CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-667

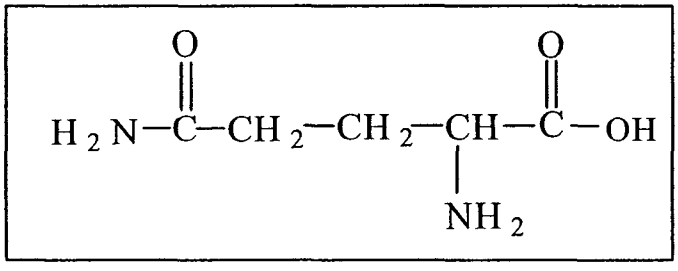
APPROVED LABELING

NutreStore ™

L-glutamine powder for oral solution

DESCRIPTION

NutreStore (L-glutamine powder for oral solution) for oral administration is formulated as a white crystalline powder in a paper-foil-plastic laminate packet. Each packet of NutreStore ™ contains 5 g of L-glutamine. The amino acid glutamine is also known as (S)-2-aminoglutaramic acid, L-glutamic acid 5-amide, (S)-2,5-diamino-5-oxopentanoic acid, or L-glutamine. The molecular formula of glutamine is $C_5H_{10}N_2O_3$, and the molecular weight is 146.15 d. Glutamine has the following structural formula:



CLINICAL PHARMACOLOGY

L-glutamine has important functions in regulation of gastrointestinal cell growth, function, and regeneration. Under normal conditions, glutamine concentration is maintained in the body by dietary intake and synthesis from endogenous glutamate. Data from clinical studies indicate that the role of and nutritional requirements for glutamine during catabolic illness, trauma, and infection may differ significantly from the role of and nutritional requirements for glutamine in healthy individuals. Glutamine concentrations decrease and tissue glutamine metabolism increases during many catabolic disease states, and thus glutamine is often considered a "conditionally essential" amino acid.

When glutamine was administered in combination with recombinant human growth hormone (rh-GH) to rats, villous height, bowel growth, plasma insulin-like growth factor I, and body weight were significantly higher than in animals when either glutamine or rh-GH was administered alone.

Pharmacokinetics
The pharmacokinetics of L-glutamine as described below are based on literature data in healthy subjects. The pharmacokinetics in patients with short bowel syndrome have not been determined. The plasma glutamine concentrations in these patients following oral administration are expected to be highly variable depending on the length, segment, and presence/absence of ileal-cecal valve for the remnant bowel.

Absorption
Following single dose oral administration of glutamine at 0.1 g/kg to six subjects, mean peak blood glutamine concentration was **1028 μM (or 150 μg/mL)** occurring approximately 30 minutes after administration. The pharmacokinetics following multiple oral doses have not been adequately characterized.

Distribution
After an intravenous (IV) bolus dose in three subjects, the volume of distribution was estimated to be approximately 200 mL/kg.

Metabolism
Endogenous glutamine participates in various metabolic activities, including the formation of glutamate, and synthesis of proteins, nucleotides, and amino sugars. Exogenous glutamine is anticipated to undergo similar metabolism.

Elimination
Metabolism is the major route of elimination for glutamine. Although glutamine is eliminated by glomerular filtration, it is almost completely reabsorbed by the renal tubules. After an IV bolus dose in three subjects, the terminal half-life of glutamine was approximately 1 hour.

Effect of Race, Age, and Gender
There are no studies to determine the effect of race, age, or gender.

Drug-Drug Interactions
No drug-drug interaction studies have been conducted. Because metabolism of glutamine is mediated via non-CYP enzymes, glutamine pharmacokinetics are unlikely to be affected by other agents through CYP enzyme inhibition or induction.

CLINICAL TRIALS

A randomized, controlled, 3-arm, double-blind, parallel-group clinical study evaluated the efficacy and safety of oral glutamine as a cotherapy with recombinant human growth hormone (rh-GH) in subjects with short bowel syndrome (SBS) who were dependent on intravenous

parenteral nutrition (IPN) for nutritional support. The primary endpoint was the change in weekly total IPN volume defined as the sum of the volumes of IPN, supplemental lipid emulsion (SLE), and intravenous hydration fluid. The secondary endpoints were the change in weekly IPN caloric content and the change in the frequency of IPN administration per week.

All subjects received a specialized oral diet (SOD) for the duration of the study. Following a two-week equilibration period, treatment was administered in a double blind manner. Group A (N=16) received rh-GH for four weeks plus oral glutamine placebo for 16 weeks, Group B (N=16) received rh-GH for four weeks plus oral glutamine for 16 weeks, and Group C (N=9), received rh-GH placebo for four weeks plus oral glutamine for 16 weeks. The efficacy of glutamine was assessed by comparing the cotherapy (rh-GH and oral glutamine) to rh-GH alone.

After 4 weeks of treatment with subcutaneous rh-GH (0.1 mg/kg/d) and oral glutamine (30 g/d) (Group B), subjects with SBS reduced their requirement for IPN volume (-7.7 L/wk), IPN caloric content (-5751 kcal/wk), and weekly frequency of IPN administration (-4.2 d/wk).

Table 1

Results for Endpoints after 4 weeks of Treatment

	Group A rhGH + SOD [1]	Group B rhGH + SOD[GLN] [1]	Group C SOD[GLN] [1]
Total IPN volume (L/wk)			
Mean at Baseline	**10.3**	**10.5**	**13.5**
Mean Change	**-5.9**	**-7.7***	**-3.8**
Total IPN Calories (kcal/wk)			
Mean at Baseline	**7634.7**	**7895.0**	**8570.4**
Mean Change	**-4338.3**	**-5751.2**	**-2633.3**
Frequency of IPN or SLE (days/week)			
Mean at Baseline	**5.1**	**5.4**	**5.9**
Mean Change	**-3.0**	**-4.2**	**-2.0**

[1] **SOD[GLN] = Specialized Oral Diet supplemented with Glutamine ; rhGH + SOD = Human Growth Hormone plus Specialized Oral Diet; rhGH + SOD[GLN] = Human Growth Hormone plus Specialized Oral Diet supplemented with Glutamine**

***p= 0.023, treatment comparison between rhGH + SOD[GLN] versus rhGH+SOD**

GROUP A: rh-GH + SOD for 4 weeks followed by SOD for 12 weeks.

GROUP B: rh-GH + SOD [GLN] for 4 weeks followed by SOD [GLN] for 12 weeks.
GROUP C: rh-GH placebo + SOD[GLN] for 4 weeks followed by SOD[GLN] for 12 weeks

IPN volume requirements were significantly reduced in subjects receiving subcutaneous rh-GH and oral glutamine (Group B) when compared with IPN volume requirements in subjects receiving either treatment alone.

Table 2

Persistence of Treatment Effect

Change in IPN* Volume, Calories, and Frequency Week 2 to Week 18 ITT Population			
Endpoint	**Group A** [n = 16]	**Group B** [n = 16]	**Group C** [n = 9]
Change in weekly IPN Volume (L/wk)	-5.9	-7.2	-4.7
Change in weekly IPN Calories (kcal/wk)	-3522.2	-5347.3	-2254.0
Change in weekly IPN frequency (days/wk)	-2.9	-3.9	-1.9
*IPN is Total IPN excluding supplemental lipid emulsion (SLE) and hydration fluid. GROUP A: rh-GH + SOD for 4 weeks followed by SOD for 12 weeks. GROUP B: rh-GH + SOD [GLN] for 4 weeks followed by SOD [GLN] for 12 weeks. GROUP C: rh-GH placebo + SOD[GLN] for 4 weeks followed by SOD[GLN] for 12 weeks.			

The change in weekly IPN volume, calories and frequency was assessed from Week 2 to Week 18. The data support that the treatment effect is maintained for 16 weeks. The efficacy of oral glutamine beyond 16 weeks of treatment has not been adequately studied.

CONTRAINDICATIONS

None known.

INDICATION AND USAGE

Treatment of Short Bowel Syndrome

NutreStore™ (L-glutamine powder for oral solution) is indicated for the treatment of Short Bowel Syndrome (SBS) in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone that is approved for this indication. (See Dosage and Administration). Glutamine and recombinant human growth hormone therapy should be used in conjunction with optimal management of Short Bowel Syndrome. Optimal management of Short Bowel Syndrome may include a specialized oral diet, enteral feedings,

parenteral nutrition, fluid and micronutrient supplements. A specialized oral diet may consist of a high carbohydrate, low-fat diet, adjusted for individual patient requirements and preferences.

PRECAUTIONS

General

In patients with SBS, NutreStore ™ should only be taken under the direction of a physician, registered dietician, or nutritionist. NutreStore ™ is not for parenteral use.

Laboratory Tests

Routine monitoring of renal and hepatic function is recommended in patients receiving IPN, particularly in those with renal or hepatic impairment. Glutamine is metabolized to glutamate and ammonia which may increase in patients with hepatic dysfunction.

Drug Interactions

Formal drug interaction studies have not been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential of L-glutamine. Studies to evaluate its potential for impairment of fertility or its mutagenic potential have not been conducted.

Pregnancy: Teratogenic Effects: Pregnancy Category C:

Animal reproduction studies have not been conducted with glutamine. It is also not known whether glutamine can cause fetal harm when administered to a pregnant woman or whether it can affect reproduction capacity. Glutamine should be given to a pregnant woman only if clearly needed.

Labor and Delivery

The effect of L-glutamine on labor and delivery is unknown.

Nursing Mothers

It is not known whether L-glutamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when L-glutamine is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of L-glutamine in pediatric patients has not been established.

Geriatric Use

The clinical trial enrolled SBS patients between the ages of 20 and 75 years. Only 8 of the 41 subjects evaluated were ≥ 65 years of age. The clinical trial of oral glutamine did not include sufficient numbers of subjects aged 65 years and over to determine if they respond differently

than younger subjects. In general, dose selection for an elderly patient should be individualized, because of the greater frequency of decreased hepatic, renal, or cardiac function, as well as concomitant disease in this population.

ADVERSE REACTIONS

Table 3 provides the number of subjects by system-organ class experiencing at least one adverse event during the 4-week treatment period of the SBS study. To be listed in Table 3, an adverse event must have occurred in more than 10% of subjects in any treatment group.

Table 3

Controlled Trial Adverse Events – Initial 4 Week Treatment Period

Adverse Experiences	Group A rhGH+SOD[1] N=16 n (%)	Group B rhGH+SOD[GLN][1] N=16 n (%)	Group C SOD[GLN][1] N=9 n (%)
Total Number of Subjects with At Least One AE	16 (100)	16 (100)	8 (89)
Body as a Whole: General Disorders	**15 (94)**	**15 (94)**	**4 (44)**
Edema, Peripheral	11 (69)	13 (81)	1 (11)
Edema, Facial	8 (50)	7 (44)	0 (0)
Pain	3 (19)	1 (6)	1 (11)
Chest Pain	3 (19)	0 (0)	0 (0)
Fever	0 (0)	1 (6)	2 (22)
Back Pain	1 (6)	0 (0)	1 (11)
Flu-like Disorder	0 (0)	1 (6)	1 (11)
Malaise	2 (13)	0 (0)	0 (0)
Edema, Generalized	2 (13)	0 (0)	0 (0)
Abdomen Enlarged	0 (0)	0 (0)	1 (11)
Allergic Reaction	0 (0)	0 (0)	1 (11)
Rigors (Chills)	0 (0)	0 (0)	1 (11)
Gastrointestinal System Disorders	**12 (75)**	**12 (75)**	**6 (67)**
Flatulence	4 (25)	4 (25)	2 (22)
Abdominal Pain	4 (25)	2 (13)	1 (11)
Nausea	2 (13)	5 (31)	0 (0)
Tenesmus	1 (6)	3 (19)	3 (33)
Vomiting	3 (19)	3 (19)	1 (11)
Hemorrhoids	1 (6)	0 (0)	1 (11)
Mouth Dry	1 (6)	0 (0)	1(11)
Musculoskeletal System Disorders	**7 (44)**	**7 (44)**	**1 (11)**
Arthralgia	7 (44)	5 (31)	0 (0)
Myalgia	2 (13)	0 (0)	1 (11)
Resistance Mechanism Disorders	**6 (38)**	**3 (19)**	**4 (44)**
Infection	0 (0)	1 (6)	3 (33)
Infection Bacterial	3 (19)	0 (0)	1 (11)
Infection Viral	1 (6)	2 (13)	0 (0)
Moniliasis	2 (13)	0 (0)	0 (0)
Application Site Disorders	**5 (31)**	**4 (25)**	**1 (11)**
Injection Site Reaction	3 (19)	4 (25)	1 (11)
Injection Site Pain	5 (31)	0 (0)	0 (0)
Central and Peripheral Nervous System Disorders	**4 (25)**	**4 (25)**	**2 (22)**
Dizziness	1 (6)	2 (13)	0 (0)
Headache	1 (6)	1 (6)	1 (11)
Hypoasthesia	1 (6)	1 (6)	1 (11)
Skin and Appendages Disorders	**4 (25)**	**4 (25)**	**2 (22)**
Rash	1 (6)	2 (13)	0 (0)
Pruritis	0 (0)	1 (6)	1 (11)
Sweating Increased	2 (13)	0 (0)	0 (0)
Nail Disorder	0 (0)	0 (0)	1 (11)
Respiratory System Disorders	**1 (6)**	**5 (31)**	**1 (11)**
Rhinitis	0 (0)	3 (19)	1 (11)
Metabolic and Nutritional Disorders	**3 (19)**	**1 (6)**	**1 (11)**
Dehydration	3 (19)	0 (0)	1 (11)
Thirst	0 (0)	0 (0)	1 (11)
Urinary System Disorders	**2 (13)**	**1 (6)**	**1 (11)**
Pyelonephritis	0 (0)	0 (0)	1 (11)
Psychiatric Disorders	**1 (6)**	**0 (0)**	**2 (22)**
Depression	0 (0)	0 (0)	2 (22)
Reproductive Disorders, Female	**2 (13)**	**0 (0)**	**1 (11)**
Breast Pain Female	1 (6)	0 (0)	1 (11)
Hearing and Vestibular Disorders	**0 (0)**	**2 (13)**	**0 (0)**
Ear or Hearing Symptoms	0 (0)	2 (13)	0 (0)

SOD[GLN] = Specialized Oral Diet supplemented with Glutamine; rhGH + SOD = Human Growth Hormone plus Specialized Oral Diet; rhGH + SOD[GLN] = Human Growth Hormone plus Specialized Oral Diet supplemented with Glutamine

GROUP A: rh-GH + SOD for 4 weeks followed by SOD for 12 weeks.
GROUP B: rh-GH + SOD [GLN] for 4 weeks followed by SOD [GLN] for 12 weeks.
GROUP C: rh-GH placebo + SOD[GLN] for 4 weeks followed by SOD[GLN] for 12 weeks.

Table 4 summarizes the number of subjects by system-organ class who experienced an adverse event during weeks 5 to18 of the randomized, controlled SBS study. To be listed in Table 4, an adverse event must have occurred in more than 10% of subjects in any treatment group.

Table 4

Controlled Trial Adverse Events –Weeks 5 to 18

Adverse Experiences	Group A rhGH+SOD[1] N=15 n (%)	Group B rhGH+SOD[GLN][1] N=16 n (%)	Group C SOD[GLN][1] N=9 n (%)
Total Number of Subjects with At Least One AE	12 (80)	13 (81)	7 (78)
Gastrointestinal System Disorders	**7 (47)**	**7 (44)**	**3 (33)**
Nausea	3 (20)	0 (0)	2 (22)
Vomiting	2 (13)	3 (19)	0 (0)
Abdominal Pain	3 (20)	1 (6)	0 (0)
Tenesmus	0 (0)	3 (19)	1 (11)
Pancreatitis	0 (0)	1 (6)	1 (11)
Constipation	0 (0)	0 (0)	1 (11)
Crohn's Disease Aggravated	0 (0)	0 (0)	1 (11)
Gastric Ulcer	0 (0)	0 (0)	1 (11)
Gastrointestinal Fistula	0 (0)	0 (0)	1 (11)
Resistance Mechanism Disorders	**6 (40)**	**5 (31)**	**5 (56)**
Infection Bacterial	0 (0)	2 (13)	3 (33)
Infection Viral	3 (20)	1 (6)	1 (11)
Infection	1 (7)	2 (13)	1 (11)
Sepsis	3 (20)	1 (6)	0 (0)
Body as a Whole: General Disorders	**4 (27)**	**2 (13)**	**1 (11)**
Fever	2 (13)	1 (6)	1 (11)
Fatigue	2 (13)	0 (0)	0 (0)
Respiratory System Disorders	**2 (13)**	**4 (25)**	**1 (11)**
Rhinitis	1 (7)	3 (19)	0 (0)
Laryngitis	0 (0)	0 (0)	1 (11)
Pharyngitis	0 (0)	0 (0)	1 (11)
Reproductive Disorders, Female	**0 (0)**	**4 (25)**	**1 (11)**
Vaginal Fungal Infection	0 (0)	0 (0)	1 (11)
Skin and Appendages Disorders	2 (13)	2 (13)	1 (11)
Rash	1 (7)	0 (0)	1 (11)
Musculoskeletal System Disorders	**2 (13)**	**2 (13)**	**0 (0)**
Arthralgia	2 (13)	2 (13)	0 (0)
Psychiatric Disorders	**0 (0)**	**1 (6)**	**1 (11)**
Depression	0 (0)	0 (0)	1 (11)
Insomnia	0 (0)	0 (0)	1 (11)
Urinary System Disorders	**0 (0)**	**0 (0)**	**2 (22)**
Pyelonephritis	0 (0)	0 (0)	1 (11)
Renal Calculus	0 (0)	0 (0)	1 (11)

Application Site Disorders	**0 (0)**	**0 (0)**	**1 (11)**
Injection Site Reaction	0 (0)	0 (0)	1 (11)
Liver and Biliary System Disorders	**0 (0)**	**0 (0)**	**1 (11)**
Hepatic Function Abnormal	0 (0)	0 (0)	1 (11)
Vascular Extracardiac Disorders	**0 (0)**	**0 (0)**	**1 (11)**
Vascular Disorder	0 (0)	0 (0)	1 (11)

GROUP A: rh-GH + SOD for 4 weeks followed by SOD for 12 weeks.
GROUP B: rh-GH + SOD [GLN] for 4 weeks followed by SOD [GLN] for 12 weeks.
GROUP C: rh-GH placebo + SOD[GLN] for 4 weeks followed by SOD[GLN] for 12 weeks.

[1] **SOD[GLN] = Specialized Oral Diet supplemented with Glutamine; rhGH + SOD = Human Growth Hormone plus Specialized Oral Diet; rhGH + SOD[GLN] = Human Growth Hormone plus Specialized Oral Diet supplemented with Glutamine**

The safety profile in patients receiving oral glutamine with growth hormone was similar to the safety profile in patients receiving growth hormone without glutamine. During the initial 4 week treatment period, 100% of patients receiving growth hormone with and without glutamine reported at least one adverse event (AE), whereas 89% of patients receiving growth hormone placebo with glutamine reported at least one AE. During weeks 5 to 18, 81% of patients receiving growth hormone with glutamine, 80% of patients receiving growth hormone without glutamine and 78% of patients receiving growth hormone placebo with glutamine experienced at least one AE. There were no deaths in this study.

OVERDOSAGE

Single oral doses of glutamine at about 20-22 g/kg, 8-11 g/kg, and 19 g/kg were lethal in mice, rats, and rabbits, respectively.

DOSAGE AND ADMINISTRATION

NutreStore™ should be administered as a cotherapy with recombinant human growth hormone [see the package insert for somatotropin (rDNA origin) for injection for full prescribing information] followed by continued NutreStore™ for up to 16 weeks.

The recommended dosage of NutreStore ™ is 30 g daily in divided doses (5 g taken 6 times each day orally) for up to 16 weeks. Each dose of NutreStore ™ (5g) should be reconstituted in 8-oz (250-mL) of water prior to consumption.

NutreStore™ should be taken with meals or snacks at 2- to 3-hour intervals while awake. The volume of water may be varied according to the patient's preference. In the event of a patient's transient intolerance to oral intake, a dose may be delayed for up to 2 hours. The safety and efficacy of NutreStore™ have not been studied beyond 16 weeks of treatment.

HOW SUPPLIED

NutreStore™ is supplied in preprinted paper-foil-plastic laminate packets containing 5 g of L-glutamine powder.

STORAGE

NutreStore™ (L-glutamine powder for oral solution) should be stored at 25°C (77°F) with excursions allowed to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

For additional information concerning NutreStore™, contact:
Cato Holding Company
4364 South Alston Ave
Durham NC 27713-2280

Manufactured by:
Anderson Packaging, Inc.
4545 Assembly Drive
Rockford, IL 61109

Revised June 2004.

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/s/

Julie Beitz
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