Vayarin® Plus

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

Each Vayarin® Plus capsule provides:

Lipirinen® ..... 225 mg

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

MEDICAL SUPERVISION
Vayarin® Plus 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]. ADHD individuals have lower blood levels of omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs) [5-9]. These lipids, found also in the brain, play an essential role in brain function. In turn, it has been reported that omega-3 fatty acid deficiency associated with ADHD is correlated with decreased brain phosphatidylserine, which is found mainly in the form of PS-Omega-3 [10, 11].
PS-Omega-3 plays 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® Plus 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

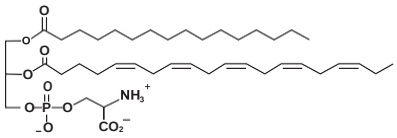

Figure 1. Schematic structure of phosphatidylserine conjugated to EPA.

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® Plus capsules contain shellfish (krill). May contain soy and fish.
Vayarin® Plus 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 [12] and protein kinase C [13, 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 [15]. 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].

- **Absorption and Metabolism**

Phospholipids can break down to different levels or remain intact and be subsequently absorbed in the circulation and brain [21, 22]. 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 [23, 24]. Once the lyso-PS is absorbed by the mucosal cells of the intestine, it can be reacylated into PS [25], while some of it may be converted into other phospholipids [26]. PS and other phospholipids formed inside the enterocytes can either be transported in the lymphatic circulation as chylomicrons [27, 28] 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 [21].

- **Drug Interactions**

There are no known contraindications, however Vayarin® Plus could potentially interact with cholinergic and anticholinergic drugs. It is recommended to consult with a physician about Vayarin® Plus 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 [29-31]. 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 Vayarin® Plus study was designed as a multi-center, randomized, double-blind, sequential parallel comparison design (SPCD) trial divided into two phases of 8 weeks each. The primary efficacy endpoint of the study was improvement of the Vayarin® Plus group vs. placebo in the Adult ADHD Investigator Symptom Rating Scale (AISRS). Additional assessments included the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) and the Clinical Global Impression of Severity (CGI-S). The mean age of the participants was 36.9 years and the treatment groups were comparable with respect to demographic and baseline characteristics. The results indicate a significantly greater reduction in the AISRS total score and the AISRS inattentive sub-scale, in the Vayarin® Plus group, compared to the placebo group. In addition, the Vayarin® Plus group exhibited higher levels of executive function and reduced ADHD severity as demonstrated by the BRIEF-A and CGI-S, respectively. Manuscript in preparation.
Previous clinical study of Vayarin® (pediatric dosage of PS-Omega-3, EPA enriched) 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 per 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) [32, 33]. 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 [32].

SAFETY ASSESSMENT
Safety was evaluated by clinical laboratory measurements including biochemical and hematological parameters and by adverse event recording, physical examination, and measurement of vital signs and weight during the study. There were no clinically meaningful differences between the groups in the tested blood parameters, and no significant findings were observed during physical examination, vital signs or weight measurements. Information regarding adverse events is elaborated in the adverse reaction section.

ADVERSE EVENTS
Vayarin® Plus was clinically shown to be safe and well tolerated with no significant adverse events. The adverse events of Vayarin® Plus were evaluated in in a multi-center, randomized, double-blind, sequential parallel comparison design (SPCD) trial divided into two phases of eight weeks each.

Number of participants reporting on Adverse Events*	Placebo N=125*	Vayarin® Plus N=102*
Headaches and dizziness	13	3
Gastrointestinal discomfort	29	27
Respiratory discomfort	1	0
Sleeping discomfort	7	5
Menstrual symptoms	2	0
General feeling of sickness	4	2
Eye discomfort	2	0
Mood fluctuation	4	3
Skin discomfort	4	4
Weight changes	4	1
Allergies	2	1
Muscle cramps and twitches	2	0
CVD-related symptoms	2	1
Total	**76**	**47**

Table 1. Adverse events reported during the two phases of the clinical trial (total of sixteen weeks), which were judged by the study physician as related, probably or possibly related to the study treatment.
*Numbers are based on the total numbers of patients who received placebo or Vayarin® Plus at some point during the trial.

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

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

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

DOSAGE AND ADMINISTRATION
Usual dose is two capsules daily or as directed by a physician.

INDICATION AND USAGE
Vayarin® Plus, 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)	0-51497-01066-9	Use under medical supervision
Item No. (180 capsules)	0-51497-01067-6	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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