Approved: December 2019

- Total Amino Acid Infusion Solution for Renal Failure -

Neoamiyu®

Designated drug, prescription drug*

Storage: Store below 30°C.
Expiration date: Indicated on the package and plastic bag.

* Caution: Use only as directed by a physician.

D401102

CONTRAINDICATIONS (Neoamiyu is contraindicated in the following patients.)

1. Patients with hepatic coma or possible hepatic coma [Imbalance of amino acids may be promoted with the use of the drug, resulting in the development or aggravation of hepatic coma.]
2. Patients with hyperammonaemia [Hyperammonaemia may aggravate due to nitrogen overload.]
3. Patients with congenital amino acid metabolism abnormality [The condition may aggravate due to failure of the metabolism of amino acid administered.]

DESCRIPTION

1. Composition

Neoamiyu contains the following ingredients per 200 mL.

Active Ingredients	Content per 200 mL bag
L-isoleucine	1.500 g
L-leucine	2.000 g
L-lysine acetate	1.400 g
L-methionine	1.000 g
L-phenylalanine	1.000 g
L-threonine	0.500 g
L-tryptophan	0.500 g
L-valine	1.500 g
L-alanine	0.600 g
L-arginine	0.600 g
L-aspartic acid	0.050 g
L-glutamic acid	0.050 g
L-histidine	0.500 g
L-proline	0.400 g
L-serine	0.200 g
L-tyrosine	0.100 g
Glycine	0.300 g
Amino acids total	12.200 g
Total concentration of amino acids	6.100 w/v%

Inactive Ingredients	Content per 200 mL bag
L-cysteine	0.050 g
Sodium hydrogen sulfite	0.050 g
Glacial acetic acid (pH regulator)	q.s.

Total nitrogen: 8.1 mg/mL
Total concentration of free amino acid: 5.90 w/v%
Essential amino acid/nonessential amino acid: 3.21
Electrolytes
Na^+: *ca.* 2 mEq/L
CH_3COO^-: *ca.* 47 mEq/L

2. Product description

Neoamiyu is a clear and colorless aqueous solution for infusion.

pH	Osmotic pressure ratio
6.6 - 7.6	*ca.* 2

3. Plastic bag

The specification of the plastic bag used for this product is as follows:

Specification	Reserve capacity of the plastic bag
200 mL plastic bag	*ca.* 250 mL

(When the solution is poured from a height of 45 cm)

INDICATIONS

Neoamiyu is indicated for the provision of amino acids in the following instances in patients with acute or chronic renal failure: hypoproteinemia, malnutrition, and before and after surgery.

DOSAGE AND ADMINISTRATION

1. Chronic Renal Failure

(1) When administered via a peripheral intravenous line in adults, Neoamiyu should be injected slowly at 200 mL once daily in patients with chronic renal failure. The usual intravenous infusion rate is 120 to 180 min. per 200 mL, and a slower rate is recommended for children, elderly patients, and patients with a serious condition. The dose may be adjusted according to the patient's age, condition , and body weight. In patients on dialysis, Neoamiyu should be injected into the venous side of the dialysis circuit from 90 to 60 minutes before completion of dialysis.
Regarding calories, more than 1500 kcal per day is recommended to be provided for the efficiency of amino acid utilization.

(2) When administered via total parenteral nutrition in adults, Neoamiyu should be injected in the central vein by intravenous drip at 400 mL once daily. The dose may be adjusted according to the patient's age, condition, and body weight. More than 500 kcal of nonprotein calories should be administered per 1.6 g of nitrogen (200 mL of this product) for the efficiency of amino acid utilization.

2. Acute Renal Failure

In adults, Neoamiyu should be administered via total parenteral nutrition in the central vein by intravenous drip at 400 mL once daily. The dose may be adjusted according to the patient's age, condition, and body weight. More than 500 kcal of nonprotein calories should be administered per 1.6 g of nitrogen (200 mL of this product) for the efficiency of amino acid utilization.

PRECAUTIONS

1. Careful Administration (Neoamiyu should be administered with care in the following patients.)

(1) Patients with impaired cardiovascular function [The use of the product is associated with increased amount of blood circulation, which may lead to overload of the heart and resultant aggravation of the patient's condition.]

(2) Patients with impaired hepatic function or gastrointestinal hemorrhage [Excessive accumulation of amino acids or hyperammonemia may develop with the use of the product.]

(3) Patients with marked electrolyte abnormality or abnormal acid-base balance [The patient's condition may aggravate with the use of the product.]

2. Important Precautions

(1) Neoamiyu should be used in patients who need parenteral nutrition due to inability or insufficience of oral food intake.

(2) It has been reported that the use of essential amino acid products for renal failure may be associated with hyperammonemia or loss of consciousness if these products are used as the only source of nitrogen. Therefore, the use of this product should be discontinued immediately if poor response to voice or other abnormalities such as decreased spontaneous speech and activities are noted during treatment.

3. Adverse Reactions

In clinical studies of Neoamiyu, 15 adverse reactions (4.7%) were reported in 10 (3.1%) of 318 patients. At the time of approval of the drug, main adverse reactions included nausea･queasy (1.9%), vomiting (0.6%), headache (0.6%), and metabolic acidosis (0.6%). Abnormal laboratory changes included decreased bicarbonate ion level 3 events (0.9%), increased AST (GOT) 1 event (0.3%), and increased blood ammonia level 1 event (0.3%). (As of the end of approval)

In post-marketing surveillance, adverse reactions (including abnormal laboratory changes) were reported in 98 (3.34%) of 2,936 patients. Main adverse reactions included increased blood urea nitrogen 23 events (0.78%), increased AST (GOT) 20 events (0.68%), increased ALT (GPT) 17 events (0.58%), hepatic disorder 13 events (0.44%), nausea 11 events (0.37%), increased blood creatinine level 8 events (0.27%), hyperammonemia 7 events (0.24%), metabolic acidosis 6 events (0.20%), vomiting 4 events (0.14%), and anorexia 4 events (0.14%).(As of the end of the re-examination)

Other adverse reactions

Appropriate measures should be instituted, such as discontinuation of treatment, if any of the following adverse reactions are observed.

	0.1 to <5%	<0.1%	Incidence unknown
Hypersensitivity		Pruritus, redness	Generalized urticaria
Gastrointestinal	Nausea, vomiting, anorexia		
Hepatic	Hepatic disorder		
Renal	Increased blood creatinine level, increased blood urea nitrogen		
Cardiovascular		Chest discomfort	Palpitations
Large dose and rapid administration			Acidosis
Other	Metabolic acidosis, hyperammonemia, decreased bicarbonate ion level	Fever, headache, nasal congestion, nasal discharge	Chills, hot feeling, burning sensation in the head, vascular pain

4. Use in the Elderly

Since the elderly have a physiological hypofunction in general,Neoamiyu should be carefully administered,such as reduceing the dose.

5. Use during Pregnancy, Delivery or Lactation

(1) Neoamiyu should be used in pregnant women or women having possibilities of being pregnant only if the expected therapeutic benefit is evaluated to outweigh the possible risks. [The safety of this product in pregnant women has not been established.]

(2) Use of Neoamiyu in nursing mothers is not recommended. If use of Neoamiyu is judged to be essential, breast feeding must be discontinued during treatment. [The safety of this product in nursing mothers has not been established.]

6. Pediatric Use

(1) The safety of Neoamiyu in children has not been established.(No sufficient clinical data has been available in this population.)

(2) Infants, especially low birth weight babies and neonates, have immature amino acid metabolism. Caution should be exercised if Neoamiyu is used in such patients, by monitoring the patient's clinical condition and laboratory results, as well as administrating the product at a slower rate and a reduced dose.

7. Precautions Concerning Use

(1) Before administration:

1) If any crystalline substances are present in the solution, these substances should be dissolved at a temperature from 50 to 60°C followed by cooling the solution down to around body temperature before infusion.

2) Do not use the solution if it is cloudy or contains particles.

3) The solution should be immediately used after opening the package, and any residual solution should be discarded.

(2) During administration:

1) In patients with chronic renal failure who are not on dialysis, the amount of protein contained in diet prior to treatment should be reduced by 5 to 10 g per 200 mL of dose of the product to be administered.

2) Neoamiyu contains sodium and acetic acid at *ca.* 2 mEq/L and *ca.* 47 mEq/L, respectively. If the product is administered in large dose or in combination with the electrolyte solution, the paitent's electrolyte balance should be monitored during treatment.

(3) Dosing rate:

Neoamiyu should be injected slowly into a vein.

CLINICAL STUDIES

1. Comparative trial

An active-controlled study of Neoamiyu versus AMIYU, an essential amino acid preparation for infusion for renal failure, was performed in patients with chronic renal failure who were on dialysis.

As shown in the table below, the efficacy and usefulness of Neoamiyu were demonstrated in the study.

	Efficacy rate (defined as effective or higher)	Usefullness rate (defined as useful or higher)
Neoamiyu (66 patients)	78.8% (52/66)	78.8% (22/29)
AMIYU (72 patients)	68.1% (49/72)	66.7% (48/72)

2. General Clinical Studies

(1) Administered via a peripheral intravenous line:

1)The efficacy and usefulness of Neoamiyu administered in 56 patients on dialysis were as follows:

	Efficacy rate (defined as effective or higher)	Usefullness rate (defined as useful or higher)
200 mL (29 patients)	75.9% (22/29)	75.9% (22/29)
300 mL (27 patients)	70.4% (19/27)	70.4% (19/27)

2)The efficacy and usefulness of Neoamiyu administered in 23 non-dialysis patients were as follows:

	Efficacy rate (defined as effective or higher)	Usefullness rate (defined as useful or higher)
Non-dialysis (23 patients)	73.9% (17/23)	73.9% (17/23)

(2) Administered in the central vein:

The efficacy and usefulness of Neoamiyu administered in 58 patients with chronic renal failure and 11 with acute renal failure were as follows:

	Efficacy rate (defined as effective or higher)	Usefullness rate (defined as useful or higher)
Chronic (58 patients)	86.2% (50/58)	91.4% (53/58)
Acute (11 patients)	100.0% (11/11)	100.0% (11/11)

PHARMACOLOGY

1. Neoamiyu was administered intraperitoneally in a rat model of chronic renal failure on a low-protein diet for 12 weeks. Improvement of nutrition was observed while maintaining the renal function in these rats.
2. The administration of Neoamiyu in the central vein of acute and chronic renal failure rats was not found with increased plasma ammonia level, which has been reported with the use of essential amino acid products. In addition, changes in plasma free amino acid level were almost within the normal range.
3. The reduction of plasma protein level was suppressed by treatment with Neoamiyu, when administered in the central vein of chronic renal failure rats on peritoneal dialysis.
4. The administration of Neoamiyu in the central vein of rats with chronic renal failure increased uptake of ^{15}N-labeled leucine into the plasma and muscular protein, while decreasing urinary 3-methylhistidine excretion. (Data on file)
5. Neoamiyu infused via the central vein in dogs with chronic renal failure improved nitrogen balance while maintaining low plasma urea nitrogen level. In addition, no adverse events such as nausea and vomiting, which have been reported with the use of essential amino acid products, were observed in these dogs.

PRECAUTIONS FOR HANDLING

1. Do not use the product if any discoloration or leakage of the solution is noted, or the outer bag is wet.
2. Do not open the outer bag until use to prevent discoloration of the solution (a deoxidizer is included in the product package to ensure the stability of the product).
3. Care should be exercised not to break the outer bag, which can cause discoloration of the solution.
4. Neoamiyu can be injected without using an air vent needle.
5. Do not use the product if the seal covering the rubber plug of the plastic bag is not in place.
6. A needle should be vertically inserted at the needle insertion (concave) portion of the rubber plug. If the needle is obliquely inserted, the drug solution may be contaminated with a broken piece of rubber plug or outlet inner wall, or the needle may penetrate through the plastic bag, resulting in leakage of the solution. In addition, a needle should not be inserted repeatedly at the same site.
7. The scale printed on the plastic bag should be used only as a guide.
8. Neoamiyu cannot be administered by the tandem system using a connecting U-shaped tube. If two plastic bags of this product are used at the same time or sequentially, use a Y-shaped transfusion set.

PACKAGING

200 mL plastic bags: Packages of 30 bags

Exported by:
EA Pharma Co., Ltd.
1-1, Irifune 2-chome, Chuo-ku, Tokyo, Japan

Manufactured by:
AY PHARMACEUTICALS CO., LTD.
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