1. NAME OF THE MEDICINAL PRODUCT .

AMINOLEBAN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

8% Amino Acid infusion

Ingredient	100 mL
L-Threonine	0.45 g
L-Serine	0.5 g
L-Proline	0.8 g
L-Cysteine Hydrochloride Hydrate	0.04 g
L-Glycine	0.9 g
L-Alanine	0.75 g
L-Valine	0.84 g
L-Methionine	0.1g
L-Isoleucine	0.9 g
L-Leucine	1.1 g
L-Phenylalanine	0.1 g
L-Tryptophan	0.07 g
L-Lysine Hydrochloride	0.76 g
L-Histidine Hydrochloride Hydrate	0.32 g
L-Arginine Hydrochloride	0.730 g

3. PHARMACEUTICAL FORM

AMINOLEBAN® is a clear and colorless or slightly yellow solution for intravenous infusion.
pH range (5-7)
Osmotic pressure ratio (relative to physiological saline): Approx. 3

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of hepatic encephalopathy in patients with chronic liver disease.

4.2. Posology and method of administration

The usual adult dose of AMINOLEBAN® 500–1000 mL per dose, infused via a peripheral vein. The usual peripheral infusion rate is 500 mL over 180–300 min in adults. For total parenteral nutrition, 500–1000 mL of AMINOLEBAN® should be combined with glucose or other solutions and administered over 24 hours via a central vein. The dosage should be adjusted according to the patient's age, symptoms, and body weight.

Precautions >
AMINOLEBAN® contains about 12 mEq/L of sodium and 94 mEq/L of chloride. Concomitant use with an electrolyte solution or administration of a large dose requires careful monitoring of electrolyte balance.

4.3. Contraindications

(AMINOLEBAN® 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.[See (3 in section 1) & (Section 2) in 4.4 Special warnings and precautions for use].

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

4.4. Special warnings and precautions for use

1- Careful Administration (AMINOLEBAN® should be administered with care 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
[Urea and other amino acid metabolites may be retained.] (See section 2. Important Precautions.)

*Contains *sodium metabisulfite*, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. Sulfite sensitivity is seen more frequently in asthmatic than in non asthmatic people."

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.

4.5. Undesirable effects

Reported incidence rates are based on data from 3324 patients with chronic liver disease, and a total of 35 patients (1.1%) experienced 52 adverse reactions. **[Note]:** The indication for use in patients with acute liver disease was deleted due to the findings obtained by the drug efficacy reevaluation. Of the 330 patients with this condition evaluated, there was one reported case of fever (0.3%).

(1) Clinically significant adverse reactions

1) Hypoglycemia (frequency unknown):

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 (frequency unknown):
Hyperammonemia has been reported. If the patient develops persistent hyperammonemia during the administration of AMINOLEBAN®, discontinue administration of nitrogen sources including AMINOLEBAN® and institute appropriate measures.

(2) Other adverse reactions
If adverse reactions are observed, discontinue the administration, and institute appropriate treatment.

Reactions	Frequency		
	Unknown	**0.1% –<5%**	**<0.1%**
Hypersensitivity	Rash, etc.		
Gastrointestinal		Nausea, vomiting, etc.	
Cardiovascular	Chest discomfort, palpitation, etc.		
Metabolic	Transient increase in blood ammonia		
Large dose and rapid administration	Acidosis		
Others	Chills, fever		Vascular pain, headache

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: Safety.reporting@egyptotsuka.com or by sending an e-mail to PV.report@edaegypt.gov.eg

4.6. Overdose

Hyperammonemia has been reported when an amino acid solution, including AMINOLEBAN ®, was administered in combination with oral intake of nitrogen (total nitrogen: 160 g). (See "**Clinically significant adverse reactions**" above.)

5. PHARMACOLOGICAL PROPERTIES

PHARMACOKINETICS
(Reference data in rats):
^{14}C-labeled amino acids formulated in AMINOLEBAN® were readily distributed to almost the entire body after intravenous infusion in rats. In 6 hours, 50 to 70% of the administered amino acids was taken up into protein fractions. The ratio of branched-chain amino acids to the total amino acids in the protein fractions was highest in the brain. Up to 72 hr, 41.7% of the administered dose was excreted in the expired air, 5.9% in the urine, and 2.6% in the feces.

CLINICAL STUDIES

AMINOLEBAN® was administered to patients with hepatic encephalopathy associated with chronic liver disease, and the clinical effect of AMINOLEBAN® was evaluated. A prompt improvement in the coma scale (an index of disturbance of consciousness) and a prompt decrease in blood ammonia concentrations were observed. In addition, patients showed improvement in neuropsychological function as assessed by writing, drawing, flapping tremor, number connection test, and orientation and calculation tests as well as by EEG tracings.

The efficacy of AMINOLEBAN® in hepatic encephalopathy in clinical studies was summarized below:

Efficacy in hepatic encephalopathy

Clinical condition	**Effectiveness rate***
Encephalopathy due to liver cirrhosis	73.3% (198/270)
Encephalopathy due to hepatocellular carcinoma	62.2% (56/90)
Encephalopathy due to other causes	62.5% (5/8)
Total	70.4% (259/368)

* Significant improvement or complete resolution of disturbance of consciousness or improvement in coma scale by one or more grades (Davidson's classification).

PHARMACOLOGY

(1) AMINOLEBAN® normalized the Fischer's ratio in the plasma and brain, improved monoamine metabolism in the brain, and corrected a sleep-wakefulness pattern in portacaval-shunted rats (chronic hepatic insufficiency model).

(2) When infused to portacaval-shunted rats loaded with ammonia, AMINOLEBAN® normalized the Fischer's ratio in the plasma and brain, decreased blood ammonia levels, and improved EEG and monoamine metabolism in the brain.

Use in the Elderly

Because elderly patients often have reduced physiological function, it is advisable to consider reducing the dose by decreasing the infusion rate.

Pediatric Use

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium metaBisulfite

Sodium Hydroxide

Water for injection

6.2. Shelf life:

3 Years

6.3. Special precautions for handling and storage

1) Because an oxygen absorbent is enclosed between the bottle and the outer wrap to maintain stability of the solution, do not remove the outer wrap until use.
2) Do not use the product 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.
3) Store below 25° C, use immediately after opening,.
4) Do not use in case oxygen indicator tablet color changed from pink to purple or color of solution changed
5) One single dose, Discard the remaining quantity in case the container not used completely.
6) Keep out of reach of children.
7) Do not puncture for ventilation during use.

6.4 Precautions Concerning Use

(1) Before administration

1) To minimize the risk of infection, carry out all procedures under aseptic conditions.
2) In cold environmental conditions, the solution should be warmed to near body temperature before use.
3) Use the solution immediately after opening the container. After use, discard all unused solution.

(2) During administration

1) Administer the solution slowly via a vein.
2) When vascular pain occurs, use an alternate site or discontinue administration.

6.4. Nature and contents of container

Carton box containing Labelled (LDPE) bottle of 500 ml with rubber cap & Package insert .a packet and a tablet of oxygen absorbent

(For tender and export) :

Carton box containing Labelled (LDPE) bottle of 250 ml with rubber cap & Package insert .a packet and a tablet of oxygen absorbent

6.5. Applicant name, Manufacturer & License holder Information

Egypt Otsuka Pharmaceutical Co.
10th of Ramadan city, Industrial Zone B3-Egypt
For Adverse Events: Safety.reporting@egyptotsuka.com
Tel: +20554500097