

# AMINOLEBAN INJECTION

## DESCRIPTION

**AMINOLEBAN** is a clear and colorless solution for injection with a pH of 5.5-6.5 and Specific gravity (20°C) of 1.025. The Osmotic pressure ratio (to physiological saline) is Approx. 3

## COMPOSITION

Each 1000ml of **AMINOLEBAN** contains:

Aminoacetic acid -----	9.0 g
L-alanine -----	7.5 g
L-arginine HCl -----	7.3 g
(L-arginine equivalent) -----	(6.0 g)
L-cysteine HCl monohydrate -----	0.4 g
(L-cysteine equivalent) -----	(0.3 g)
L-histidine HCl monohydrate -----	3.2 g
(L-histidine equivalent) -----	(2.4 g)
L-isoleucine -----	9.0 g
L-leucine ----	11.0 g
L-Lysine HCl -----	7.6 g
(L-lysine equivalent) -----	(6.1 g)
L-methionine -----	1.0 g
L-phenylalanine -----	1.0 g
L-proline -----	8.0 g
L-serine -----	5.0 g
L-threonine -----	4.5 g
L-tryptophan -----	0.7 g
L-valine -----	8.4 g
Water for injection q.s -----	1000 ml

---

Amino Acids	7.99% (w/v)
Branched-chain amino acids	35.5% (w/w) of total amino acids
Fischer's Ratio*	37.05
E/N ratio	1.09
Total Nitrogen	12.2 g/L
Na <sup>+</sup> (Approx)	14 mEq/L
Cl <sup>-</sup> (Approx)	94 mEq/L

---

\*Molar ratio of (valine+leucine+isoleucine) / (tyrosine+phenylalanine).  
This product contains Sodium bisulfite 0.3 g/L as a stabilizer.

---

## INDICATIONS

**AMINOLEBAN** is indicated for the treatment of hepatic encephalopathy, in patients with chronic liver disease.

## CONTRAINDICATIONS

**AMINOLEBAN** is contraindicated in the following patients:

1. Patients with severe renal disorder
2. Patients with abnormal amino acids metabolism

## DOSAGE AND ADMINISTRATION

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

## PRECAUTIONS

### 1. Careful Administration

**AMINOLEBAN** should be administered with care in the following patients:

- a. Patients with severe acidosis
  - b. Patients with congestive cardiac failure
2. **AMINOLEBAN** contains about 14 mEq/L sodium and 94 mEq/L chloride. Concomitant use with an electrolyte solution or administration of a large dose requires careful monitoring of electrolyte balance.

### 3. Use In The Elderly

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

### 4. Pediatric Use

The safety in children has not been established

## ADVERSE REACTIONS

Reported incidence rates are based on data from 3,324 patients with chronic liver disease, and a total of 35 patients (1.1%) experienced 52 adverse reactions.

### 1. Clinically significant adverse reactions

#### a. 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.

#### b. 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, headaches

[ ] : common adverse reactions in amino acids injections

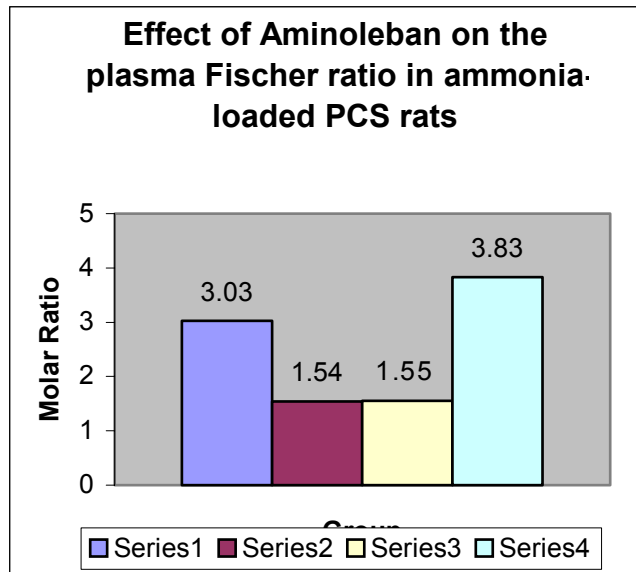
# PHARMACOLOGY

## 1. Free Amino Acid Pattern

Aminoleban improves the free amino acid pattern in the blood and brain in hepatic failure. In experiments on rats with hepatic failure induced by portacaval shunt (PCS) followed by hepatic devascularization, the infusion of Aminoleban specifically increased the concentration of branched-chain amino acids (isoleucine, leucine and valine) in the blood and brain one hour after infusion, and suppressed an increase in aromatic amino acids (phenylalanine, tyrosine and tryptophan) and methionine in the brain.

## 2. Fischer Ratio

Aminoleban improves the Fischer Ratio [a molar ratio of (Isoleucine + Leucine + Valine / Phenylalanine + Tyrosine)] in the blood and brain in hepatic failure condition. In experiments on portacaval shunted (PCS) rats loaded with ammonia, the infusion of Aminoleban for 24 hours to those animals normalized the Fischer Ratio, an important parameter for hepatic encephalopathy, by suppressing the transport of aromatic amino acids (phenylalanine, tyrosine and tryptophan) from the plasma to the brain. The plasma concentrations of these amino acids increases in hepatic encephalopathy



Series 4: Aminoleban group	Series 1:Sham operated control group	Series 2: Normal saline group	Series 3:FAO/WHO amino acid injection group
Significance vs	P < 0.05	P < 0.01	P < 0.01

### **3. Cerebral Amine Metabolism**

Aminoleban improves amine metabolism in the brain in hepatic failure. In experiments in which it was infused for 24 hours to PCA rats loaded with ammonia, Aminoleban suppressed the transport of tryptophan from the blood into the brain and the cerebral production of serotonin, 5-hydroxyindoleacetic acid and octopamine, etc., while maintaining normal intracerebral levels of norepinephrine and dopamine, thereby normalizing amine metabolism in the brain.

### **4. Improvement of the Sleep-Wakefulness Cycle**

Aminoleban improves the sleep-wakefulness cycle in hepatic failure. Aminoleban was repeatedly infused at 30 ml/kg/day for three consecutive days to PCS rats, and the sleep-wakefulness cycle was determined as an index of hepatic encephalopathy. The latency of paradoxical sleep was shortened to the value before the PCS operation, and the incidence of paradoxical sleep was reduced to the level before the OCS operation.

### **5. Improvement of the Brain Wave Pattern**

Aminoleban improves the brain wave pattern in hepatic failure. Aminoleban was infused for 24 hours to PCS rats loaded with ammonia and the electroencephalogram in the arousal state was treated with a power spectrum. As a result the  $\delta$  (slow) wave component was decreased, and the  $\alpha$  and  $\beta$  (fast) wave components were increased, thus indicating an ameliorating effect on the brain wave pattern.

## PHARMACOKINETICS

All amino acids in Aminoleban injected intravenously at 5 ml/kg/hour for 2 hours, whether to normal rats or rats with hepatic failure, were quickly utilized in the body, and the retention of each amino acid in the body was over 98% during and 24 hours after administration.

Amino Acid	Normal Rats	Rats with Liver Disorder Induced by D-Galactosamine
L-Ala	99.9 ± 0.2	99.7 ± 0.6
L-Arg	99.9 ± 0.3	99.9 ± 0.1
Gly	99.8 ± 0.3	99.9 ± 0.4
L-His	99.8 ± 0.4	98.8 ± 0.4
L-Ile	100.0 ± 0.1	99.9 ± 0.1
L-Leu	100.0 ± 0.1	99.9 ± 0.1
L-Lys	99.9 ± 0.3	9.7 ± 0.1
L-Met	100.0 ± 0.0	98.8 ± 0.6
L-Phe	99.4 ± 1.3	99.2 ± 1.4
L-Pro	98.7 ± 0.5	99.6 ± 0.9
L-Ser	99.7 ± 0.3	99.7 ± 0.1
L-Thr	99.9 ± 0.7	98.8 ± 1.3
L-Trp	100.0 ± 0.0	100.0 ± 0.0
L-Val	99.9 ± 0.1	100.0 ± 0.0

(Means ± SD)

### **Percentage of Amino Acids retained in the body during and 24 hours after administration of Aminoleban into normal and hepatic failure rats**

Aminoleban, including 15 different L- [ U – <sup>14</sup>C ] amino acids, was administered into normal rats at 5 ml/kg/hour for 2 hours, after which the excretion percentage was measured. As a result, excretion accounted for 5.9% in the urine, 2.6% in the feces, and 41.7% in the expired air at 72 hours after administration.

Route of Excretion	<sup>14</sup> C – Excretion (%)	Total Excretion (%)
Urine	5.90 ± 0.41	50.12 ± 2.84
Feces	2.55 ± 0.03	
Expired air	41.66 ± 2.51	

(Means ± SD)

### **Excretion of Radioactivity in normal rats at 72 hours after Administration**

# SAFETY PROFILE

## 1. Acute Toxicity

Animal	Administration Route	Administration Rate	Sex	LD <sub>50</sub> (ml/kg)
Wistar Rats M: 165-220 g F: 140-185 g	Continuous infusion	20 ml/kg/min	M F	82(68.9–97.6)* 102(87.9-118.3)*
New Zealand White Rabbits 2.2-2.8 kg	Continuous infusion	Approx. 1.6 ml/kg/min	M F	> 200 > 200

\* The values in parenthesis show 95% confidence interval

LD<sub>50</sub> value for Aminoleban

## 2. Subacute and Chronic Toxicity

No Aminoleban-specific toxicity was observed at any time during a 30- or 90-day intravenous administration period in rabbits.

## 3. Antigenicity

In induction tests on guinea pigs and rabbits using bovine serum albumin as a control substance, Aminoleban was negative for systemic anaphylaxis, Schultz-Dale reaction, and passive cutaneous anaphylaxis (PCA) reaction.

## 4. Local Irritation

In hemolytic tests using human blood, hemolysis was not observed. Similarly, in muscle injury tests in rabbits, no gross or histological damage was observed.

## CLINICAL EFFICACY

Aminoleban was highly effective against hepatic encephalopathy in chronic liver disease and was demonstrated to be useful in clinical studies.

The efficacy of **AMINOLEBAN** in hepatic encephalopathy in clinical studies is summarized below:

### 1. 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).

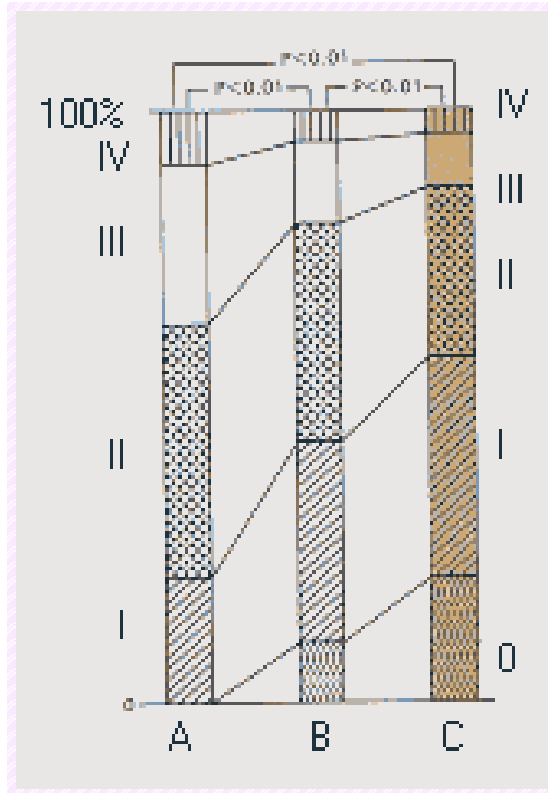
Stage	Mental State	Flapping Tremor	Brain Waves
Level I (Prodrome)	Euphoria, occasional depression, slow mentation and arrhythmic sleep	(±) – (+)	Tendency for slow waves
Level II (Impending Coma)	Euphoria, disorientation, dyscalculia, mental confusion, dystrophy (able to follow physician's instructions)	(++)	Slow wave; rhythmic high voltage $\delta$ wave; and triphasic wave
Level III (Stupor)	Delirium, excitement and drowsiness (arousable), (unable or refuses to follow physician's instructions)	(++)	Disappearance of dominant rhythm; rhythmic high voltage $\delta$ wave; and triphasic wave
Level IV (Semicoma or Coma)	Unconsciousness and (+) or (-) reaction to noxious stimuli	(-)	Flattening

Level O : Alert

Davidsons's Classification of Hepatic Encephalopathy

## 2. Amelioration and Improvement of Coma

Aminoleban caused prompt improvement of hepatic coma (in 3-4 hours), and its therapeutic effect was persistent even at 24 hours.

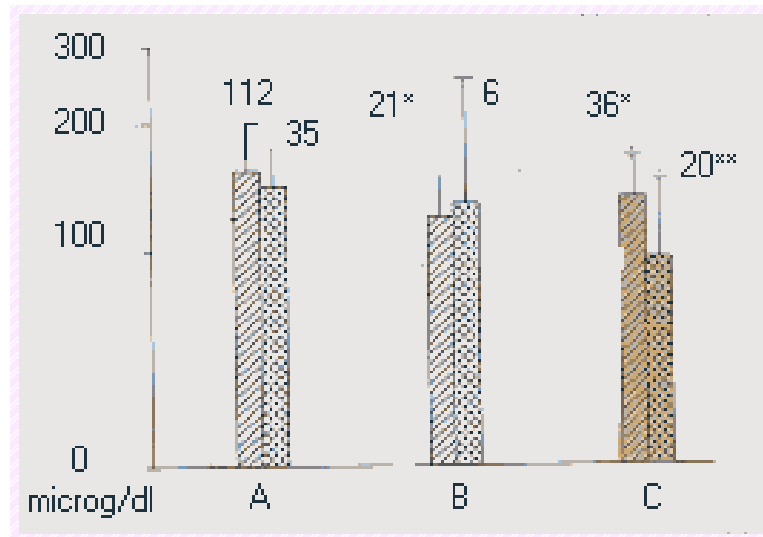


A: Before administration; B:3-4 hours; C:24 hours

Improvement of Encephalopathic Grade During the Initial 24 hours after the Start of Aminoleban Infusion

### 3. Correction of Blood Ammonia Concentration

Blood ammonia concentrations are often high in hepatic encephalopathy. Aminoleban promptly lowered blood ammonia concentrations immediately after infusion in hyperammonemia.



A: Before administration; B:3-4 hours; C:24 hours

\*p<0.01; \*\*p< 0.001

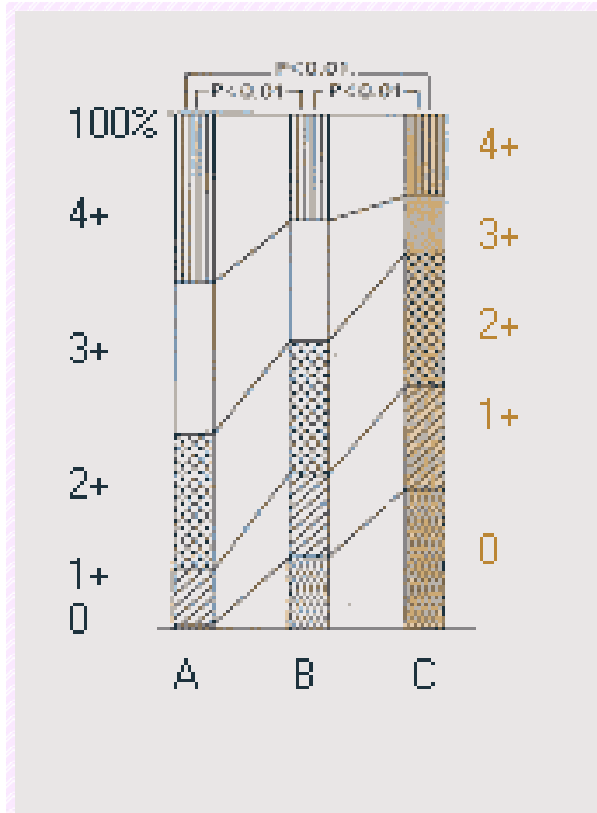
slashes: cirrhosis patients

dots: hepatic cancer patients (some complicated by cirrhosis)  
(the numbers represent the number of patients)

Changes in Blood Ammonia Concentrations During the Initial 24 hours after the Start of  
Aminoleban Infusion

#### 4. Results of Neuropsychological Tests

Patient improvement with Aminoleban was checked using the following neuropsychic tests: writing and drawing, flapping tremor, number connection, orientation, calculation, brain wave observation, etc. The infusion of Aminoleban promptly improved the patient's condition on these tests.



A: Before administration; B:3-4 hours; C:24 hours

4: illegible; 3: markedly disturbed;  
2: apparently disturbed; 1: suspicious  
0: Normal

Effects on Writing and Drawing

