Approval Date

Package Insert for Sodium Oligomannate Capsules

Please read this Package Insert carefully and use only as directed by your physician

[Drug Name]

Generic Name: Sodium Oligomannate Capsules

Trade Name: GV-971

English Name: Sodium Oligomannate Capsules

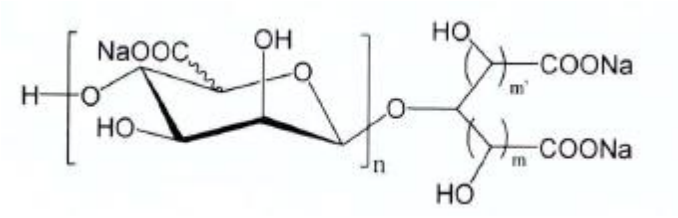
Chinese Pinyin: Ganlutena Jiaonang

[Ingredients]

The main ingredient of this product is sodium oligomannate.

Chemical name: Oligomeric -β-1 → 4-D- mannuronic acid sodium

Chemical structural formula:



Molecular formula: $(C_6H_7O_6Na)n\ (CH_2O)m+m'C_3H_2O_5Na_2$; n=1~9; m=0, 1, 2; m'=0, 1

Molecular weight: 670-880

Excipients: Corn starch, talcum powder, magnesium stearate, gelatin hollow capsule

[Properties]

The content of this drug is off-white to light yellow powder or granules.

[Indications]

To be used for mild to moderate Alzheimer's disease, to improve the patient's cognitive function.

[Specification]

150 mg

[Administration and Dosage]

Oral administration. 3 capsules (450 mg) each time, 2 times a day. Can be taken on an empty stomach or with food.

This drug should be prescribed by a physician who is experienced in the diagnosis and treatment of Alzheimer's disease and be used by the patient as directed by the physician.

The patient should have a reliable caregiver who can monitor him or her in taking the medication from time to time.

The evidence for the clinical safety and efficacy of this drug comes from randomized controlled clinical trials for up to 36 weeks. If the patient needs longer treatment, the physician should re-evaluate the benefits and risks for the patient to continue taking this drug according to the suggestions from the clinical diagnosis and treatment guidelines. If the benefits are obvious and the patient can tolerate [the drug], [the physician] may consider continuing the treatment with this drug; otherwise, [the physician] should consider discontinuation of the treatment with this drug.

Patients with hepatic insufficiency: For patients with mild hepatic insufficiency, there is no need to adjust the dose based on liver function. At present, there has been no study data from patients with moderate and severe hepatic insufficiency. For patients with hepatic insufficiency, during the course of taking this drug, liver function needs to be tested regularly, and if there is any abnormality, it is necessary to seek medical treatment in a timely manner.

Patients with renal insufficiency: For patients with mild renal insufficiency, there is no need to adjust the dose based on renal function. At present, there has been no study data from patients with moderate and severe renal insufficiency. For patients with renal insufficiency, during the course of taking this product, renal function needs to be tested regularly, and if there is any abnormality, it is necessary to seek medical treatment in a timely manner.

[Adverse Reactions]

This Package Insert describes the adverse reactions observed in clinical trials that may be caused by this drug and their approximate incidence. As the clinical trials were conducted under different conditions, the incidence of adverse reactions observed in one clinical trial cannot be directly compared with the incidence of adverse reactions observed in another clinical trial, and may not reflect the actual incidence in clinical practice.

In clinical trials of this drug, a total of 1199 subjects were included. In the clinical trials of this drug for patients with Alzheimer's disease, a total of 577 samples from the drug group were included in the safety analysis. In the clinical trials, the overall incidence of adverse reactions (adverse events related to or possibly related to the study drug as judged by the investigators) was 14.6%, which was not significantly different from the placebo group (18.0%), and the severity of adverse reactions was mild and moderate.

By using MedDRA as a reference, according to system organ classification (SOC) and preferred term classification (PT), in each category, the incidence of adverse reactions is described according to the statistical method recommended by the Council for International Organizations of Medical Sciences (CIOMS) as follows: very common (≥10%), common (1%-10%, inclusive of 1%), occasional (0.1%-1%, inclusive of 0.1%), rare (0.01%-0.1%, inclusive of 0.01%), and very rare (<0.01%). Table 1 and Table 2 list the incidences of adverse reactions (excluding laboratory test abnormalities) and laboratory test abnormalities, respectively.

Table 1 Adverse Reactions of Subjects in Clinical Trials of Sodium Oligomannate Capsules for Patients with Alzheimer's Disease (Excluding Laboratory Test Abnormalities)

Adverse Reaction Name	Sodium Oligomannate Group (n=577)	Placebo Group (n=495)
Common (1%-10%, inclusive of 1%)		

Cardiovascular System		
Arrhythmia	1.4%	2.4%
Gastrointestinal System		
Dry Mouth	1.0%	0.4%
Urinary System		
Hematuria	1.0%	0.2%
Occasional (0.1%-1%, inclusive of 0.1%)		
Hepatobiliary System		
Liver Damage	0.2%	0.0%
Discomfort in liver area	0.2%	0.0%
Cardiovascular System		
Myocardial Ischemia	0.2%	0.0%
Hypotension	0.2%	0.0%
Gastrointestinal System		
Constipation	0.2%	0.2%
Gastritis	0.2%	0.0%
Gastroesophageal Reflux	0.2%	0.0%
Diarrhea	0.2%	0.4%
Loss of Appetite	0.2%	0.2%
Nutrition and Metabolism		
Type 2 Diabetes	0.2%	0.0%
Weight Loss	0.2%	0.2%
Neuropsychiatric System		
Dizziness	0.9%	1.2%
Sleep Disorder	0.3%	0.2%
Irritability	0.3%	0.0%
Lethargy	0.2%	0.6%
Headache	0.2%	0.4%
Epilepsy	0.2%	0.0%
Muscle Weakness	0.2%	0.2%
Tremor	0.2%	0.0%
Head Discomfort	0.2%	0.0%
Infection		
Urinary Tract Infection	0.7%	0.6%
Lung Infection	0.2%	0.0%
Urinary System		
Proteinuria	0.5%	0.2%
Crystalluria	0.3%	0.2%
Ear and Labyrinth		
Hearing Loss	0.2%	0.2%
Giddiness	0.2%	0.0%
Skin and Subcutaneous Tissue		
Itching	0.3%	0.2%
Rash	0.2%	0.8%
Reproductive System and Mammary Gland		
Hyperplasia of Mammary Gland	0.2%	0.2%

Respiratory System, Chest and Mediastinum		
Nasal Congestion	0.2%	0.0%
Chest Discomfort	0.2%	0.2%
Whole Body and Administration Site		
Peripheral Edema	0.2%	0.2%

Table 2 Laboratory Test Abnormalities of Subjects in Clinical Trials of Sodium Oligomannate Capsules for Patients with Alzheimer's Disease

Adverse Reaction Name	Sodium Oligomannate Group (n=577)	Placebo Group (n=495)
Common (1%-10%, inclusive of 1%)		
Hepatobiliary System		
Elevated Alanine Aminotransferase	1.9%	0.4%
Elevated Aspartate Aminotransferase	1.7%	0.8%
Elevated *y*-glutamyltransferase	0.7%	0.4%
Elevated Bilirubin	1.2%	0.2%
Nutrition and Metabolism		
Elevated Low-Density Lipoprotein	1.2%	1.0%
Elevated Cholesterol	1.2%	1.2%
Elevated Triglycerides	0.5%	1.8%
Occasional (0.1%-1%, inclusive of 0.1%)		
Hepatobiliary System		
Elevated Alkaline Phosphatase	0.2%	0.2%
Cardiovascular System		
Elevated Hydroxybutyrate Dehydrogenase	0.2%	0.2%
Elevated Lactate Dehydrogenase	0.2%	0.2%
Nutrition and Metabolism		
Elevated Blood Sugar	0.9%	1.2%
Elevated Uric Acid	0.2%	0.2%
Urinary System		
Elevated Serum Urea Nitrogen	0.2%	0.6%

The severe adverse reaction occurred in patients treated with this drug was pneumonia, which occurred in 1 case with an incidence of 0.2%.

The adverse reactions led to suspension of medication in 3 patients (0.5%) who were taking this drug. The adverse reactions that led to suspension of medication included: dizziness (1 case, 0.2%), seizures (1 case, 0.2%), and gastritis (1 case, 0.2%)

The adverse reactions led to discontinuation of treatment in 7 patients (1.2%) who were taking this drug. The adverse reactions that led to discontinuation of treatment included: decreased platelet counts (1 case, 0.2%), type 2 diabetes (1 case, 0, 2%), acid reflux (1 case, 0.2%), abnormal liver function (2 cases, 0.3%), irritability (1 case, 0.2%), and rash (1 case, 0.2%).

[Contraindications]

This drug should not be used by people who are allergic to its main ingredient or excipients.

[Precautions]

1. This drug should be prescribed by a physician who is experienced in the diagnosis and treatment of Alzheimer's disease and be used by the patient as directed by the physician.

2. The patient should have a reliable caregiver who can monitor him or her in taking the medication from time to time.

3. The evidence for the clinical safety and efficacy of this drug comes from randomized controlled clinical trials for up to 36 weeks. If the patient needs longer treatment, the physician should re-evaluate the benefits and risks for the patient to continue taking this drug according to the suggestions from the clinical diagnosis and treatment guidelines. If the benefits are obvious and the patient can tolerate [the drug], [the physician] may consider continuing this drug treatment; otherwise, [the physician] should consider discontinuation of the treatment with this drug.

4. So far, no studies have been conducted on the application of this drug in the treatment of other types of dementia or memory impairment and the efficacy of the application of Sodium Oligomannate Capsules in patients with other types of dementia or memory impairment (such as age-related cognitive function decline) has not been fully observed.

5. Cardiovascular system: Of the 818 subjects randomized in the phase III clinical trial of this drug, a total of 78 subjects experienced a transient QT / QTc interval prolongation during the trial, of which 38 were in the drug group and 40 were in the placebo group. Although no clear cardiovascular risk related to the mechanism of this drug has been observed, due to the limited number of people currently taking this drug, if patients experience cardiovascular system abnormalities when taking this drug, they should seek medical treatment in a timely manner.

6. Immune system: This drug may have a certain immunomodulatory effect. For patients who are taking immunological preparations, it may affect the efficacy of the immunological preparations. Among the subjects in the phase III clinical trial of this drug, there were no significant differences in the incidences of inflammation or immune-related adverse events (including immune system disorders, infections, and infectious diseases classified according to MedDRA) between the two groups. In the phase III clinical trial of this drug, 0.3% (2/577 cases) of patients treated with this drug developed autoimmune encephalitis. Although the investigators judged that it was probably not related to the drug, we recommend that patients taking this drug pay attention to the risks associated with encephalitis.

7. Digestive system: This drug may take effect in the treatment through remodeling the intestinal flora. Therefore, using it in combination with other drugs that may change the intestinal flora (such as antibiotics or other drugs that may cause intestinal flora imbalance) may affect the efficacy of this drug.

8. Impact on the ability to drive vehicles and operate machines: Dementia may affect the ability to drive or operate machines. In clinical trials of this drug, there were reports of patients experiencing dizziness, lethargy and muscle weakness. Therefore, physicians should routinely assess patients' ability to drive vehicles or operate complex machines.

9. Use in combination with cholinergic drugs: At present, there has been no study data on the use of this drug in combination with acetylcholinesterase inhibitors, cholinergic agonists or inhibitors.

[Administration for Pregnant and Lactating Women]

Pregnancy

At present, there has been no study data on the use of this drug in pregnant women. Although this drug has not been found to have reproductive toxicity in animal testing, it should not be taken during pregnancy unless clearly needed and only if there is a favorable risk-benefit ration.

Lactation

At present, there has been no study data on the use of this drug in lactating women. This drug was found to be secreted from the milk of lactating rats, so it should be used with caution in lactating women.

Fertility

At present, there has been no study data on the effect of this drug on human fertility.

[Pediatric Use]

There has been no study data on the use of this drug in children and adolescents.

[Geriatric Use]

See **[Administration and Dosage].**

[Drug Interactions]

At present, there have been no studies on drug interactions in the human body. The in vitro trials showed that: sodium oligomannate has no inhibitory effect on CYP450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) and no induction effect on CYP450 enzymes (CYP1A2, 2B6, and 3A4). Sodium oligomannate is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, P-gp, and BCRP. Sodium oligomannate has no inhibitory effect on OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT2, P-gp, and BCRP.

[Drug Overdose]

There had been limited experience with drug overdose from clinical trials. Healthy young subjects had safety tolerance with a single dose of 1500 mg and continuous administration for 5 days (1500 mg / day). If a drug overdose occurs, the drug should be discontinued immediately and medical treatment should be sought.

[Clinical Trials]

This drug underwent a phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group, 36-week dosing period clinical trial in patients with mild to moderate Alzheimer’s disease. During the trial, the dosing regimen of the drug group was 450 mg / time, twice a day (daily dose was 900 mg / day), and the drug administration continued for 36 weeks. The main efficacy indicator was the change in the patient’s cognitive function scale (ADAS-Cog) score, and the secondary efficacy indicators included changes in overall status (CIBIC-Plus),

ability to perform daily activities (ADCS-ADL), and neuropsychiatric inventory (NPI). During the trial, randomized a total of 818 patients, with mild to moderate Alzheimer's disease (57.2% female; mean age was 70) from 34 study sites in China, were randomized. Among them, 678 subjects completed the trial (334 in the drug group and 344 in the placebo group). The cognitive function of the patients in the drug group became significantly better compared with that of the placebo group. The improvement was seen starting from week 4 of the administration of the drug, and the average difference between the groups was 0.62, P<0.05. The improvement was more significant at the end of 36 weeks, and the average difference between the groups was 2.54, P<0.0001.

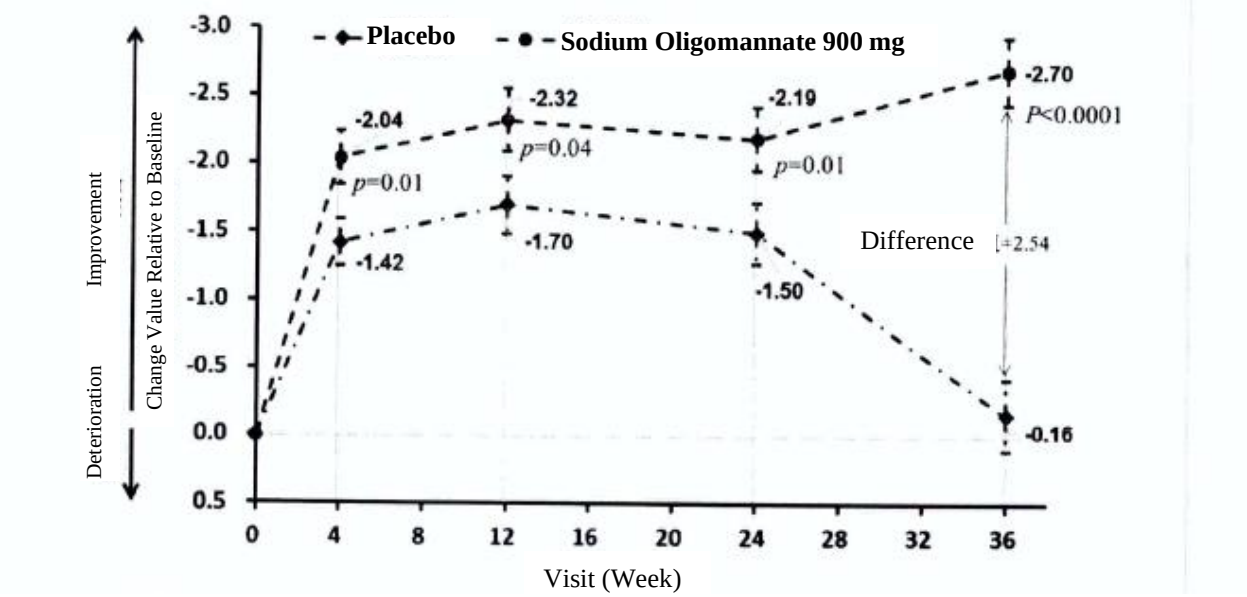


Figure. Trend Graph of Change in Measured Value Relative to Baseline at Each Visit for Main Efficacy Indicator ADAS-Cog of Phase III Clinical Trial of Sodium Oligomannate Capsules (FAS Set)

[Pharmacology and Toxicology]

Pharmacological Action

The animal testing results showed that sodium oligomannate helps improve the learning and memory of amyloid-β (Aβ), D-galactose-induced memory impairment model mice and scopolamine-induced memory impairment model rats.

The mechanism of action of sodium oligomannate on Alzheimer's disease is still unclear.

Sodium oligomannate 100 mg / kg was administered orally to 5X FAD transgenic mice continuously for one month during the neuroinflammation period (7 months of age), and changes in the intestinal flora were seen. The proportion of intestinal lamina propria lymphocytes Th1, the proportion of Th1 cells in the brain and peripheral blood decreased, and the level of amyloid (Aß) deposition and Tau protein phosphorylation in the brain decreased.

Toxicological Study

Genotoxicity

The results from the sodium oligomannate Ames test, chromosome aberration test of Chinese hamster lung fibroblasts in vitro, and bone marrow micronucleus test in mice were negative.

Reproductive Toxicity

In rat fertility and early embryonic development toxicity tests, sodium oligomannate 300, 1000, and 3000 mg / kg were orally administered to male rats 4 weeks before mating until mating success and to female rats 2 weeks before mating until the 6th day of pregnancy. No effects on female and male fertility and early embryonic development were seen.

In the embryo-fetal development toxicity test, sodium oligomannate 120, 480, and 1920 mg / kg were orally administered to rats from the 6th to the 15th day of pregnancy, and sodium oligomannate 120, 400, 1200 mg / kg were orally administered to rabbits from the 6th to 18th day of pregnancy. No teratogenicity and no effects on embryo-fetal development were seen.

In the perinatal toxicity test of rats, sodium oligomannate 300, 1000, 3000 mg / kg were orally administered to rats from the 6th day of pregnancy to the 21st day of lactation. No significant effects on the childbirth and lactation of F0 generation female rats, the growth, development, neurobehavioral development and reproductive capacity of F1 generation offspring, and the survival of F2 generation offspring were seen.

Carcinogenicity

In the carcinogenicity test with oral administration in Tg.rasH2 transgenic mice for 26 weeks, when the doses of sodium oligomannate were 0, 300, 1000, and 3000 mg / kg, the incidence of spleen angiosarcoma increased in a dose-dependent manner (incidences were 0/50, 1/50, 2/50, and 5/50, respectively). The relevance of this result to that of humans is still unclear.

The carcinogenicity test with oral administration in rats for 104 weeks has not been completed yet.

[Pharmacokinetics]

Absorption

The oral bioavailability of Sodium Oligomannate Capsules is low. Food has no significant effect on the absorption of sodium oligomannate.

In healthy subjects who took 450 mg, 600 mg, and 750 mg of Sodium Oligomannate Capsules orally, the peak time of sodium oligomannate in plasma was 2.6-5.4 hours, their C_{max} values were respectively: 96.6 ± 44.4 ng / mL, 122.7 ± 72.3 ng / mL, and 112.7 ± 55.9 ng / mL; their $AUC_{0-\infty}$ values were respectively: 1992.1 ± 2055.7 ng * h / mL, 1607.4 ± 808.0 ng * h / mL, 2252.4 ± 1712.4 ng * h / mL. The half-life of sodium oligomannate was about 11-22 hours.

Distribution

After a single oral administration of 450 mg, 600 mg, and 750 mg of Sodium Oligomannate Capsules in healthy subjects, the apparent volume of distribution of sodium oligomannate was approximately 6142.7-9608.7 L.

Metabolism

So far, there has been no study data on human metabolites.

Excretion

Excretion pathways are still not very clear. After a single oral administration of Sodium Oligomannate Capsules (450mg-750mg) in healthy subjects, the apparent clearance of sodium oligomannate was about 405.7-482.3 L / h. After continuous administration for 5 days (Bid), the apparent clearance of sodium oligomannate was about 117.4-158.0 L / h, and the accumulation factor was about 2.1-2.6.

Specific Population

Pharmacokinetic studies have not been conducted in specific populations (such as those with hepatic insufficiency or renal insufficiency).

[Storage]

Sealed tightly and stored at below 25 ℃.

[Packaging]

Aluminum-plastic-aluminum packaging.

14 capsules / plate, 3 plates / box.

[Validity Period]

24 months.

[Executing Standard]

YBHxxxxxxxx

[Approval Number]

NMPA Approval Number Hxxxxxxxxx

[Manufacturer]

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