 30ºC, protected from light.

EXPIRATION DATE
24 months from the date of manufacture (as indicated on the container)

PACKAGING

Soft Double Bag @ 500 mL	REG NO: DKL1618708449A1
Soft Double Bag @ 1000 mL	REG NO: DKL1618708449A1

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Otsuka
Manufactured by:
PT. Otsuka Indonesia
Jl. Sumber Waras No. 25
Lawang, Malang 65216, Indonesia