VASCAZEN®

RECOMMENDED USE

VASCAZEN® (omega-3-acid ethyl esters) is a prescription only Medical Food intended for the dietary management of Omega-3 Deficiency in patients with Cardiovascular Disease (CVD).

Must be administered under physician supervision. Dispensed by prescription only.

VASCAZEN® softgel capsules to be administered orally, and is dispensed by prescription only for the dietary management of Omega-3 Deficiency in patients with CVD. The adult dose is four (4) capsules daily, supplying 3g/day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).**VASCAZEN®** should only be taken under the supervision of a physician, and is only dispensed by prescription. Do not take **VASCAZEN®** if you have a known allergy to fish or soy. If you are pregnant, nursing, or under the age of 18 years, consult your physician prior to taking **VASCAZEN®** .

PRODUCT DESCRIPTION

Primary Ingredients

VASCAZEN® consists of a proprietary formulation of Omega-3 fatty acid ethyl esters, containing a minimum of 900mg of Omega-3 fatty acid ethyl esters, including 680mg of EPA and 110mg of DHA in a ratio of 6:1, per 1g capsule.

Other Ingredients

VASCAZEN® contains the following inactive carriers or excipients: gelatin, glycerol, purified water, mixed natural tocopherols, and trace amounts of soy.

MEDICAL FOODS

Medical Food products are often used in hospitals and outside of a hospital setting under a physician's care for the dietary management of diseases in patients with particular, unique or distinctive medical or metabolic needs due to their disease or condition. Congress defined "Medical Food" in the Orphan Drug Act and Amendments of 1988 as "a food which is formulated to be consumed or administered enterally [or orally] under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Medical Foods are complex formulated products, requiring sophisticated and exacting technology, and that are used only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the Medical Food. **VASCAZEN®** has been developed, manufactured and labeled in accordance with the statutory definition of a Medical Food. **VASCAZEN® must be used while the patient is under the ongoing care of a physician.**

BACKGROUND

Omega-3 Deficiency

A critical component of the definition of a Medical Food is that the product must address the distinct nutritional requirements of a particular disease or condition. **VASCAZEN®** meets the definition of distinctive nutritional requirements as follows: "the dietary management" of patients with specific diseases requires, in some instances, the ability to meet nutritional requirements that differ substantially from the needs of healthy persons. For example, in establishing the recommended dietary allowances for the general, healthy population, the Food and Nutrition Board of the Institute of Medicine National Academy of Sciences recognized that different or distinctive physiologic requirements may exist for certain persons with special nutritional needs arising from metabolic disorders, chronic diseases, or other medical conditions. Thus, the distinctive nutritional needs associated with a disease reflects the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism, and excretion. It was also proposed that in patients with certain disease states who respond to nutritional therapies, a physiologic deficiency of the nutrient is assumed to exist. For example, more than 80% of patients with CVD are Omega-3 Deficient, i.e. residing in the highest risk quartiles as defined[1,2] by measuring either the Omega-Score™ or Omega-3 Index. The Omega-Score™ is a measure of Omega-3 fatty acid (EPA, DHA and docosapentaenoic acid (DPA)) levels in blood and the Omega-3 Index is a measure of EPA and DHA in red blood cells. Epidemiological and subsequent human studies have established that Omega-3 fatty acids are essential nutrients and have pleiotropic effects in cell function and regulate multiple metabolic pathways controlling blood lipids, inflammatory factors, cellular and molecular events in heart cells, and vascular endothelial cells. Metabolic deficiency of Omega-3 fatty acids can lead to high blood pressure, a change in the blood lipid profile, with elevations in low density lipoprotein cholesterol (LDL-C; "bad cholesterol"), decrease in high density lipoprotein cholesterol (HDL-C; "good cholesterol"), triglyceride (TG) increase, with increased inflammation (excess of 2-series eicosanoids). Correction of Omega-3 Deficiency is thought to have a positive effect on the above and can promote a shift from 2-series (pro-inflammatory), to 3-series (less inflammatory) eicosanoids as the ratio of arachidonic acid (AA)/ EPA decreases[3].

VASCAZEN® is a prescription Medical Food for the dietary management of Omega-3 Deficiency in patients with CVD, providing EPA and DHA to levels not attainable through normal dietary modifications alone. This deficiency can be corrected by providing prescription **VASCAZEN®**, reducing a key risk factor in patients with CVD.

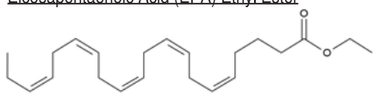
A review of the scientific and medical literature identifies there are medically determined Omega-3 nutrient requirements in patients with CVD[1,2,4,5], supporting the recommendation of consuming 3g of EPA and DHA per day[6]. It would be difficult to achieve and sustain this high level of EPA and DHA through mere modification of the "normal" diet. Consumption of fatty fish every day may approach the level of 3g of EPA and DHA per day. However, the typical American diet consists of approximately 1/15th of these levels[7] and increasing fish consumption 15-fold, to reach the clinically beneficial EPA and DHA levels through diet alone, would not be considered "normal" as required under the Medical Food definition. **VASCAZEN®** delivers 3g/day of EPA and DHA, levels not reasonably achievable through diet modifications alone.

Omega-3 Fatty Acids

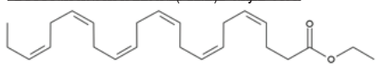
Omega-3 fatty acids are polyunsaturated fatty acids with a double bond at the third carbon atom from the end of the carbon chain (methyl terminal). The main Omega-3 fatty acids are EPA and DHA. Dietary sources of EPA and DHA are largely from cold water, oily fish including anchovies, sardines, mackerel and salmon and have demonstrated therapeutic benefits for overall cardiovascular health[3,8]. However, to attain the sustained and stable levels of Omega-3 required for cardio-protective effects, a diet consisting predominately of fish can be difficult to maintain on a daily basis. There is also a growing public concern for toxin accumulation in fish (e.g. mercury, other heavy metals, PCBs etc.), contributing to lower desire to include fish as a regular dietary staple.

Structural formulas for EPA and DHA ethyl esters are:

Eicosapentaenoic Acid (EPA) Ethyl Ester



Docosahexaenoic Acid (DHA) Ethyl Ester



The molecular weight of EPA ethyl ester is 330.5 and has an empirical formula of $C_{22}H_{34}O_2$, and DHA ethyl ester has a molecular weight of 356.6 and an empirical formula of $C_{24}H_{36}O_2$.

Physical Description

VASCAZEN® is distributed as an ultra-purified, light yellow, fish oil-filled, transparent softgel capsule in 15-count blister cards. Capsules are intended for oral administration and contain a minimum of 900mg Omega-3 fatty acids by weight comprised of a combination of at least 680mg EPA and 110mg DHA in a weight ratio of 6:1 in each 1g capsule. **VASCAZEN®** undergoes multiple independent third party testing for safety and purity.

CLINICAL PHARMACOLOGY OF OMEGA-3's

VASCAZEN® is intended to restore and sustain healthy levels of EPA and DHA in Omega-3 Deficient patients with CVD. Increasing dietary levels of EPA and DHA have been shown to have a host of cardio-protective benefits[9,10]. Scientific literature suggests a correlation between high circulating blood levels of EPA and DHA with a reduction in the risk of cardiovascular events[2,5]. Beneficial effects of EPA and DHA have been documented in a number of clinical studies[9,10]. These include positive effects on lipid metabolism, blood pressure, heart rate, platelet aggregation, inflammation and helping to reduce the risk of cardiovascular disease [2,3,8].

CLINICAL EXPERIENCE

Clinical dietary management of Omega-3 Deficiency in patients with CVD can be achieved with **VASCAZEN®** at a dose of four (4) capsules per day.

VASCAZEN® Open Label Safety and Efficacy Study

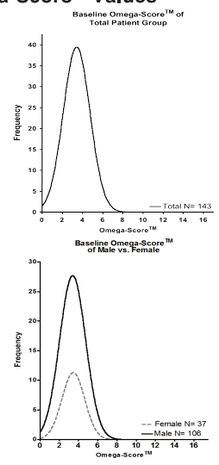
The safety and efficacy of **VASCAZEN®** was evaluated in an open label clinical study that assessed Omega-3 Deficiency and efficacy of **VASCAZEN®** treatment for two to six weeks. The study involved a treatment regime consisting of four capsules daily of **VASCAZEN®** and monitoring of blood Omega-3 levels over a six week period. The Open label study consisted of 143 study subjects enrolled for baseline Omega-3 Deficiency assessment, of which 63 subjects were scheduled to receive **VASCAZEN®** (3g EPA and DHA at a ratio of 6:1 EPA:DHA per day) for two weeks, and 31 patients received **VASCAZEN®** for six weeks. The primary endpoint was the subjects' Omega-Score™, presented as a percentage of total whole blood fatty acids. Subjects in the study had an average age of 51 years. This study revealed a baseline Omega-3 Deficiency[2] in over 84.5% of the study group participants, irrespective of age or sex (Table 1, Figure 1). **VASCAZEN®** treatment resulted in a significant ($p<0.0001$) improvement in Omega-3 blood levels within two weeks, raising the mean Omega-Score™ from 3.4% to 5.7%, and to 7.5% ($p<0.0001$) within six weeks (Table 2, Figure 2).

TABLE 1.
Study Participant Baseline Characteristics

	Patient Group		
	Total N=143	Males N=106	Females N=37
Age (years)	46.9±15.0	50.9±14.6	52.1±13.6
Omega-Score™	3.4±1.3	3.4±1.4	3.5±1.19
Mean 95% CI	3.2 to 3.6 (±1.1 to 1.6)	3.2 to 3.7 (±1.1 to 1.6)	3.2 to 3.7 (±1.0 to 1.4)
% of Patients at Risk (<6.1% Omega-Score™)	84.5	82.1	89.2

The average age of patients was 50.9 years, with a slightly, but not significant age difference observed between the male (52.1 years) and female (46.9 years) groups. Mean Omega-Score™ values were in the "very high risk"[2] quartile and nearly identical between males and females. The vast majority of patients in the study had Omega-Score™ values less than 6.1%, signifying at least a moderate level of risk. Results showed 84.5% of patients were at risk, with similar trends in both the male and female populations. Confidence interval (CI), "±" (means ± standard deviation).

FIGURE 1. Study Participant Baseline Omega-Score™ Values



Out of 143 study participants, the majority of patients had a baseline Omega-Score™ of less than 6.1%, indicating an Omega-3 Deficiency, irrespective of sex.

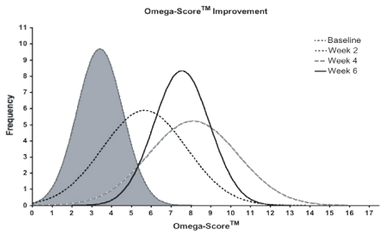
TABLE 2.
Timecourse of Study Subject's Omega-Score™ Values

	Week			
	0	2	4	6
Omega-Score™	3.4±1.3	5.7±1.9	7.9±2.4	7.5±1.2
Mean 95% CI	3.1 to 3.7 (±0.9 to 3.7)	5.4 to 6.3 (±1.4 to 2.3)	6.6 to 9.1 (±1.2 to 3.7)	7.0 to 8.0 (±0.7 to 1.7)
% of Patients at Risk (<6.1% Omega-Score™)	84.5%	43.2%	15%	13.2%

VASCAZEN® rapidly increases patient group Omega-Score™ means with significant improvements ($P<0.0001$) as early as two weeks after treatment (3.4 at baseline, to 5.7 after two weeks). After four weeks, Omega-Score™ means surpass 6.1% into the "low risk" quartile, and remain in this range through week 6 ($P<0.0001$). At the beginning of the study, 84.5% of patients were Omega-3 Deficient, and by week six, only 13.2% of study subjects were deficient, illustrating the efficacy of **VASCAZEN®** for use as an aid in the dietary management of Omega-3 Deficiency. Confidence interval (CI), "±" (means ± standard deviation).

VASCAZEN®

FIGURE 2. Six Week Treatment with VASCAZEN®



Study subjects were administered four capsules per day of **VASCAZEN®**, supplying 3g EPA and DHA per day and were monitored for safety and efficacy of increasing Omega-Score™ values from baseline levels. A significant improvement was observed within two weeks, with 86.8% of subjects reaching the low risk Omega-Score™ quartile within six weeks.

VASCAZEN®-REVEAL Trial

VASCAZEN® safety and efficacy was evaluated in a multicenter, double-blind, randomized, placebo-controlled trial. The study screened 655 candidates for Omega-3 plasma levels, and 89% were found to be Omega-3 Deficient. Of the 655 screened subjects, 110 met all study inclusion and exclusion criteria including the requirement for being Omega-3 Deficient, with one or more risk factors for CVD were enrolled in the trial. Patients with CVD risk factors included hypertension (32%), overweight or obesity (81%, BMI>25), diabetes (13%), elevated TG, (65%, >150mg/dL), low HDL cholesterol (Men: 64%,<40mg/dL; Women: 73% <50mg/dL), elevated LDL cholesterol (65%). The enrolled subjects were stratified by TG levels (Cohort 1: 90-199mg/dL, or Cohort 2: 200-500mg/dL), randomized and treated with four(4) capsules/day of **VASCAZEN®** (supplying 3g/day of EPA and DHA) or corn oil (placebo) for eight weeks.

The results show that **VASCAZEN®** effectively corrected the Omega-3 Deficiency by increasing Omega-3 blood levels from those associated with "moderate to very high risk" to those associated with "low risk" of sudden death from cardiac causes.[1,2] Specifically, **VASCAZEN®** treatment of subjects with high TG (Cohort 2) resulted in a significant improvement (121%, p<0.0001) in median Omega-Score™ levels (Figure 3) and Omega-3 Index levels (112%, p<0.0001) within eight weeks with a placebo-adjusted 48% reduction of TG (p=0.0005), a 30% reduction on VLDL-C (p=0.0023), and a 9% increase in HDL-C (p=0.0069) without a statistically significant increase in LDL-C (p=0.1164) or other secondary endpoints (Table 3). In the normal to moderately high TG group (Cohort 1), **VASCAZEN®** treatment also significantly corrected the Omega-3 Deficiency and improved patients' Omega-Score™ by 132% (p<0.0001) with a TG reduction trend (-8%, p=0.1140), and non-significant changes in other blood lipid parameters (Table 3). Correction of the Omega-3 Deficiency in both cohorts brought subjects from very high CVD risk category to low risk quartile, as stipulated by Albert et. al., 2002[2].

FIGURE 3. Correction of Omega-3 Deficiency (OM3D) with VASCAZEN® Treatment.

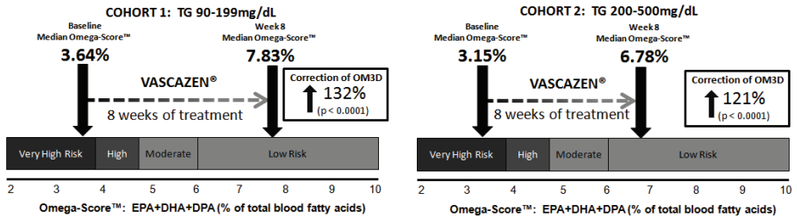


TABLE 3: Median Baseline, Percent Change, and Placebo-Adjusted Differences in Blood Lipids.

Blood Lipids mg/dL	VASCAZEN® 4 capsules/day		Placebo 4 capsules/day		Placebo-Adjusted	
	Baseline mg/dL	% Change[(c)]	Baseline mg/dL	% Change[(c)]	Difference %[(d)]	P-Value
Cohort 1 (TG 90-199mg/dL)						
Omega-3 Index[(a)]	3.81	127	3.56	3	124	**p<0.0001***
Omega-Score™[(b)]	3.64	132	3.68	0	132	**p<0.0001***
AA/EPA[(e)]	21	-86	21	7	-93	**p<0.0001***
TG	155	-6	131	2	-8	p=0.1140
VLDL-C	26	-2	27	0	-2	p=0.3426
Total-C	187	2	180	2	0	p=0.5033
HDL-C	41	-2	46	-2	-2	p=0.4160
LDL-C	116	7	103	1	6	p=0.1197
ApoB-100	102	6	90	3	3	p=0.3232
Non-HDL-C	145	3	125	3	-1	p=0.2227
Cohort 2 (TG 200-500mg/dL)						
Omega-3 Index	3.34	109	3.54	-3	112	**p<0.0001***
Omega-Score™	3.15	119	3.36	-2	121	**p<0.0001***
AA/EPA[(d)]	16	-75	15	11	-87	**p<0.0001***
TG	275	-47	264	0	-48	**p=0.0005***
Total-C	185	4	186	3	2	p=0.3642
VLDL-C	185	-30	36	0	-30	**P=0.0023***
HDL-C	39	3	39	-6	9	**p=0.0069***
LDL-C	115	13	102	2	11	p=0.1164
ApoB-100	105	0	100	2	-2	p=0.7440
Non-HDL-C	148	2	143	4	-2	p=0.6757

[(a)]Omega-3 Index = EPA + DHA in red blood cells (rbc) expressed as a percentage of total rbc fatty acids levels. [(b)]Omega-Score™ =EPA+DHA+DPA expressed as a percentage of total plasma fatty acids levels. [(c)]% Change = Median % Change from baseline. [(d)]Difference = Median of (**VASCAZEN®** Percent Change) – (Placebo Percent Change). [(e)]Arachidonic Acid (AA) / EPA, both expressed as a percentage of total plasma fatty acids levels. TG (Triglycerides), Total-C (Total Cholesterol), VLDL-C (Very Low Density Lipoprotein Cholesterol), HDL-C (High Density Lipoprotein Cholesterol), LDL-C (Low Density Lipoprotein Cholesterol), ApoB-100 (Apolipoprotein B-100), Non-HDL-C (Non High Density Lipoprotein Cholesterol). [(*)] Statistically Significant.

ALLERGEN STATEMENT

VASCAZEN® contains fish oil and soy products. Patients with known hypersensitivity to fish or soy products should notify their physician.

ADVERSE REACTIONS

In an open label and a double-blind, randomized, placebo-controlled **VASCAZEN®-REVEAL Trial**, **VASCAZEN®** treatment for six to eight weeks was well-tolerated and adverse events were minimal and minor in degree with no severe adverse events reported. In the Open Label study, two subjects experienced a mild reflux/aftertaste, while an additional subject showed minor leg bruising that disappeared within three days. In the **VASCAZEN®-REVEAL Trial**, minor adverse reactions were reported: fishy burp (5% of patients), flatulation (4% of patients), and nausea (4% of patients), although 5% of patients in the placebo group also experienced nausea.

FOOD EFFECTS

VASCAZEN® may be taken with or without other foods. Some patients may experience a fishy aftertaste/burp, and taking **VASCAZEN®** with food may help reduce this effect.

DRUG INTERACTIONS

Although clinical studies investigating the effect of **VASCAZEN®** plus anticoagulants have not been completed, caution should be taken when taking **VASCAZEN®** with anticoagulant drugs. Omega-3 fatty acids may extend bleeding time and patients receiving treatment with **VASCAZEN®** along with drugs that affect coagulation, should be monitored by a physician.

CAUTIONS

If you are pregnant, nursing or planning on becoming pregnant, ask your physician if **VASCAZEN®** is right for you. Safety studies have not yet been completed for the use of **VASCAZEN®** in pregnant or nursing women or pediatric patients (children under 18 years of age). Also, this product contains fish components and trace amounts of soy. Patients with a known hypersensitivity to any of the ingredients in **VASCAZEN®** should consult their physician prior to taking **VASCAZEN®**.

HOW SUPPLIED

VASCAZEN® capsules are supplied as transparent softgel capsules, filled with light yellow, ultra-purified fish oil. **VASCAZEN®** is manufactured according to Food and Drug Administration (FDA) current Good Manufacturing Practices (cGMP). Commercial product is supplied in 60-capsule cartons.

Commercial Product (60 Capsules)	27843-0172-46	Use Under Medical/Physician Supervision.
Sample Product (15 Capsules)	27443-0172-48	Professional Samples (Not for sale)

PHYSICIAN SUPERVISION

VASCAZEN® is a Medical Food product dispensed by prescription only under ongoing physician supervision.

STORAGE

59-77ºF (15-25ºC). Keep from freezing. Protect from direct sunlight.

Manufactured by:
Captek Softgel Inc., Cerritos, CA, 90703

Manufactured for:
Pivotal Therapeutics (US), Inc.
Boca Raton, FL, 33431
P: 561-288-5231
Website: www.pivotaltherapeutics.us

REFERENCES

1. Siscovick DS, Raghunathan TE et. al. (1995). Dietary Intake and Cell Membrane Levels of Long-Chain n-3 Polyunsaturated Fatty Acids and the Risk of Primary Cardiac Arrest. JAMA. **274**:17;1363-1367.

2. Albert CM, Campos H, Stampfer MJ et al. (2002). Blood Levels of Long-Chain n-3 Fatty Acids and the Risk of Sudden Death. New England Journal of Medicine **346**:1113-1118.

3. De Caterina R. (2011). N-3 Fatty Acids in Cardiovascular Disease. New England Journal of Medicine **364**:25;2439-2450.

4. Danaei G, Ding EL, Mozaffarian D. et al. (2009). The Preventable Causes of Death in the United States: Comparative Risk Assessment of Dietary, Lifestyle, and Metabolic Risk Factors. PLoS Medicine. **6**(4):1-23.

5. Mozaffarian D, Lemaitre RN et. al. (2013) Plasma Phospholipid Long Chain Omega-3 Fatty Acids and Total and Cause-Specific Mortality in Older Adults: A Cohort Study. Annals of Internal Medicine **158**(7):515-525.

6. Kris-Etherton PM, Harris WS et. al. (2002) Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease. Circulation **106**:2747-2757.

7. Kris-Etherton PM, Taylor DS, et. al. (2000) Polyunsaturated fatty acid in the food chain in the United States. American Journal of Clinical Nutrition. **71(suppl):**179S-88S.

8. Harris WS, Miller M. (2008) Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives. Atherosclerosis. **197**:12-24.

9. GISSI-Prevenzione Investigators (1999). Dietary Supplementation with n-3 Polyunsaturated Fatty Acids and Vitamin E after Myocardial Infarction: Results of the GISSI-Prevenzione Trial. Lancet **354**:447-455.

10. Yokoyaa M, Origasa H, Matsuzaki M, et al. (2007). Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open- label, blinded endpoint analysis. Lancet. **369:**1090-1098.

Pivotal THERAPEUTICS