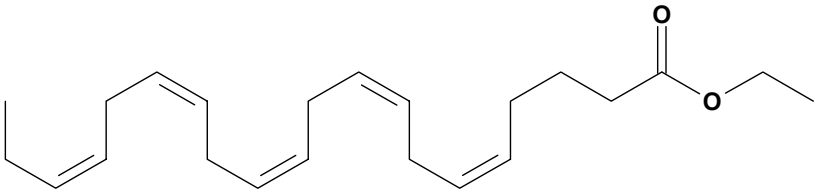
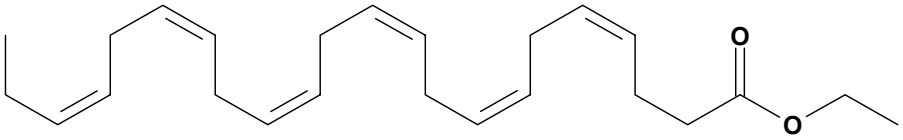
OMACOR®
Omega-3-acid ethyl esters, capsules
Rx only

DESCRIPTION

Omacor®, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each one gram capsule of Omacor® (omega-3 acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).
The structural formula of EPA ethyl ester is:



The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51.
The structural formula of DHA ethyl ester is:



The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.
Omacor® capsules also contain the following inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of Omacor® is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal β-oxidation in the liver. Omacor® may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

Pharmacokinetic and Bioavailability Studies

In healthy volunteers and in patients with hypertriglyceridemia (HTG), EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (Omacor®) induced significant, dose–dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with Omacor® was independent of age (<49 years vs. ≥49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Omacor® in children are not available.

Drug Interactions

Cytochrome P450-Dependent Monooxygenase Activities

The effect of a mixture of free fatty acids (FFA), EPA/DHA and their FFA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 μM concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 μM concentration, the FFA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Since the free forms of the EPA and DHA are undetectable in the circulation (<1 μM), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism EPA/DHA combinations are not expected in humans.

CLINICAL STUDIES

The effects of Omacor® 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on Omacor®, 42 on placebo) with very high triglyceride levels (Table 1). Patients whose baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16 weeks duration. The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.

Table 1. Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (≥ 500 mg/dL)

	TG		LDL-C		CHOL		HDL-C		VLDL-C		non-HDL-C	
	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg
Placebo	788	+6.7	108	-4.8	314	-1.7	24	0.0	175	-0.9	292	-3.6
Omacor 4g/day	816	-44.9	89	+44.5	296	-9.7	22	+9.1	175	-41.7	271	-13.8
Difference		-51.6		+49.3		-8.0		+9.1		-40.8		-10.2

BL = Baseline (mg/dL); % Chg = Percent Change from Baseline; Difference = Omacor - Placebo

Omacor® 4 g per day reduced median TG, VLDL-C, and non HDL-C levels and increased median HDL-C from baseline relative to placebo. Omacor® treatment to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should be monitored to ensure that the LDL-C level does not increase excessively.

The effect of Omacor® on the risk of pancreatitis in patients with very high TG levels has not been evaluated. The effect of Omacor® on cardiovascular mortality and morbidity in patients with very high TG levels has not been determined.

INDICATIONS AND USAGE

Omacor® is indicated as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride (TG) levels in adult patients.

Usage Considerations

According to accepted clinical guidelines, excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia (HTG) and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy for HTG.

The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet. (See PRECAUTIONS).

CONTRAINDICATIONS

Omacor® is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

PRECAUTIONS

General

Initial Therapy

Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Omacor® therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG–lowering drug therapy.

Continued Therapy

Laboratory studies should be performed periodically to measure the patient's TG levels during Omacor® therapy. Omacor® therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.

Information for Patients

Omacor® should be used with caution in patients with known sensitivity or allergy to fish.

Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.

Laboratory Tests

In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Omacor® therapy.

In some patients, Omacor® increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Omacor® therapy.

Drug Interactions

Anticoagulants

Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Omacor® and concomitant anticoagulants. Patients receiving treatment with both Omacor® and anticoagulants should be monitored periodically.

Cytochrome P450-Dependent Monooxygenase Activities

Omega-3-fatty acid containing products have shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Omacor® to induce P450 activities in humans has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation. No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. It is unknown whether Omacor® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Omacor® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison.

In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).
In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 thorough 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000mg/kg/day (7 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Nursing Mothers

It is not known whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Omacor is administered to a woman who is breastfeeding.

Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use

A limited number of patients over 65 years of age were enrolled in the clinical studies. In the pooled analyses, safety and efficacy findings in subjects over 60 years of age (approximately 25% of the study population) did not appear to differ from those of subjects less than 60 years of age.

ADVERSE REACTIONS

Treatment-emergent adverse events reported in at least 1% of patients treated with Omacor® 4 g per day or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in Table 2. Adverse events led to discontinuation of treatment in 3.5% of patients treated with Omacor® and 2.6% of patients treated with placebo.

Table 2. Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel–Group Studies for Hypertriglyceridemia That Used Omacor® 4 g per Day

BODY SYSTEM Adverse Event	Omacor® (N = 226)		Placebo* (N = 228)	
	n	%	n	%
Subjects with at least 1 adverse event	80	35.4	63	27.6
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4.4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1.3	2	0.9
Digestive				
Dyspepsia	7	3.1	6	2.6
Eructation	11	4.9	5	2.2
Skin				
Rash	4	1.8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.

* Placebo was corn oil for all studies.

Additional adverse events reported by 1 or more patients from 22 clinical studies for HTG are listed below:

BODY AS A WHOLE: enlarged abdomen, asthenia, body odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, sudden death, and viral infection.

CARDIOVASCULAR SYSTEM: arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia.

DIGESTIVE SYSTEM: anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting.

HEMATOLOGIC-LYMPHATIC SYSTEM: lymphadenopathy.

METABOLIC AND NUTRITIONAL DISORDERS: edema, hyperglycemia, increased ALT, and increased AST.

MUSCULOSKELETAL SYSTEM: arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder.

NERVOUS SYSTEM: central nervous system neoplasia, depression, dizziness, emotional lability, facial paralysis, insomnia, vasodilatation, and vertigo.

RESPIRATORY SYSTEM: asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis.

SKIN: alopecia, eczema, pruritis, and sweating.
SPECIAL SENSES: cataract.
UROGENITAL SYSTEM: cervix disorder, endometrial carcinoma, epididymitis, and impotence.

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

In the event of an overdose, the patient should be treated symptomatically, and general supportive care measures instituted, as required.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving Omacor®, and should continue this diet during treatment with Omacor®. In clinical studies, Omacor® was administered with meals.

The daily dose of Omacor® is 4 g per day. The daily dose may be taken as a single 4-g dose (4 capsules) or as two 2-g doses (2 capsules given twice daily).

HOW SUPPLIED

Omacor® (omega-3-acid ethyl esters) capsules are supplied as 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation OMACOR in bottles of 120 (NDC 0074-5792-01).

Recommended Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Do not freeze.

Keep out of reach of children.

Distributed by Ross Products Division, Abbott Laboratories, Columbus, OH 43215, USA.

Black
Pantone Violet
PMS 1245
Non-varnish area inside
Label Size: 6.3" x 4"

LOT
EXP.

2742M400

N 3 65726 42427 2

NDC 65726-424-27

Omacor®
(omega-3-acid ethyl esters) Capsules

Rx only

120 Capsules

Reliant PHARMACEUTICALS, INC.

Each capsule contains 1 gram omega-3-acid ethyl ester liquid concentrate consisting of at least 900 mg omega-3-acid ethyl esters.

Each capsule provides:
Eicosapentaenoic acid (EPA) ethyl ester: 465 mg
Docosahexaenoic acid (DHA) ethyl ester: 375 mg

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].
Do not freeze.

See package insert for complete prescribing information.

Manufactured for:
Reliant Pharmaceuticals, Inc.
Liberty Corner, NJ 07938
by:
Cardinal Health
St. Petersburg, FL 33716

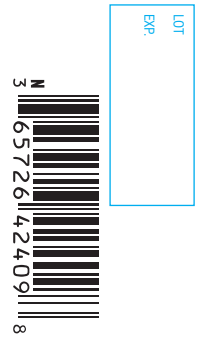
Black

Pantone Violet

PMS 1245

Non-varnish area inside

Label Size: 4.3" x 2.125"



0942M400

NDC 65726-424-09

Omacor®

(omega-3-acid ethyl esters)

Capsules

Rx only

28 Capsules

Professional Sample - Not For Sale

Reliant PHARMACEUTICALS, INC.

Each capsule contains
1 gram omega-3-acid
ethyl ester liquid concentrate
consisting of at least 900 mg
omega-3-acid ethyl esters.

Each capsule provides:
Eicosapentaenoic acid (EPA)
ethyl ester: 465 mg
Docosahexaenoic acid (DHA)
ethyl ester: 375 mg

Store at 25°C (77°F); excursions
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[see USP Controlled Room Temperature].
Do not freeze.

See package insert for complete
prescribing information.

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by:
Cardinal Health
St. Petersburg, FL 33716