*Approved: June 2018

Rx Prescription drug

- Branched-Chain Amino Acid Preparation -

LIVACT® Granules

< L-Isoleucine, L-Leucine and L-Valine Granules JP (Japanese Pharmacopoeia) >

DESCRIPTION

1. Composition

Each packet (4.15 g) of LIVACT® Granules contains the following ingredients.

L-Isoleucine	952 mg
L-Leucine	1,904 mg
L-Valine	1,144 mg

Excipients: Povidone, partially hydrolyzed polyvinyl alcohol, tartaric acid, saccharin sodium hydrate and perfume agents as additives.

2. Product description

LIVACT® Granules is white coated granules having a slightly fragrant odor.

INDICATIONS

LIVACT® Granules is indicated for improvement of hypoalbuminemia in patients with decompensated hepatic cirrhosis with an albumin level of 3.5 g/dL or less despite adequate dietary intake.

<Precautions>

1. **LIVACT® Granules is indicated for use in patients** presenting with hypoalbuminemia despite adequate dietary intake or in whom total dietary calories and protein (amino acids) intake is restricted due to complicated diabetes mellitus or hepatic encephalopathy, among patients with decompensated hepatic cirrhosis presenting with hypoalbuminemia as indicated by a serum albumin level of 3.5 g/dL or less with current or a history of ascites/oedema or hepatic encephalopathy. A dietetic instruction should be provided to the patient in case of dietary deficiency despite the patient being amply capable of food ingestion in the absence of diabetes mellitus and hepatic encephalopathy. If the patient is deficient in dietary intake due to development of hepatic encephalopathy, a drug containing calories and protein (amino acids) should be administered.

This product should not be administered to **the following patients with markedly advanced hepatic cirrhosis since such patients may not respond to LIVACT® Granules:**

(1) Patients with stage III or more in the severity of coma due to hepatic encephalopathy

(2) Patients with a total bilirubin level of 3 mg/dL or more

(3) Patients with a markedly depressed hepatic function for protein synthesis

DOSAGE AND ADMINISTRATION

The usual adult dose for oral use is one packet three times a day after meals or as prescribed by physician.

<Precautions>

1. LIVACT® Granules consists of branched-chain amino acids alone and **does not contain all amino acid required for protein synthesis.** Therefore, the patient taking LIVACT® Granules must ingest the amount of protein (amino acids) and calories required (daily protein intake, 40 g or more; and daily calorie intake, 1000 kcal or more) in the diet according to the patient's condition. If the patient is on restricted protein intake, in particular, caution must be exercised in that the patient may not respond LIVACT® Granules therapy and, moreover, long-term use of this product may lead to aggravation of nutriture unless the minimum protein and calorie requirements are secured.

2. **If abnormal BUN or blood ammonia is noted following administration of LIVACT®** Granules, caution must be taken because it may be attributable to overdose. Caution should also be observed regarding long-term overdosage since it may give rise to aggravation of nutriture.

3. **If no improvement in hypoalbuminemia is attained in 2 months or longer with the use of LIVACT®** Granules, appropriate measures should be taken such as replacement with other therapy.

CONTRAINDICATIONS (LIVACT® Granules is contraindicated in the following patients.)

Patients with congenital branched-chain amino acid metabolic abnormality [The use of LIVACT® Granules may be induced with convulsions or respiratory disturbances in patients with maple syrup urine disease.]
Do not use for patient who is allergic to any ingredient of LIVACT® Granules.

PRECAUTIONS

Read carefully the instructions before use. For further information please consult your doctor.
This drug is used upon doctor's prescription only.

1. Use in the Elderly

LIVACT® Granules should be administered to elderly patients with caution since such patients often have decreased physiological functions, and metabolic disorders such as blood ammonia elevation can be more sensitive to develop during LIVACT® Granules therapy.

2. Use during Pregnancy, Delivery, or Lactation

The safety of LIVACT® Granules in pregnant women and nursing mothers has not been established. Therefore, the product should not be used in pregnant women, women suspected of being pregnant, and nursing mothers unless the expected benefits outweigh the potential risks.

3. Pediatric Use

The safety of LIVACT® Granules in children has not been established. (no clinical experience)

INTERACTION WITH OTHER DRUGS AND OTHER FORMS OF INTERACTIONS

There is no report to indicate the interaction with other drugs

EFFECTS ON ABILITY TO DRIVE AND OPERATE MACHINE

In case of LIVACT® Granules, no instance which ability to drive or operate machinery might be affected, has been reported.

ADVERSE REACTIONS

Among 420 cases studied prior to the time of approval, 40 adverse reactions were reported in 27 cases (6.4%). The commonly reported adverse reactions by the time of approval included abdominal distension (9 reactions, 2.1%), diarrhea (5 reactions, 1.2%) and constipation (4 reactions, 1.0%).(At the approval)

267 adverse reactions were reported in 178 cases (6.2%) of 2,877 cases surveyed in the postmarketing surveillance. The commonly reported adverse reactions included hyperammonemia (23 reactions, 0.8%), queasy (15 reactions, 0.5%), diarrhea (14 reactions, 0.5%), increased BUN (14 reactions, 0.5%) and abdominal pain (12 reactions, 0.4%).(Data from the result of re-examination)

63 adverse reactions were reported in 41 cases (12.3%) of 334 cases in postmarketing clinical studies (including long-term studies). The commonly reported adverse reactions included abdominal distension (13 reactions, 3.9%), constipation (9 reactions, 2.7%), diarrhea (5 reactions, 1.5%), itching (4 reactions, 1.2%), queasy (3 reactions, 0.9%) and vomiting (3 reactions, 0.9%).(Data from the result of re-examination)

	0.1 to 5%	<0.1%	Incidence unknown
Gastrointestinal[Note 1)]	Abdominal distension, queasy, diarrhea, constipation, abdominal discomfort, abdominal pain, vomiting, anorexia, heartburn, etc.	Thirst, eructation	
Renal[Note 1)]	Increased BUN, increased serum creatinine, etc.		
Metabolism[Note 1)]	Increased blood ammonia, etc.		
Hepatic	Increased serum AST (GOT), increased serum ALT (GPT), increased total bilirubin, etc.		
Skin	Rash, itching, etc.		
Others	Malaise, oedema (facial, lower extremities, etc.)		Redness, hot flushes

Note 1): If any of these reactions are noted, the dose of LIVACT® Granules should be reduced or the treatment should be interrupted.

Inform your doctor of undesirable effects occurred during the use of drug.

PHARMACOKINETICS

Plasma concentrations of branched-chain amino acids were measured in healthy adult male volunteers (n = 48) taken with single oral LIVACT® Granules (1 packet; containing L-isoleucine 952 mg, L-leucine 1904 mg, and L-valine 1144 mg) on an empty stomach. The pharmacokinetic parameters (AUC, Cmax, etc.) calculated from the change in concentration from the baseline are presented below.

The pharmacokinetic parameters of LIVACT® Granules

ingredients	Cmax (μg/mL)	AUC(μg・hr/mL)	Tmax(hr)	$t_{1/2}$(hr)
L-isoleucine	30.982±5.872	43.126±9.884	0.677±0.178	0.787±0.305
L-leucine	58.531±10.587	103.088±19.671	0.688±0.175	1.428±0.243
L-valine	46.796±8.332	92.495±19.948	0.724±0.173	1.823±0.492

1) **Distribution:** Amino acids administrated orally are promptly distributed and used via the same pathway as internal amino acids.
2) **Absorption:** When LIVACT® Granules are administrated orally, each amino acid is absorbed via its transporter in small intestine.
3) **Metabolism:** Each amino acid is pooled and can be used as substrates for synthesis of protein and bioactive substances. On the other hand, deaminated amino acids enter TCA cycle, gluconeogenesis or biosynthesis of fatty acids as energy substrate. Nitrogen in amino acids decomposes into urea in urea cycle.
4) **Excretion:** The carbon skeleton in each amino acid could be decomposed into CO_2 and H_2O. CO_2 could be excreted into expiration. Nitrogen could be excreted into urine as urea or ammonia.

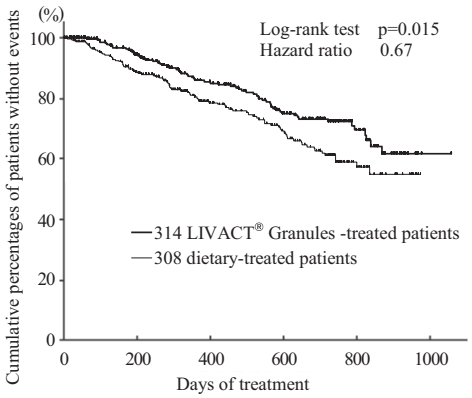
CLINICAL STUDIES

1. A six-month open clinical trial performed in hypoalbuminemic patients with decompensated hepatic cirrhosis revealed resolution of hypoalbuminemia as indicated by increased serum albumin levels; improvement in nutritional parameters such as serum total protein, transferrin and body weight; and improvement of malaise and fatigability during 2-weeks to 2-month period of the study treatment. Subsidence in ascites was noted at the fifth month. These improvements kept until the completion of the study. The usefulness rate of LIVACT® Granules, determined based on overall assessment of data regarding subjective symptom, objective symptom, nutriture, psychoneurological symptoms, quality of life, and safety, was 51.2% (104/203 patients). A subsequent survey on prognosis of these patients revealed a more favorable life prognosis in those showing improvement in nutriture after the study and in patients receiving long-term LIVACT® Granules therapy.

2. A 12-week double-blind placebo-controlled clinical study was conducted in hypoalbuminemic patients with decompensated hepatic cirrhosis. Treatment with LIVACT® Granules increased the serum albumin level, the primary endpoint, by 0.2 g/dL on average, and 31.5% of patients treated (17/54) showed serum albumin levels increased by 0.4 g/dL or more, indicating a significantly greater improvement as compared with the placebo treatment. The total improvement rate, determined based on overall assessment of data regarding subjective and objective symptoms, nutriture, psychoneurological symptoms, and quality of life, was 45.8% (38/83 patients) for the LIVACT® Granules -treated group and 17.3% (14/81 patients) for the placebo group. The usefulness rate, determined based on evaluation of safety in addition to the above variables, was 49.4% (42/85 patients) for the LIVACT® Granules -treated group and 18.1% (15/83 patients) for the placebo group.

3. An open-label follow-up clinical trial was performed for 2 years to investigate the relationship between serum albumin levels and clinical manifestations and prognosis for survival. The results revealed that changes in serum albumin levels over time were significantly correlated with status of ascites, oedema and performance status. As for the relationship to prognosis for survival, the risk of mortality (hazard ratio) per unit time based on no change group in serum albumin levels invariance was estimated to be 0.77 for subjects showing a serum albumin level increased by 0.2 g/dL, and to be 0.59 for those showing a serum albumin level increased by 0.4 g/dL in a year.

4. To evaluate the effect of LIVACT® Granules on the prognosis for survival, randomized controlled clinical trials were conducted for at least 2 years by comparison with dietary treatment in terms of study treatment time to discontinuation or dropout using significant events related to the prognosis for survival such as exacerbation of hepatic insufficiency in patients with liver cirrhosis, as indicated by occurrence of ascites, oedema, hepatic encephalopathy, and jaundice; rupture of oesophageal varices (rupture of the gastric varices); development of hepatic cancer; and death, which were determined as serious complications occurring in association with advancing hepatic cirrhosis. The results showed that LIVACT® Granules significantly inhibited the development of the above serious complications of hepatic cirrhosis among the 622 patients included in the analyses (308 and 314 patients in dietary-treated patients and LIVACT® Granules -treated patients, respectively). The hazard ratio for LIVACT® Granules -treated patients against dietary-treated patients was 0.67 with 95% confidence interval ranging from 0.49-0.93.



PHARMACODYNAMICS

1. Effect and action
   The dose responsiveness trial was conducted on liver cirrhosis patients with hypoalbuminemia to confirm the priority of the clinical dose. In the trial, 6g, 12g, 18g of LIVACT® Granules were administrated per day and compared with placebo administration in a non-blind trial. A significant increase in serum albumin level was seen in 12g group and 18g group compared to placebo group. Also, the significant increase of Fischer's ratio in blood between pre-administration data and data collected in the 12th week after administration was observed. The improvement of general symptoms was shown in 12g group and 18g group compared to other two groups.
2. Mechanism of action
   Administration of LIVACT® Granules in patients with decompensated hepatic cirrhosis will promote albumin synthesis in liver through the improvement of the imbalance of amino acids in blood.

OVERDOSES AND TREATMENT

Well-controlled clinical study for overdoses of LIVACT® Granules has not been conducted.

PACKING SIZE

Box of 84 sachets x 4.15 g

STORAGE

Store at temperature below 30°C .

Keep out of reach of children.
Do not use the medicine after the expiry date stated on the package.

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