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EA Pharma Co., Ltd.

Standard Commodity Classification No. of Japan
873253

- Amino Acids Infusion for Hepatic Failure -

MORIHEPAMIN®

Prescription drug*

*** Caution: Use only as directed by a physician, etc.**
Read package insert carefully before use. If you need further information, please contact your doctor.
Inform your doctor any side effects occur when using drug.

Approval No.	22000AMX00198
Date of listing in the NHI reimbursement price	June 2008
Date of initial marketing in Japan	January 1993
Date of latest re-evaluation	March 1998

COMPOSITION - DESCRIPTION

1. Composition

MORIHEPAMIN contains the following ingredients:

Active ingredients	Content per 200mL bag	Content per 500mL bag
L-Isoleucine	1.840 g	4.600 g
L-Leucine	1.890 g	4.725 g
L-Lysine Acetate	0.790 g	1.975 g
L-Methionine	0.088 g	0.220 g
L-Phenylalanine	0.060 g	0.150 g
L-Threonine	0.428 g	1.070 g
L-Tryptophan	0.140 g	0.350 g
L-Valine	1.780 g	4.450 g
L-Alanine	1.680 g	4.200 g
L-Arginine	3.074 g	7.685 g
L-Aspartic acid	0.040 g	0.100 g
L-Histidine	0.620 g	1.550 g
L-Proline	1.060 g	2.650 g
L-Serine	0.520 g	1.300 g
L-Tyrosine	0.080 g	0.200 g
Glycine	1.080 g	2.700 g
Total amino acids	15.170 g	37.925 g
Total concentration of amino acids	7.585 w/v%	

Inactive ingredients	Content per 200mL bag	Content per 500mL bag
L-Cysteine	0.050 g	0.125 g
Sodium Bisulfite	0.050 g	0.125 g
Glacial Acetic Acid (pH regulator)	q.s.	q.s.

Concentration of total nitrogen: 13.18 mg/mL
Concentration of free amino acids: 7.470 w/v%
Concentration of branched-chain amino acids: 2.755 w/v%
Fischer's ratio†: 54.13
† Branched-chain amino acids / (phenylalanine + tyrosine) [molar ratio]
Concentration of electrolytes
Na^+: Approx. 3 mEq/L
CH_3COO^-: Approx. 100 mEq/L

2. Product description

MORIHEPAMIN is a clear and colorless aqueous solution for injection. The pH and the osmotic pressure ratio are as follows:

pH	Osmotic pressure ratio
6.6 - 7.6	Approx. 3

3. Description of Containers (plastic bag)

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

	Reserve capacity of the plastic bag
200mL plastic bag	Approx. 250 mL
500mL plastic bag	Approx. 220 mL

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

DOSAGE FORM

I.V. Infusion

PACKAGING

Bag of 200 mL
Bag of 500 mL

INDICATIONS

MORIHEPAMIN is indicated for supportive treatment for hepatic encephalopathy syndrome in patients with chronic liver disorder.

DOSAGE AND ADMINISTRATION

MORIHEPAMIN is usually intravenously drip-infused at a single dose of 500 mL in adult patients. The standard infusion rate in adults is 180 minutes or longer per 500 mL.

If MORIHEPAMIN is administrated via a central venous line, a 500 mL of MORIHEPAMIN should be mixed with a carbohydrate-containing solution and be infused continuously via a central vein for 24 hours. The dosage may be adjusted according to the patient's age, symptoms and body weight.

CONTRAINDICATIONS (MORIHEPAMIN is contraindicated in the following patients.)

1. Patients with serious renal disorder [The symptoms may be aggravated due to overload of nitrogen compounds.]
2. Patients with amino acid metabolism abnormality other than liver disorder [Imbalance of amino acids may be aggravated.]

PRECAUTIONS

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

(1) Patients with severe acidosis [The high doses of the product may aggravate acidosis.]
(2) Patients with congestive cardiac failure [An increase in the circulating blood volume may worsen cardiac stress in such patients.]

2. Important Precautions

If blood ammonia level increases and psychoneurotic symptoms aggravate following administration of MORIHEPAMIN, MORIHEPAMIN should be interrupted or changed to another therapy.

3. Use in the Elderly

In general, since physiological function is decreased in the elderly, MORIHEPAMIN should be carefully administered and taking measures such as dose reduction.

4. Pediatric Use

The safety of MORIHEPAMIN in children has not been established. (No clinical experience)

5. Use in pregnancy and lactation

The safety of MORIHEPAMIN in pregnant woman and nursing mothers has not been established. Therefore, the product should not be used in pregnant woman, woman suspected of being pregnant, and nursing mothers unless the expected benefit outweigh the potential risks.

6. Precautions for Use

(1) Before administration

1) If crystal formation appears in the solution, it should be heated at a temperature of 50 to 60°C and dissolved, followed by being cooled down to around body temperature before use.
2) Do not use the solution if it is absolutely not clear.
3) The solution should be immediately used after opening the package, and all residual solution must be discarded.

(2) During administration

MORIHEPAMIN contains approximately 100 mEq/L of acetate ions. If a large dose or a concomitant electrolyte solution is used, the patient's electrolyte balance should be monitored carefully.

(3) Dosing rate

MORIHEPAMIN should be injected slowly into a vein.

7. Precautions for Handling

1. MORIHEPAMIN can be injected without using an air vent needle.
2. Do not open the outer wrap until use to prevent discoloration of the solution (a deoxidizer is included inside the outer wrap to maintain stability of the product).
3. Do not use the product if any discoloration or leakage of the solution is noted, or droplets are present inside the outer wrap.
4. Do not use the product if the seal covering the rubber plug of a plastic bag is peeled off.
5. 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.
6. Caution should be exercised not to damage the outer wrap. If the outer wrap was damaged, the solution may be discolored.
7. The scale printed on a plastic bag should be used only as a guide.
8. MORIHEPAMIN can not be infused by the tandem system using a connecting tube (U-shaped tube). If two plastic bags are infused at the same time or sequentially, a Y-shaped infusion set must be used.

8. Effects on ability to drive and use machine

Need to use with precaution because this drug can cause tremor, hypoglycaemia, fever, headache, chest discomfort, palpitations.

INTERACTION

There is no report to indicate the interaction with other drug.

ADVERSE REACTIONS

Among 243 cases studied prior to the time of approval, 9 adverse reactions (3.7%) were reported in 9 cases (3.7%). The commonly reported adverse reactions by the time of approval included nausea/queasy (0.8% each), sweaty, transient increased blood ammonia level, vascular pain, urticaria, tremor limb by hypoglycaemia (0.4% each).

	Incidence unknown	0.1 to <5%
Hypersensitivity		Rash, etc.
Gastrointestinal		Nausea/queasy, etc.
Cadiovascular		Chest discomfort, Palpitations, etc.
Glucose metabolism		Hypoglycaemia
Large dose or bolus infusion	Acidosis	Transient increased blood ammonia level
Others		Chills, Fever, Headache, Vascular pain, Sweaty

OVERDOSE

Acetate ion is contained by about 100 mEq/L, therefore in the case of large-dose administration or combined use with electrolyte, due attention should be paid to the electrolyte balance.

PHARMACOKINETICS[1)]

After 500 mL or 1,000 mL of MORIHEPAMIN was administered intravenously in healthy male volunteers, plasma amino acids level and urinary amino acids excretion were assessed. Plasma total amino acids concentration reached the peak soon after completion of administration. And then the concentration rapidly decreased and returned to the baseline value 24 hours after administration. The pattern of plasma amino acids level was considered to reflect the composition of amino acids in MORIHEPAMIN. Urinary excretion of the amino acids (i.e., threonine, serine, glycine, histidine, and lysine), higher levels of which are contained in the urine, increased in proportion to dosage amount of MORIHEPAMIN.

PHARMACOLOGY

1. Improvement of nervous symptoms[3,4)]

In rats with carbon tetrachloride-induced chronic liver dysfunction, MORIHEPAMIN improved nervous symptoms, decreased plasma ammonia levels and suppressed ammonia-induced coma. Similar results were obtained in dogs with anastomosis of the portal vein and the inferior vena cava.

2. Improvement of electroencephalogram, free amino acids levels in plasma and brain, and amine metabolism in brain[5,6)]

In rats with anastomosis of the portal vein and the inferior vena cava, MORIHEPAMIN decreased ammonia-induced abnormal electroencephalogram. MORIHEPAMIN also improved indoleamine metabolism in the plasma and brain by decreasing blood ammonia levels and improving the plasma Fischer's ratio.

3. Mechanism of promoting ammonia metabolism[7)]

It was considered that MORIHEPAMIN rapidly promoted ammonia metabolism by increasing renal ammonia excretion in addition to activating urea cycle in the liver and upregulating glutamine synthesis in the brain and muscule.

CLINICAL STUDIES

1. General Clinical Studies

The results of general clinical studies of MORIHEPAMIN conducted in patients of chronic hepatic failure with hepatic encephalopathy or hyperammonaemia were as follows:

	Improvement rate (defined as "improved" or "better")	Usefullness rate (defined as "useful" or "better")
Hepatic encephalopathy	78.2% (68/87)	63.2% (55/87)
Hyperammonaemia	64.7% (11/17)	52.9% (9/17)

2. Controlled Studies[2)]

When the controlled study by using 500 mL of MORIHEPAMIN was conducted in patients of chronic hepatic failure with hepatic encephalopathy, the result showed that the improvement rate, defined as the percentage of patients with a response rated as "improved" or better, was 77.2% (34/44 cases) and the usefulness rate, defined as the percentage of patients in whom treatment was rated as "useful" or better, was 63.6% (28/44 cases). The effect indicated that blood ammonia level rapidly decreased.

Storage
Store below 30°C

Expiration date
36 months from date of manufacturing. Use before date of expiry shown on the label.

Manufactured by:

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REFERENCES

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3) Kokuba, Y., et al.: *Jpn Pharmacol Ther*, **18**(11), 4293, 1990
4) AY PHARMACEUTICALS CO., LTD.: In-house data (Effects of MORIHEPAMIN to alleviate nervous symptoms)
5) Matsuda, A., et al.: *Jpn Pharmacol Ther*, **18**(11), 4307, 1990
6) Chaki, H., et al.: *Jpn Pharmacol Ther*, **18**(11), 4313, 1990
7) Kokuba, Y., et al.: *Jpn Pharmacol Ther*, **18**(11), 4323, 1990

REQUESTS FOR LITERATURE (INCLUDING IN-HOUSE DATA) SHOULD BE MADE TO:

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