

Vayarin®

DESCRIPTION

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

Each Vayarin® capsule provides:

Lipirinen® 75 mg

Lipirinen® is a proprietary composition containing phosphatidylserine (PS) conjugated to omega-3 fatty acids enriched with Eicosapentaenoic acid (EPA).

MEDICAL SUPERVISION

Vayarin® 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 low levels of certain lipids are associated with Attention Deficit Hyperactivity Disorder (ADHD). While ADHD is a complex disorder, the etiology of which is multi-factorial, ADHD has been shown to be associated with metabolic disturbances such as lipid and glucose metabolism [1, 2]. The abnormalities in lipid metabolism that may occur in ADHD are associated with increased oxidative stress, higher rates of lipid degradation and decreased synthesis of phospholipids containing omega-3 fatty acids. Reduced levels of phosphatidylserine containing omega-3 fatty acids (PS-Omega-3) have implications in membrane structure and function, where they are believed to play an important role in signal transduction pathways, secretory vesicle release, and cell growth regulation [3, 4].

Compared to healthy children of the same age, children with ADHD have lower blood levels of omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs) [5-13]. These lipids, found also in the brain, play an essential role in brain development and function. In turn, it has been reported that omega-3 fatty acid deficiency is correlated to decreased brain phosphatidylserine, which is mainly in the form of PS-Omega-3 [14, 15]. PS-Omega-3 play an important role in the functioning of neuronal membranes, such as signal transduction, secretory vesicle release, cell-to-cell communication, and cell growth regulation [4]. Thus, reduced levels of PS-Omega-3 and omega-3 may represent a complex lipid imbalance playing a role in the etiology/pathogenesis of ADHD.

Vayarin® is a proprietary lipid composition of Phosphatidylserine-Omega-3 (PS-Omega-3), enriched with EPA. This form has been specially designed to deliver these essential lipids to the brain in order to support and maintain proper brain function.

CHEMICAL STRUCTURE

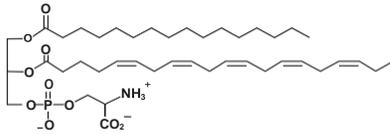


Figure 1. Schematic structure of phosphatidylserine conjugated to EPA.

INGREDIENTS

Phosphatidylserine (PS), hydroxypropyl methylcellulose, silicon dioxide, contains less than 1% of sunflower oil, Caramel (color), titanium dioxide (color), 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). Vayarin® capsules contain shellfish (krill). May contain soy and fish. Vayarin® 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 omega-3 fatty acids, 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 [3]. 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 [16] and protein kinase C [17, 18] 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 [19]. Additionally, PS has been found to influence neurotransmitter activity, such as the release of acetylcholine, dopamine and noradrenaline [20-22] and to increase brain glucose levels [23]. 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 [24].

Absorption and Metabolism

Phospholipids can break down to different levels or remain intact and be subsequently absorbed in the circulation and brain [25, 26]. 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 [27, 28]. Once the lyso-PS is absorbed by the mucosal cells of the intestine, it can be reacylated into PS [29], while some of it may be converted into other phospholipids [30]. PS and other phospholipids formed inside the enterocytes can either be transported in the lymphatic circulation as chylomicrons [31, 32] 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 [25].

Drug Interactions

There are no known contraindications, however Vayarin® could potentially interact with cholinergic and anticholinergic drugs. It is recommended to consult with a physician about Vayarin® 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 [33-35]. 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 [34]. 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 [34]. 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 [34].

CLINICAL EXPERIENCE

The Vayarin® 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 two hundred ADHD children (aged 6-13 years) were randomly assigned to receive Vayarin® or placebo (four capsules a day). In order to evaluate the effect of a reduced dose, an OLE was conducted in 150 participants, assigned to consume two Vayarin® capsules per day. The effect of Vayarin® was assessed by rating scales and questionnaires, including the Conners' parent (CRS-P) and teacher (CRS-T) rating scales and the child health questionnaire (CHQ) [36].

Following 15 weeks of Vayarin® administration, significant improvement in both ADHD scores and quality of life were observed in the Vayarin® group as compared to the placebo group, specifically in a subgroup of children with more pronounced hyperactive/impulsive behavior, as well as emotional dysregulation (Fig. 2) [36].

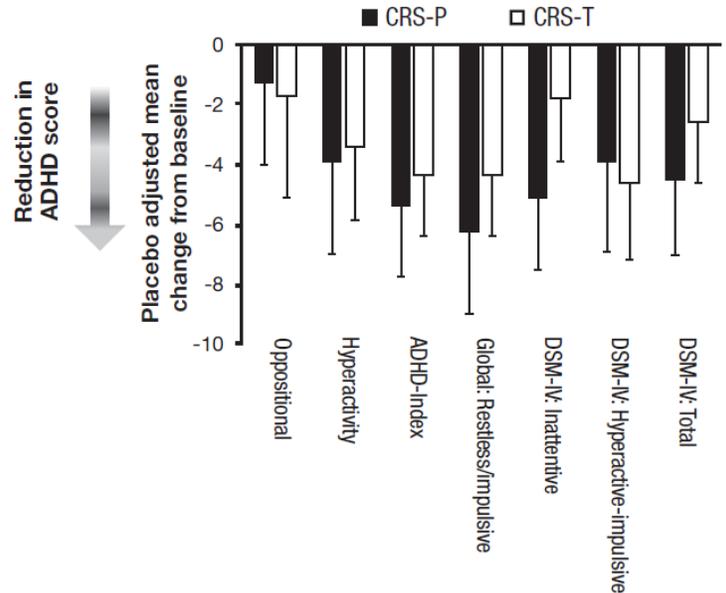


Figure 2. Effect of Vayarin® (n=46-50) versus placebo (n=23-25) on CRS-P and CRS-T scores following 15 weeks of administration during the double-blind phase, within the subgroup of participants with more pronounced emotional dysregulation. Values are presented as placebo-adjusted mean change from baseline ± SE. P values are based on analysis of covariance controlled for gender, age. * p<0.05, #p<0.2.

CHQ RESULTS:

	Vayarin® (n=49)		Placebo (n=28)		P value
	Baseline score	Change from baseline	Baseline score	Change from baseline	
Parent impact-emotional	48.3±2.80	10.88±3.31	55.06±3.30	-4.46±3.65	0.004
Family activities	71.7±2.94	3.78±2.65	78.3±3.00	-2.86±3.20	0.124

Table 1. Effect of Vayarin® versus placebo on CHQ scores following 15 weeks of administration during the double-blind phase, within the subgroup of participants with more pronounced emotional dysregulation. Values are presented as mean ± SE. p values are based on two-sided t-test for independent samples.

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 [37]. There were no clinically meaningful differences between treatment groups on the tested blood parameters in the double-blind study and within the treatment groups in the open-label extension. In addition, no significant findings were observed during physical examination or in vital signs or weight measurements in both study phases. Information regarding adverse events is elaborated in the adverse reaction section [37].

CONTRAINDICATIONS

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

PRECAUTIONS

Safety and effectiveness of Vayarin® in pregnant or lactating patients have not been established. Therefore, Vayarin® is not recommended for these populations. Vayarin® contains shellfish (krill) and should be used with caution in patients with known hypersensitivity to shellfish.

DRUG ABUSE

Vayarin® does not have any known drug abuse or withdrawal effects.

ADVERSE EVENTS

The adverse events of Vayarin® were evaluated in a randomized, double blind, placebo-controlled study of 15 weeks followed by an open label extension of an additional 15 weeks [37].

Adverse events reported during the course of the double-blind phase (table 2): 12 participants from the Vayarin® group and 5 participants from the placebo group were classified by the study physicians as suffering from treatment related, or probably related, adverse events (13 and 5 adverse events, respectively). There were no significant differences between the study groups in either the incidence or number of adverse events recorded (p= 0.848 and p = 0.982, respectively).

Adverse events reported during the course of the open-label extension (table 2): 5 participants reported 7 adverse events that were classified by the study physicians as related or probably related to the study treatment.

Study design	Double-blind study (4 capsules/day)		Open-label extension (2 capsules/day)
	Treatment Group Vayarin® (n=137)	Placebo (n=63)	Vayarin® (n=150)
Adverse event*			
Gastrointestinal discomfort	6	4	4
Atopic dermatitis	1	0	0
SGOT value	1	0	0
Headache	0	1	1
Insomnia	0	0	1
Tics	1	0	0
High triglycerides	0	0	1
Nausea	1	0	0
Hyperactivity	1	0	0
Tantrum	2	0	0

Table 2. 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 two capsules daily or as directed by a physician.

INDICATION AND USAGE

Vayarin®, an orally administered medical food for the clinical dietary management of ADHD, is designed to address the distinct, medically determined nutritional requirements of ADHD, 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 60 or 180 capsules.

Item No. (60 capsules)	75959-233-60	Use under medical supervision
Item No. (180 capsules)	75959-233-18	Use under medical supervision

STORAGE

Store at up to 77°F (25°C). Protect from light and moisture.

WARNING

Keep this product out of the reach of children.

Vayarin®, and Lipirinen® are registered trademarks of Enzymotec Ltd.
US Patents No. 7,935,365; 7,968,112; 8,470,345; 8,052,992 and 8,975,299

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