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* Revised: December 2009

Standard Commodity Classification No. of Japan:
873253

Combined amino acid preparation for pediatric total parenteral nutrition

Pleamin-P Injection

Approval No.	(7AM) 524
Date of listing in the NHI reimbursement price	July 2004
Date of initial marketing in Japan	July 2004
Date of latest reexamination	June 2007

Storage : Store at room temperature.
(See Precautions for Handling.)
Expiration date: Do not use after the expiration date indicated on the outer package.
Caution : See the section "PRECAUTIONS FOR HANDLING"
Prescription drug:
(Caution – Use only pursuant to the prescription issued of physician, etc.)

CONTRAINDICATIONS (Pleamin-P is contraindicated in the following patients.)

(1) Patients with confirmed hepatic coma or at increased risk of developing hepatic coma [The product may aggravate or induce hepatic coma.]
(2) Patients with severe renal dysfunction or azotemia [In patients with severe renal failure, urinary excretion of nitrogen compounds generated as a result of protein/amino acid metabolism (e.g., urea) may be inhibited, potentially inducing azotemia.]
(3) Patients with aberrant amino acid metabolism [Imbalance of amino acids in the circulation may lead to any adverse effect.]

DESCRIPTION

** * **1. Composition**

Pleamin-P Injection contains the following ingredients per bag:

		200 mL
L-Isoleucine		1,600 mg
L-Leucine		3,200 mg
L-Lysine acetate		1,354 mg
L-Methionine		300 mg
L-Phenylalanine		500 mg
L-Threonine		480 mg
L-Tryptophan		240 mg
L-Valine		1,200 mg
L-Arginine		2,000 mg
L-Histidine		500 mg
Glycine		400 mg
L-Alanine		1,040 mg
L-Glutamic acid		160 mg
L-Aspartic acid		160 mg
L-Proline		1,200 mg
L-Serine		800 mg
L-Tyrosine		120 mg
L-Cysteine		300 mg
Taurine		40 mg
Inactive ingredients	Sodium hydrogen sulfite	60 mg
	pH adjuster	

Total free amino acid content : 7,600 mg/100 mL
Essential amino acid content (E) : 4,240 mg/100 mL
Non-essential amino acid content (N) : 3,360 mg/100 mL
E/N : 1.26

Total nitrogen content : 1,175 mg/100 mL
Branched-chain amino acid content (%) : 39%

Electrolyte level:
Na^+ : approximately 3 mEq/L
Acetate level : approximately 80 mEq/L

2. Product Description

Pleamin-P Injection occurs as a clear colorless aqueous injection supplied in a polyethylene bag (flexible container). It has pH between 6.5 and 7.5 and osmotic pressure ratio between 2.3 and 2.8

INDICATIONS

Pleamin-P Injection is indicated for amino acid supplementation in neonates (weighing ≥ 2 kg at birth, in principle), infants, and children aged 1-3 years in the following conditions: hypoproteinemia, malnutrition, and before and after operation.

DOSAGE AND ADMINISTRATION

The usual recommended dosage of Pleamin-P Injection for total parenteral nutrition is 23-36 mL (equivalent to 1.75-2.75 g amino acids) per kg per day for neonates weighing ≥ 2 kg at birth and infants; 20-33 mL (equivalent to 1.50-2.50 g amino acids) per kg per day for children aged 1-3 years. All doses should be administered by continuous intravenous infusion.
The dosage may be modified according to patients' symptoms and laboratory data.

PRECAUTIONS

1. Careful Administration: Pleamin-P Injection should be administered with care to the following patients:

(1) Patients with severe acidosis [The product may aggravate the acidosis.]
(2) Patients with congestive heart failure [The product may aggravate the heart failure.]
(3) Patients with hyponatremia [The product may aggravate the hyponatremia because it contains sodium only at a very low level.]

2. Adverse Drug Reactions

Of 168 patients treated with this product during its development, 3 infants (1.8%) were reported to develop any adverse reaction. The adverse reactions reported were increased AST (GOT) (n=2; 1.2%), increased ALT (GPT) (n=3; 1.8%), and increased ALP (n=1; 0.6%) (data obtained by the time of marketing approval).
In postmarketing Drug Use Results Surveys and Special Surveillance, adverse drug reactions were reported in 27 of 994 patients treated with the product (2.7%). The most common adverse reactions were increased AST (GOT) (n=9; 0.9%), increased ALT (GPT) (n=6; 0.6%), hepatic function disorder (n=6; 0.6%), and increased direct bilirubin (n=4; 0.4%) (data obtained by the time of re-examination).
If any adverse reaction occurs, appropriate measures must be taken, such as discontinuing the product use.

	0.1-<5%	Incidence unknown
Hypersensitivity		(e.g., rash)
Gastrointestinal		(e.g., nausea and vomiting)
Cardiovascular		(e.g., chest discomfort and palpitations)

Hepatic	Jaundice (increased bilirubin) and increased AST (GOT), ALT (GPT), and/or ALP.	
Massive/rapid infusion		(Acidosis after massive and/or rapid infusion).
Miscellaneous		(Chills, pyrexia, and headache)

The adverse reactions listed as those having unknown incidence (in parentheses) are based on data on combined amino acid preparations for the 15th drug re-evaluation in 1979.

3. Use in Pediatrics

Safety of Pleamin-P Injection in infants weighing < 2 kg at birth has not been established (insufficient clinical data).

The product can be administered to infants weighing < 2 kg at birth only if the expected therapeutic benefits outweigh the possible risks associated with treatment and only with care using a dosage modified according to their symptoms and laboratory data.

Of the 994 patients treated with the product during postmarketing phase (enrolled in postmarketing drug use or special investigations), 293 were infants weighing < 2 kg at birth and 10 of them (3.4%) were reported to develop any adverse reaction. The most common adverse reactions reported in this population were increased AST (GOT) (n=4; 1.4%), increased direct bilirubin (n=3; 1.0%), and increased ALT (GPT) (n=2; 0.7%).

4. Precautions for Use

(1) **Precautions before dosing:**
1) Before dosing, adequate measures should be taken to prevent infection (such as disinfecting the skin at the puncture site and sterilizing the dosing equipment).
2) In a cold environment, warm the product to body temperature before use.
3) Use immediately after inserting a needle into the bag. Never use the solution from a previously opened bag.

(2) **Precautions during dosing:** Since the product contains acetate at about 80 mEq/L, pay attention to the electrolyte homeostasis when infusing a massive volume of the product or infusing it in combination with an electrolyte fluid.

(3) **Precautions about infusion rate:** Slowly infuse the product intravenously.

(4) **Precautions common to total parenteral nutrition:** During total parenteral nutrition, particularly in its early phase, AST (GOT) and ALT (GPT) may show small transient elevations. In such cases, the patient's symptoms and laboratory data should be monitored carefully, and reducing the dose (or energy intake) until acclimatization should be considered.

PHARMACOKINETICS[1)]

(Referential data)

◊ Absorption and excretion
When male SD rats, 3 weeks old, were given a 90-min continuous intravenous infusion of this product with the 19 amino acids labeled with ^{14}C, the blood radioactivity level reached a peak at 2 hours after the end of the infusion and gradually decreased thereafter. During the first 5 hours after the end of the infusion, the highest level of radioactivity was observed in the liver, followed by the pancreas, the kidneys, and the brain.
By 7 days after administration, about 46%, 5%, and 6% of the radioactivity administered were recovered in expired gas, urine, and feces, respectively.

CLINICAL STUDIES[2-4)]

In a phase 2 study, Pleamin-P Injection was judged as "effective" or better in 30 out of 31 patients treated (97%) in improving their nutrition, weight gain, nitrogen balance, plasma protein level, and plasma aminograms. In phase 3 controlled and open-label studies, the product was judged as "effective" or better in 90 out of 97 patients treated (93%).

PHARMACOLOGY[5)]

◊ Plasma level of free amino acids
When Pleamin-P Injection was used for total parenteral nutrition of rats in pre-weaning, weaning and post-weaning periods, the plasma level of free amino acids was more likely to be within or near the normal range in younger rats.

◊ Nutritional effect
When Pleamin-P Injection was used for total parenteral nutrition of rats, pre-weaning and weaning rats gained weight in a dose-dependent manner, and weaning rats achieved positive nitrogen balance.

PRECAUTIONS FOR HANDLING

1) Do not open the outer bag of this product until immediately before its use.
2) Do not use this product if there is any water drop inside its outer bag.
3) Do not use this product if the indicator (pink) tablet has turned into blue-purple or blue.
4) Do not expose the product under direct sunlight so as to keep the indicator's function normal.
5) Crystals may form if the product is placed in a cold environment or if there is a sudden change in temperature. In such cases, shake the bag to dissolve the crystals before use. Do not use the product if the crystals cannot be dissolved after shaking.
6) Do not use the product if the solution has leaked out of the bag or become turbid.
7) Do not use the product if the overseal (applied to prevent soiling of the rubber stopper) should have been peeled off.
8) A ventilation needle is not needed.
9) In puncturing a rubber stopper provided on this product, keep the needle perpendicular to the surface of the stopper and slowly push it forward. If the needle is slanted, it may cause contamination of the solution with (core) rubber pieces or may damage the injection port, thereby inducing leakage of the solution.
10) Use the graduations on the infusion bag only to make a rough estimate of the volume administered.

PACKAGING

Flexible containers (200 mL): Boxes of 10

The flexible container is a polyethylene bag developed specifically for intravenous fluids by Fuso Pharmaceutical Industries, Ltd.

REFERENCES

1) Kuroda S, et al.: *Jpn Pharmacol Ther*. 19, 3161, 1991.
2) Okada T, et al.: *Jpn J Parenter Enteral Nutr*. 14, 537, 1992.
3) Okada T, et al.: *Jpn J Parenter Enteral Nutr*. 14, 561, 1992.
4) Okada T, et al.: *Jpn J Parenter Enteral Nutr*. 14, 595, 1992.
5) Tanaka S, et al.: *Jpn Pharmacol Ther*. 19, 3125, 1991.

REQUEST FOR LITERATURE SHOULD BE MADE TO:

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