Vayacog®

DESCRIPTION

Vayacog® is an orally administered medical food for the clinical dietary management of complex lipid imbalances associated with early memory impairment. Vayacog® is a specially formulated and processed composition designed to address the distinct, medically determined lipid nutritional requirements of people with early memory impairment, the dietary management of which cannot be achieved by modification of the normal diet or use of dietary supplements.

Each Vayacog® capsule provides:

Lipicogen® ..... 100 mg

Lipicogen® is a proprietary composition containing phosphatidylserine (PS) conjugated to omega-3 fatty acids enriched with Docosahexaenoic acid (DHA).

MEDICAL SUPERVISION

Vayacog® is a medical food product intended for use under supervision of a physician or licensed healthcare provider.

LIPID IMBALANCES IN ADHD

Scientific evidence demonstrates that that low levels of certain lipids are associated with Early Memory Impairment (EMI), part of a progressive decline in cognitive function. EMI is characterized by elevated oxidative stress and brain and body inflammation leading to abnormalities in lipid metabolism, including increased lipid degradation and reduced lipid synthesis [1-5].
Compared to healthy individuals of the same age, individuals with EMI have lower levels of certain lipids [6-10]. These lipids, found primarily in the brain, play an essential role in neuronal health and memory functions. It's been demonstrated that brains derived from cognitively deteriorated patients contain a significantly lower percentage of the lipid phosphatidylserine (PS) attached to Docosahexaenoic acid (DHA), or PS-DHA, as compared to healthy individuals [7, 9]. Reduced PS-DHA levels in the brain have implications in membrane structure and function, where PS-DHA is believed to play an important role for proper cognitive function. These complex lipid imbalances may represent a major modifiable factor underlying losses in brain function. Vayacog® is a proprietary lipid composition of Phosphatidylserine-Omega-3 (PS-Omega-3), enriched with DHA, that has been specially designed to efficiently deliver these essential lipids to the brain in order to support and maintain proper brain function [7, 9, 11-15].
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CHEMICAL STRUCTURE

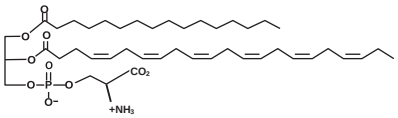

Figure 1. Schematic structure of phosphatidylserine conjugated to DHA.

INGREDIENTS

Phosphatidylserine (PS), maltodextrin, hydroxypropyl methylcellulose, silicon dioxide, Contains less than 1% of titanium dioxide (color), sunflower oil, and antioxidants to inhibit oxidation: mixed tocopherols (D-alpha-tocopherol, D-beta-tocopherol, D-gamma-tocopherol, D-delta-tocopherol), ascorbyl palmitate, rosemary extract (rosemary leaf, propylene glycol, distilled monoglycerides).
Vayacog® capsules contain soy and fish (Herring and/or Blue Whiting)
Vayacog® capsules do not contain sugar, lactose, yeast or gluten.

PHARMACOLOGY

- **Mechanism of Action**

Phosphatidylserine (PS) in the mammalian nervous system, which is characterized by relatively high levels of DHA, has been implicated in numerous membrane related functions, such as maintaining the integrity of cell membranes, cell excitability and cell-to-cell recognition and communication [12]. While the exact mechanism by which PS exerts its effects is not fully understood, PS has been found to regulate key proteins in neuronal membranes, including sodium/calcium ATPase [15] and protein kinase C [11, 14] which undertake crucial functions in diverse signal transduction pathways. Similarly, PS interacts with Raf-1 protein kinase to promote a cascade of reactions that are believed to be involved in cell survival [13]. Additionally, PS has been found to influence neurotransmitter activity, such as the release of acetylcholine, dopamine and noradrenaline [16-18] and to increase brain glucose levels [19]. Moreover, administration of a specially processed formulation consisting of PS conjugated to omega 3 fatty acids was found to significantly increase DHA levels in the brains of rats [20]. DHA brain and plasma levels are reported to be positively associated with cognitive performance [6, 8-10].
Interestingly, it was recently reported that in brains derived from cognitively deteriorated patients, there is significantly lower percentage of DHA specifically in PS conjugated to DHA (PS-DHA) as compared to healthy individuals [7]. The reduced PS-DHA levels in these brains may represent a key biochemical modification underlying losses in brain function. Indeed, it was recently suggested that PS-DHA serve as a neuro-protective agent in neural tissue, promoting neural survival [21].

- **Absorption and Metabolism**

Phospholipids can break down to different levels or remain intact and be subsequently absorbed in the circulation and brain [22, 23]. Following dietary ingestion of PS, fatty acids esterified to the PS molecule can be hydrolyzed by pancreatic digestive enzymes, forming lyso-PS and free fatty acids [24, 25]. Once the lyso-PS is absorbed by the mucosal cells of the intestine, it can be reacylated into PS [26], while some of it may be converted into other phospholipids [27]. PS and other phospholipids formed inside the enterocytes can either be transported in the lymphatic circulation as chylomicrons [28, 29] or in the portal circulation, and subsequently enter the general circulation for distribution to the body. Available evidence indicates that ingested PS reaches the systemic circulation and is incorporated into the phospholipid pool [22].

- **Drug Interactions**

There are no known contraindications, however Vayacog® could potentially interact with cholinergic and anticholinergic drugs. It is recommended to consult with a physician about Vayacog® interactions that may apply to specific medical conditions.

- **Toxicity**

The safety profile of PS conjugated to omega-3 (PS-Omega-3) is supported by several pre-clinical studies [30-31]. Repeat-dose safety studies in rats and dogs showed that oral administration of PS-Omega-3 at doses up to 1000 mg/kg/day for up to 6 months was without any significant adverse effects of toxicological concern [30]. The results of teratogenicity studies in rats at doses up to 200 mg/kg/day and in rabbits at doses up to 450 mg/kg/ day showed that oral administration of PS-Omega-3 did not affect embryonic and fetal development [30]. The mutagenic potential of PS-Omega-3 was investigated in several cell types and revealed no significant findings. In a micronucleus test, PS-Omega-3 was administered to mice at total dosages of 30, 150 and 300 mg/kg in two equal doses separated by 24-hours. The results of the study did not reveal any evidence of mutagenic potential or bone marrow toxicity [30].

CLINICAL EXPERIENCE

The Vayacog® study was designed as a single-center randomized double blind placebo-controlled study of 15 weeks followed by an open label extension (OLE) of an additional 15 weeks. In the double-blind phase, 157 men and women (aged 50-90 years) with memory complaints were randomly assigned to receive Vayacog® or placebo (three capsules a day). In order to evaluate the effect of a reduced dose, an OLE was conducted in 122 participants, assigned to consume one Vayacog® capsule per day. Cognitive performance was evaluated using the Rey Auditory Verbal Learning Test (Rey-AVLT) in the double-blind phase and using a computerized cognitive assessment tool in the OLE [32, 33].
Following 15 weeks of Vayacog® administration, a significant improvement in memory abilities was observed in the Vayacog® group as compared to the placebo group (Fig. 2), specifically in a subgroup of participants with relatively good performance and cognitive status at the beginning of the study (Fig. 3).
In addition, results from the OLE show that memory abilities in participants switching from placebo (during the double-blind phase) to Vayacog® (1 capsule/day) were significantly improved as well (Fig. 4).

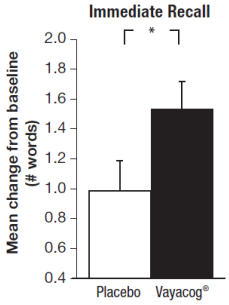

Figure 2. Effect of Vayacog® (n=60) versus placebo (n=62) on Rey-AVLT results following 15 weeks of administration (per-protocol participants) during the double-blind phase. Values are presented as mean change from baseline ± standard error (SE). * p< 0.05 based on ANCOVA controlled for Mini-Mental State Examination (MMSE) and baseline mean score.

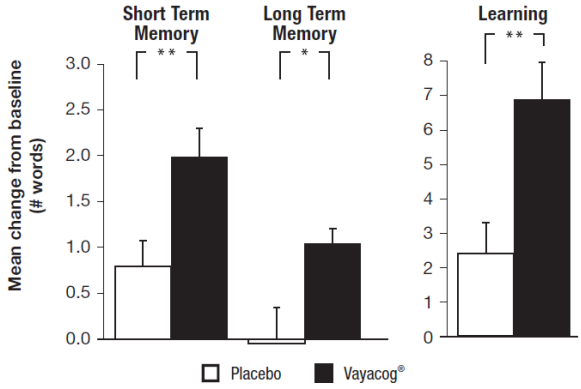

Figure 3. Effect of Vayacog® (n=40) versus placebo (n=38) on Rey-AVLT results following 15 weeks administration during the double-blind phase, within a subgroup of participants with relatively good cognitive status prior to treatment. Values are presented as mean change from baseline ± SE. * p<0.05 and ** p<0.01 based on two-tailed T-test comparison of the mean difference from baseline for independent samples.

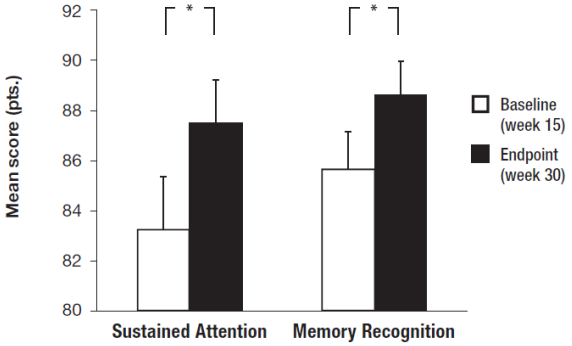

Figure 4. Effect of Vayacog® on parameters of the computerized cognitive assessment tool following 15 weeks administration during the open-label phase (n=55, participants who consumed placebo during the double-blind phase). Values are presented as mean ± SE. * p < 0.05 based on paired two tailed Student's t-test.

SAFETY ASSESSMENT

Safety was evaluated by clinical laboratory measurements including biochemical and hematological parameters and by adverse events recording, physical examination and measurement of vital signs and weight [34]. No significant differences were found in any of the tested safety parameters between the study groups, or

within each group during the double-blind phase. At the end of the open label phase, there was a reduction in resting diastolic blood pressure and a slight weight gain among participants who consumed Vayacog® for 30 weeks [34]. Additional safety information is detailed in the Adverse Events section.

CONTRAINDICATIONS
Vayacog® is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to Vayacog® or any of its components.

PRECAUTIONS
- Safety and effectiveness of Vayacog® in pediatric patients or pregnant or lactating patients have not been established. Therefore, Vayacog® is not recommended for these populations.
- Vayacog® should be used with caution in patients with known hypersensitivity to soy and/or fish.

DRUG ABUSE
Vayacog® does not have any known drug abuse or withdrawal effects.

ADVERSE EVENTS
The adverse events of Vayacog® were evaluated in a randomized, double blind, placebo-controlled study of 15 weeks followed by an open label extension of additional 15 weeks [34].
Adverse events reported during the course of the double-blind phase: 10 participants from the Vayacog® group and 8 participants from the placebo group were classified by the study physicians as suffering from treatment related, or probably related, adverse events (16 and 11 adverse events, respectively). There were no significant differences between the study groups in the number of participants who reported an adverse event (P=0.637) or in the number of reported adverse events (P=0.472).
Adverse events reported during the course of the open-label extension: 3 participants reported 3 adverse events that were classified by the study physicians as related or probably related to the study treatment.

Study design	Double-blind phase		Open-label extension
30-WEEK STUDY PERIOD			
Treatment Group / Adverse event*	Placebo [n=79]	Vayacog® [n=78]	Vayacog® [n=122]
Gastrointestinal discomfort	2	13	1
Rash	0	1	0
Increased appetite and weight	1	0	0
Strange general feeling	1	0	0
Headache	2	1	1
Dizziness	2	0	0
Mood swings	1	0	0
Weight loss	0	1	0
Tenesmus	0	0	1
Redness in the mouth	1	0	0
Pruritus	1	0	0
Sum	*11 events in 8 participants*	*16 events in 10 participants*	*3 events in 3 participants*

Table 1. Adverse events reported during the course of the double-blind and the open label phase.

***Judged by the study physicians as related or probably related to the study treatment**

DOSAGE AND ADMINISTRATION
Usual dose is one capsule daily or as directed by a physician.

INDICATION AND USAGE
Vayacog®, an orally administered medical food for the clinical dietary management of Early Memory Impairment, is designed to address the distinct, medically determined nutritional requirements of Early Memory Impairment, the dietary management of which cannot be achieved by modification of the normal diet alone.

HOW SUPPLIED
Available as hard-shell capsules. Supplied in bottles of 30 or 90 capsules.

Item No. (30 capsules)	75959-344-30	Use under Medical supervision
Item No. (90 capsules)	75959-344-90	Use under medical supervision

STORAGE
Store at up to 77ºF (25ºC). Protect from light and moisture.

WARNING
Keep this product out of the reach of children.

Distributed by: VAYA Pharma™ Inc.
10480 Little Patuxent Pkwy
Columbia, Maryland 21044

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