AMINOLEBAN®
8% Amino Acid
For Intravenous Administration

Etiologically the onset of hepatic encephalopathy has been related to excess ammonia, short–chain fatty acids and mercaptans. Recent studies have emphasized the importance of other contributory factors involved in severe hepatic impairment: disturbance of the free amino acid pattern in plasma characterized by an increase of L–Phenylalanine, L–Tryptophan, L–Tyrosine and L–Methionine and a decrease of branched–chain amino acids such as L–Leucine, L–Isoleucine and L–Valine.

The disturbance of the free plasma amino acid pattern causes disturbances in the transport of amino acid across the blood–brain barrier, blocks synthesis of false neurotransmitters in the brain, resulting in the disturbance of the overall cerebral amine metabolism. This disturbance of cerebral amine metabolism is suspected to be the major cause of hepatic encephalopathy.

With these findings as background information, Fischer et al developed a special formula of amino acids, containing high concentrations of branched–chain amino acids and low concentrations of L–Phenylalanine, L–Tryptophan and L–Methionine, without L–Tyrosine, to correct the disturbance of the plasma free amino acid pattern. They have conducted experimental and clinical studies of the special formula for the treatment of hepatic encephalopathy and demonstrated that the normalization of the plasma free amino acid pattern is effective in improving hepatic encephalopathy.

AMINOLEBAN® is prepared with an amino acid composition identical to that of Fischer's formula. Clinical studies have shown that the injection is effective in correcting plasma amino acid concentrations and the clinical symptoms of hepatic encephalopathy.

COMPOSITION

Each 500 mL of AMINOLEBAN® contains the following ingredients:

L–Threonine	2.25 g	L–Leucine	5.50 g
L–Serine	2.50 g	L–Phenylalanine	0.50 g
L–Proline	4.00 g	L–Tryptophan	0.35 g
L–Cysteine HCl H_2O	0.20 g	L–Histidine HCl H_2O	1.60 g
(L–Cysteine equivalent	0.15 g)	(L–Histidine equivalent	1.20 g)
Aminoacetic acid	4.50 g	Lysine HCl	3.80 g
L–Alanine	3.75 g	(L–Lysine equivalent	3.05 g)
L–Valine	4.20 g	L–Arginine HCl	3.65 g
L–Methionine	0.50 g	(L–Arginine equivalent	3.00 g)
L–Isoleucine	4.50 g	Water for injection	Ad 500 mL

Amino acids	7.99% (w/v)	Total Nitrogen	12.2	g/L
Branched–chain amino acid	35.5% (w/w)	Cl^- Approx.	94	mEq/L
Fischer's ratio*	37.05	Na^+ Approx.	12	mEq/L
E/N ratio	1.09	Osmolarity Approx.	768	mOsm/L

* Molar ratio of (L–Valine + L–Leucine + L–Isoleucine) / (L–Tyrosine + L–Phenylalanine)

Sodium bisulfite 0.3 g/L is used as a stabilizer.

INDICATIONS

Treatment of hepatic encephalopathy in patients with chronic liver disease.

DOSAGE AND ADMINISTRATION

The usual adult dose of AMINOLEBAN® is 500 – 1000 mL per dose by intravenous drip infusion. The usual peripheral infusion rate is 500 mL over 180 – 300 minutes in adults (approx. 25 – 40 drops per minute). For total parenteral nutrition, 500 – 1000 mL of the injection should be suitable combined with dextrose or other solutions and administered over 24 hours via the central vein. The dosage may be adjusted depending on the patient's age, symptoms and body weight.

PRECAUTIONS

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

(1) Patients with serious renal disorder (patients on dialysis or hemofiltration are excluded) [Urea and other amino acid metabolites may be retained, which may worsen the patient's clinical condition.]

(2) Patients with abnormal amino acid metabolism (Since the infused amino acids are not adequately metabolized, the patient's clinical condition may be worsened.)

1. **Careful Administration (AMINOLEBAN® Infusion should be administered with caution in the following patients.):**
   (1) Patients with severe acidosis (The patient's clinical condition may be worsened.)
   (2) Patients with congestive cardiac failure (An increase in the circulating blood volume may worsen the patient's clinical condition.)
   (3) Patients on dialysis or hemofiltration with serious renal disorder

2. **Important Precautions**
   The volume of urea, etc. removed and accumulated in patients on dialysis or hemofiltration with serious renal disorder 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 (rarely: < 0.1%, infrequently: 0.1% – < 5%, no specific designation: 5%: or frequency unknown)**
   1) Clinically significant adverse reactions:
      (1) Hypoglycemia: Hypoglycemia may occur. If the patient develops hypoglycemia, glucose should be administered promptly by intravenous infusion. In addition, appropriate nutrition management is recommended in such patients.
      (2) Hyperammonemia: Hyperammonemia has been reported. If the patient develops persistent hyperammonemia during the administration of AMINOLEBAN®, discontinue administration and take measures to eliminate other nitrogen sources.
   2) Other adverse reactions:
      (1) Hypersensitivity
      Symptoms such as skin rash may occur rarely. In the event of skin rash, discontinue the administration and institute appropriate treatment.
      (2) Gastrointestinal
      Symptoms such as nausea and vomiting may occur infrequently.

(3) Cardiovascular
Symptoms such as chest discomfort and palpitation may occur infrequently.
(4) Metabolic
The nitrogen content of this preparation may induce a transient increase in blood ammonia concentrations.
(5) Large dose and rapid administration
Acidosis may occur when large doses are administered rapidly.
(6) Others
Chills, fever, headache and vascular pain may infrequently occur.

4. Use in the Elderly
Since elderly patients often have a reduced physiological function, it is advisable to take such measures as reducing the dose by decreasing the infusion rate.

5. Pediatric Use
Safety in children has not been established.

6. Cautions in Use
(1) Before administration:
1. To prevent associated infection, carry out all procedures under aseptic conditions.
2. Use the solution after warming to near body temperature during cold environmental conditions.
3. Use the solution immediately after opening the package. After use, discard all unused solution.

(2) During administration:
a. The solution contains about 12 mEq/L of sodium and 94 mEq/L chloride. Concomitant use with an electrolyte solution or a large dose requires careful monitoring of electrolyte balance.
b. Administer slowly via a peripheral vein.
c. When vascular pain occurs, use an alternate site or discontinue the administration.

7. Overdosage
Hyperammonemia has been reported after the administration of amino acid preparations, including this solution, in combination with oral intake of nitrogen (total nitrogen dose: 160 g).
(See "Clinically significant adverse reactions" above).

PHARMACOLOGY
1. AMINOLEBAN® normalized the pattern of free amino acids in the plasma and brain, improved serotonin metabolism in the brain and corrected a sleep–wakefulness pattern in a rat model of chronic hepatic insufficiency which underwent a portacaval shunt operation.

2. When infused to portacaval–shunted rats loaded with ammonia, AMINOLEBAN® improved EEG pattern and corrected amine metabolism in the brain as evidenced by correction of the free amino acid pattern in the plasma and brain and by suppression of an increase of the false neurotransmitter octopamine.

DESCRIPTION

AMINOLEBAN® is a sterile and pyrogen free, colorless solution for injection.
pH: Approx 5.9 (mean obtained immediately after manufacture) and 5.5 – 6.5 (specification).
Spesific gravity (20^0C): 1.025
Osmolarity: Approx. 768 mOsm/L

PRECAUTION AND HANDLING

1. A crystalline precipitate may form due to temperature changes during storage. Shake the solution at temperature of 15 – 25^0C to dissolve precipitate before use and after cooling to near body temperature.
2. Do not use the product if the solution is discolored or a precipitate that cannot be dissolved by shaking has formed.
3. Open the outer wrap just before use.
4. Do not use if bag is leaking, solution cloudy or contains foreign matters.

STORAGE

Store below 30°C, protected from light.

PACKAGE

Soft Bag of 500mL

REG. NO.: FT20190524BP06992

ON MEDICAL PRESCRIPTION ONLY

Otsuka

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