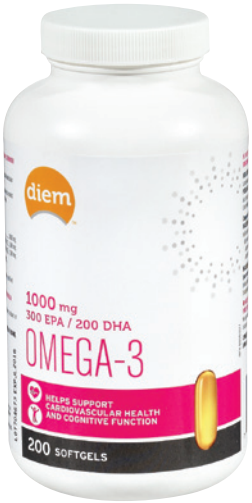
Omega-3 1000 mg Softgels



Product Summary:

A source of Omega-3 Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) from fish oil this product supports general well-being, cognitive health, and, particularly, cardiovascular health.

Properties/Uses:

The claim as approved by the *Natural Health Products Directorate* (NHPD): Helps support cardiovascular health and cognitive function.

CARDIOVASCULAR

Pharmacology:

The omega-3 fatty acids, EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), are indispensable mediators of plasma and intracellular membrane structure and function. As well, omega-3 EPA provides critical eicosanoid regulatory balance, particularly in North America, where the dietary prominence of omega-6 vegetable oils adversely impacts eicosanoid metabolic balance. Typically such imbalance causes inflammation, exacerbating many health problems, including cardiovascular disease, inflammatory conditions (e.g. rheumatoid arthritis, Inflammatory Bowel Disease), mood disorders and cognitive health.

Cardiovascular Effects of EPA and DHA

The beneficial effects of EPA and DHA on cardiovascular disease have been demonstrated in an abundance of animal and tissue culture studies, and in human clinical trials.[1] Epidemological data have shown that increased intake of fish is associated with lower cardiovascular disease morbidity and mortality.[2] Omega-3 polyunsaturated fatty acids (PUFAs) from ocean fish are clearly protective and through a number of mechanisms, are documented to prevent deaths from coronary artery disease, particularly cardiac arrest.[1,3] Supplemented EPA and DHA help to prevent cardiovascular problems through a variety of actions. Fish oil is associated with:[1,2,4-8]

- Prevention of arrhythmias (ventricular tachycardia and fibrillation)
- Beneficial series-3 eicosanoid impact
- Decreased blood pressure and heart rate
- Anti-inflammatory properties
- Inhibited synthesis of inflammatory cytokines (IL-6, TNF-alpha and mitogens)
- Stimulated endothelial-derived nitric oxide
- Anti-thrombotic properties
- Decreased platelet aggregation and adhesion
- Hypolipidemic properties with effects on triglyceride and VLDLs
- Inhibited atherosclerosis and improved plaque stability
- Decreased sympathetic nervous system activity
- Decreased production of vasoconstrictive, pro-inflammatory eicosanoids

The Diet and Reinfarction Trial (DART) found that male myocardial infarction (MI) survivors that consumed more oily fish (~500 to 800 mg/day of omega-3) had a 29% reduction in total mortality. A subgroup from this study used fish oil capsules providing 450 mg EPA and DHA per day. With this subgroup, it was found that there was a 62% reduction in CVD-related death and a 56% reduction in all-cause mortality in those that used the fish oil capsules.[9]

Fish oils combined with statin therapy have been shown to have additional triglyceride-lowering effects. The COMBOS trial, a multicenter, randomized, double-blind study, indicated a combination of omega-3 with 40mg per day of simvastatin resulted

in a 29.5% reduction of triglycerides, a 27.5% reduction of VLDL cholesterol, and an increase of 3.4% in HDL-C levels.[10] In one study, the addition of 3 grams of fish oil to 40mg of pravastatin was shown to reduce triglycerides by an additional 33%.[11] Similarly, the combination of 3.4 grams of fish oil to patients taking 10-40 mg simvastatin reduced triglycerides by 20% to 30%.[12] The combination of statins and omega-3 fatty acids is efficacious and has not been associated with any serious adverse reactions.[8]

It should be noted, that fish oils alone may confer greater benefit than statins alone or even combined therapy. A systematic review of 97 randomized controlled trials (RCTs) on various lipid-lowering interventions found that in 33 studies where statins were used, and overall 22% reduction in cardiac mortality was observed, while 12 studies employing a higher intake of omega-3 fatty acids demonstrated a 32% reduction in cardiac mortality.[13] This demonstrates that omega-3 fatty acids have equivalent, if not superior, ability to statins with respect to reduction of cardiac mortality.

For heart attack patients, omega-3 fatty acids can be life-saving. In the largest-scale clinical trial of its kind, the GISSI-Prevenzione trial in Italy, 11,324 heart attack patients were supplemented with 850mg of combined EPA and DHA (EPA + DHA) per day. After 3.5 years, the incidence of sudden cardiac death was reduced by 45%, coronary mortality declined by 30% and the total death rate from all causes fell by 20%.[14] Other researchers found that consuming omega-3 fatty acids significantly reduced coronary mortality for people with no history of cardiovascular disease.[15]

A 16-year study of 84,000 women showed that dietary intake of fish and omega-3 fatty acids significantly reduced the incidence of fatal and non-fatal coronary heart disease. The study showed the higher the omega-3 fatty acid intake, the lower the likelihood of coronary heart disease.[16]

Omega-3 has also demonstrated the ability to reduce death in patients suffering from heart failure. The GISSI-Heart Failure Trial enrolled approximately 7,000 subjects with heart failure and randomized them to receive 850 mg EPA+DHA per day or placebo. After 3.9 years, the omega-3 group experienced a 9% reduction in death, and death or hospital admission for cardiovascular reasons. There was also a 7% reduction in sudden cardiac death.[17]

Omega-3 fatty acids have also established modest benefit in another major risk factor for cardiovascular disease and heart attack – hypertension. Meta-analysis reveals that high dose (3.7 g per day) omega-3 fatty acids can lower systolic blood pressure (SBP) 2.1 mmHg and diastolic blood pressure (DBP) 1.5 mmHg, with effects found to be greatest in older populations and hypertensive patients (BP≥ 140/90 mmHg).[18]

EPA and Eicosanoids in Cardiovascular, Anti-inflammation, and Thrombotic Health

EPA supplementation reduces the risk for an unbalanced promotion of inflammation in several ways. Firstly, EPA appears to attenuate the delta-5 desaturase action in the conversion of omega-6 dihomogamma-linolenic acid (DGLA) to arachidonic acid (AA)[19,20], allowing more DGLA to be shunted into favorable series-1 eicosanoids. Secondly, EPA is able to displace AA in membrane phospholipids, thus AA membrane availability for inflammatory eicosanoid formation is reduced.[21] Thirdly, EPA has a greater affinity for cyclooxygenase and lipoxygenase than does AA, curtailing eicosanoid formation from AA by competitive inhibition.[21] Fourthly, EPA inhibits the 5-lipoxygenase pathway in neutrophils and monocytes, and inhibits the leukotriene B4 mediated functions of neutrophils.[21,22] And fifthly, some amount of EPA itself is converted to *series-3* eicosanoids (prostaglandins, prostacyclins, thromboxane A3, and leukotrienes LTB5), which compete with AA eicosanoids for the same cellular receptors, but exert a considerably weaker response in most cases than their AA analogues.[23]

EPA can attenuate the effects of inflammatory cytokines by favoring anti-inflammatory eicosanoid balance. Flaxseed oil given over four weeks has been observed to reduce TNF-alpha and mononuclear cell IL1-Beta by 30%. However, fish oil EPA proved more effective over four weeks, reducing mononuclear TNF-alpha and IL1-Beta by 74% and 80% respectively.[21,22] This observation further indicates fish oil is superior to flaxseed oil in promoting cardiovascular health, especially in older people.

Omega-3 and Metabolic Syndrome

Often preceding the onset of type 2 diabetes and cardiovascular disease is metabolic syndrome; a clustering of chronic disease risk factors that include abdominal obesity, dyslipidemia (elevated triglycerides and/or low HDL cholesterol), elevated blood pressure and elevated fasting blood glucose.[24] Metabolic syndrome affects approximately ¼ of Canadians and is particularly prevalent among people of South Asian and Aboriginal descent.[25]

Early animal studies found that diets high in lard and omega-6 oils caused insulin resistance.[26] Human muscle cells low in omega-3 (especially DHA) and high in omega-6 were more likely to be insulin resistant, with corresponding obesity in the tested subjects.[27] The greater the omega-3 to omega-6 imbalance, the more severe was the insulin resistance and obesity.[27] Preliminary human trials found that fish oil supplementation led to decreased insulin response to oral glucose load by 40%[28], reduced insulin resistance, as well as reduced weight, blood pressure and triclycerides.[29]

More recent data has continued to support the role of omega-3 fatty acids in the prevention of metabolic syndrome. Cross sectional data indicates that subjects with metabolic syndrome have lower total polyunsaturated fatty acid (PUFA), omega-3 PUFA and omega-3 to omega-6 ratio compared to healthy subjects.[30] Similarly, a Korean study showed that high consumption of fish and omega-3 fatty acids was significantly

associated with lower risk of metabolic syndrome.[31] In particular, men who were in the top decile of omega-3 fatty acid intake, were 50% less likely to develop metabolic syndrome. The role of diet in conjunction with omega-3 fatty acids has also shown significant results for metabolic syndrome. The prevalence of metabolic syndrome fell by 20.5% after subjects were given a low-fat, high complex carbohydrate diet plus 1.24 g/d of omega-3 PUFAs compared to a 10.4% decrease in subject consuming the same diet, but without omega-3 PUFA supplementation.[32] Additionally, improvements in other parameter of metabolic syndrome were seen in 89 metabolic syndrome subjects supplemented with 180 mg EPA and 120 mg DHA. Researchers found improved cardiovascular risk profile, markers of inflammation and autoimmunity. [33]

Omega-3 and Mood Disorders

There is good evidence that depression is, in part, caused by too little omega-3. Researchers from the National Institute of Health observed that cultures where ocean fish is a dietary staple have lower rates of depression.[34,35] Examples are Japan, Taiwan, and Hong Kong. Japanese consume about 15 times more omega-3 than do Americans, and have only one tenth as much depression. Conversely, rates of depression were lowest in countries that had the greater intakes of fish.[36,37] Further evidence examining the levels of EPA and DHA in cell membranes of psychiatric patients compared to controls suggested that individuals with a psychiatric diagnosis had significantly lower levels of EPA and DHA in phospholipid membranes.[38-40]

Depression and Bipolar Disorder Research

Research shows that taking 1 gram of EPA twice daily with standard therapy seems to improve symptoms of recurrent major depression, such as depressed mood, guilt feelings, worthlessness, and insomnia after two weeks of treatment.[41] The majority of the studies examining fish oil in depression and bipolar disorder have used oil providing more EPA than DHA (EPA-dominant oil) and have shown that the intervention significantly improves symptoms of both conditions.[41-54] EPA-dominant oils have demonstrated mood stabilizing as opposed to strictly antidepressant activity. Most studies above confirm antidepressant activity, while two studies demonstrated stabilization of mania in individuals suffering from manic episodes associated with bipolar disorder.[50,53]

A recent trial published in the area of omega-3 fatty acids and depressive disorders compared omega-3 fatty acids to a prescription SSRI medication.[46] Sixty patients were followed for eight weeks taking either 1000 mg ethyl-EPA or 20 mg Fluoxetine or combination. 50% of patients receiving Fluoxetine, 56% of patients receiving ethyl-EPA, and 81% of patients receiving both medications combined, achieved the endpoint of a 50% or greater reduction in the Hamilton Depression Rating Scale (HDRS).

Anxiety and Other Psychiatric Disorders Research

Supplementation with omega-3 fatty acids has produced clinical efficacy in controlled human trials in a variety of other areas of psychiatry. Some disorders demonstrating the benefit of supplementation with omega-3 fatty acids include: anxiety[55,56], epilepsy[57,58], anorexia nervosa[59], antisocial behaviour in a prison setting[60], individuals with repeated episodes of self-harm[45], borderline personality disorder[54], ADHD[61] and autism.[62]

Omega-3 and Cognitive Support

Essential fatty acids are basic building blocks of neurons and are used as fuel substrates for brain metabolism.[63] DHA is very important for optimal functioning of the brain, retina, testes, and adrenal glands. DHA is the predominant structural fatty acid in the cerebral cortex, in the membranes of synaptic communication centers, mitochondria and photoreceptors of the retina. Almost 50% of the weight of neuronal membranes is accounted for by DHA.[64] Deficiency of DHA is associated with cognitive decline and is thought to be an important contributing factor in conditions including depression, dementia, Alzheimer disease, attention deficit disorder and dyslexia.

Cross-sectional studies have linked low DHA levels with dementia, while prospective studies have linked all-cause dementia and Alzheimer disease with decreased fish intake. The Framingham Heart Study followed 899 men and women who were free of dementia for nine years, for the development of all-cause dementia and Alzheimer disease. At follow-up, subjects that had an average DHA intake of 180 mg/d and a mean fish intake of 3.0 servings per week, had a significant 47% reduction in the risk of developing all-cause dementia.[65] Patients with dementia due to Alzheimer disease have been reported to have 30% less DHA in brain tissue than do age-matched controls.[66]

Manufactured product information:

Manufacturer:
WN Pharmaceuticals® Ltd

Size / UPC:
200s. 7 77747 10302 7

NPN:
80003127

Expiry Date:
36 months from date of manufacture

Active Ingredients:
Each softgel contains:

Fish Oil (anchovy, sardine and/or mackerel)	1000 mg
Eicosapentaenoic Acid (EPA) (EE)	300 mg
Docosahexaenoic Acid (DHA) (EE)	200 mg

Non-Medicinal Ingredients (in descending order):
Softgel capsule (gelatin, glycerin, purified water), natural tocopherols.

Appearance:
Clear yellowish oil encapsulated in an oblong clear soft gelatin shell.

Packaging:
625 cc white round bottle with safety seal under a 53 mm white cap with vented interior seal and a label applied to the bottle. Lot number and expiry date are printed on the label applied to the exterior of the bottle.

Storage:
Store in a cool, dry place.

Dose:

Recommendations from Various Organizations and Expert Panels.

ORGANIZATION, YEAR	RECOMMENDATION
American Heart Association (AHA), 2005	**No CVD:** consume fatty fish at least twice/week and foods rich in ALA (walnuts, canola, soy, and flaxseed). **Documented CVD:** consume ~1 g EPA + DHA/day, preferably from fatty fish, but also in supplement form. **For triglyceride lowering effects:** 2-4 g of EPA + DHA/day per day provided as capsules under a physician's care.
International Society for the Study of Fatty Acids and Lipids (ISSFAL), 2004	Recommends pregnant women receive 300 mg of DHA/day.
Natural Health Product Directorate (NHPD), 2006	**For maintenance of good health:** 100-3000 mg EPA + DHA/day **To support cognitive health / brain function:** 100-3000 mg EPA+DHA including at least 100 mg DHA in a daily dose: **To support development of the brain, eyes and nerves:** 150-2500 mg EPA+DHA including at least 150 mg DHA in a daily dose and indicated for children 18 and younger. **To maintain / support cardiovascular health:** 500-3000 mg EPA+DHA in a daily dose and containing a ratio of EPA:DHA between 0.5:1 and 2:1. **To reduce serum triglycerides:** 1000-3000 mg EPA+DHA in a daily dose and containing a ratio of EPA:DHA between 0.5:1 and 2:1. **In conjunction with conventional therapy to help reduce the pain of rheumatoid arthritis:** 2800-3000 mg EPA+DHA in a daily dose and containing a ratio of EPA:DHA between 0.5:1 and 2:1.

National Institute of Health (NIH) supported expert panel, 1999	300 mg DHA per day for pregnant or lactating females
World health Organization (WHO), 2003	Recommends 1-2 servings of fish per week each containing 200-500 mg EPA and DHA
American Psychiatric Association, 2006	**Position Statement, 200667** "All adults should eat fish >/= 2 times per week. Patients with mood, impulse control, or psychotic disorders should consume 1g EPA+DHA per day. As a supplement may be useful in patients with mood disorder (1-9g per day). Use of > 3g per day should be monitored by a physician."

Directions:

(Adults): 3 softgels daily with meals or as recommended by a physician

Caution:

The caution as approved by the *Natural Health Products Directorate* (NHPD): KEEP OUT OF THE REACH OF CHILDREN. STORE AT ROOM TEMPERATURE IN A DARK, DRY PLACE. DO NOT USE IF SEAL UNDER CAP IS BROKEN OR MISSING.

Deficiency Symptoms:

A deficiency in Omega-3 can lead to host of health issues including cardiac and circulatory disorders, disorders of the skin (eczema, xerosis), neurological disorders, poor memory, disorders of the kidneys and liver, various inflammatory problems, arthritis, weight disorder, mood swings and depression and failure of the immune system.[68]

Drug Interactions/Contraindications:

The effect of fish oil on anticoagulant therapy has been uncertain. Positive interactions between omega-3 polyunsaturated fatty acid intake and oral anticoagulants have been noted, without clinically relevant bleeding problems.[69,70] However, making changes in the pattern of supplemental fish oil intake after the establishment of an anticoagulant dosage may be a risk factor for loss of coagulation control (EPA may alter prothrombin time), as evidenced by case reports[71] and supervision by a physician is suggested.

Such effect on coagulation is not consistent with observations. Fish oil supplementation in doses of 3-6 grams per day does not seem to create a statistically significant effect on the anticoagulation status of patients receiving chronic warfarin.[72] Furthermore, clinical trials have shown high-dose fish oil supplementation to be safe when co-administered with other agents such as aspirin and warfarin.[73]

EPA in a high dose range may present an additive effect with other natural products known to be blood thinners. Other common mild natural blood thinners include garlic, MSM, grape seed extract, cayenne, Ginkgo biloba, and perhaps vitamin E > 400 IUs.

Supplementation of omega-3 fish oils may predispose a person to bleeding problems following surgery. However, various papers explicitly mention the absence of easy bruising or clinical signs of postoperative bleeding after fish oil intake by patients with cardiovascular disease.[69,74-76]Nevertheless, it seems prudent to recommend that fish oil 3 supplements be discontinued at least one week before surgery, and resumed upon the recommendation of the patient's physician.

Caution may be warranted in those on antihypertensive medication due to possible additive effects. Monitoring of blood pressure after initiation of omega-3 therapy for those already taking antihypertensives is suggested.

Omega-3 may play a supportive role in mood disorders as an adjunctive treatment.

Toxicity/Adverse Reactions:

Ocean fish and fish oils have been consumed in significant quantities worldwide for centuries without being associated with adverse effects. In more sensitive individuals, fish oil products may cause mild GI discomfort, fishy after-taste upon burping, belching, nausea, flatulence, or loose stools.[69]

Allergen Content/Ingredient Sensitivity:

NO	YES
Artificial Colors	Fish
Artificial Flavors	Sulphites (<10 ppm)
Artificial Sweeteners	
Corn Products	
Egg Products	
Gluten	
Hydrolyzed Plant Protein	
Lecithin	
Milk Products	
Peanuts	
Preservatives	
Sesame Products	
Shellfish	
Soy Products	
Starch/Modified Starch	
Tartrazine	
Tree Nuts	
Wheat Products	
Yeast	

NOT ACCEPTABLE FOR THE FOLLOWING DIETARY RESTRICTIONS:

Free of animal products

Kosher

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Revision #: 00