PRODUCT INFORMATION

OMACOR®

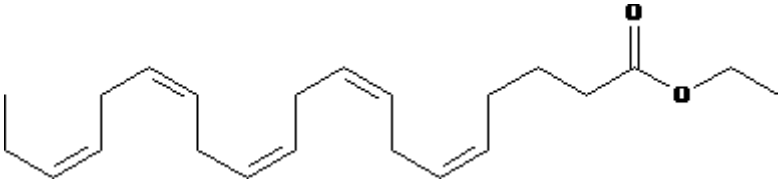
NAME OF THE MEDICINE

Non-proprietary Name

Eicosapentaenoic acid (EPA) ethyl ester.
Docosahexaenoic acid (DHA) ethyl ester.

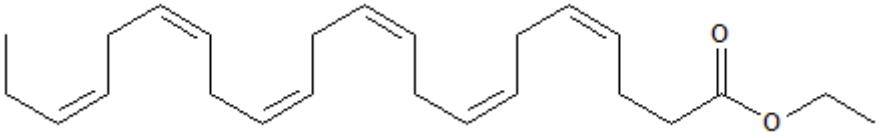
Chemical Structure

Eicosapentaenoic acid (EPA) ethyl ester



Molecular Formula: $C_{22}H_{34}O_2$
Molecular Weight: 330.51

Docosahexaenoic acid (DHA) ethyl ester.



Molecular formula: $C_{24}H_{36}O_2$
Molecular Weight: 356.55

CAS Number

Eicosapentaenoic acid (EPA) ethyl ester: 86227-47-6
Docosahexaenoic acid (DHA) ethyl ester: 81926-94-5

DESCRIPTION

Each capsule is comprised of 840 mg of the omega-3-acid esters; eicosapentaenoic acid (EPA) ethyl ester 46% and docosahexaenoic acid (DHA) ethyl esters 38%. Omega-3 acid ethyl esters are obtained by the transesterification of the body oil of fat fish species.

The empirical formula of EPA is $C_{22}H_{34}O_2$. MW: 330.51. It is a pale yellow liquid. Very soluble in methanol, ethanol, acetone and heptane. Practically insoluble in water. Slight smell.

The empirical formula for DHA is $C_{24}H_{36}O_2$. MW: 356.55. It is a pale yellow liquid. Very soluble in ethanol, acetone, heptane, and freely soluble in methanol. Practically insoluble in water. Slight smell.

The capsules also contain d-alpha-tocopherol: 4 mg (antioxidant), gelatin, glycerol, purified water, medium chain triglycerides and lecithin (soya).

Omacor® capsules are gluten-free.

PHARMACOLOGY

Pharmacodynamics

The omega-3 series polyunsaturated fatty acids (OFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential fatty acids. They are essential nutrients that cannot be synthesised by the human body in sufficient amounts and have to be obtained in the diet. Like all fatty acids, omega-3 fatty acids are used to provide energy and are stored in adipose tissue; small amounts are incorporated into cell membranes as well.

Omacor® is active on the plasma lipids by lowering triglyceride levels as a result of a fall in VLDL (very low density lipoprotein), and the substance is also active on haemostasis and blood pressure.

The mechanism of action of Omacor® in lowering plasma triglycerides (TG) is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β-oxidation of fatty acids in the liver and decreased lipogenesis in the liver. Omacor® may reduce the synthesis of TG 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.

The exact mechanism of action in the secondary prevention after a myocardial infarction is not yet known and is currently being evaluated. Several studies have been performed with omega-3 formulations showing that OFA induce several beneficial changes in traditional risk factors for Coronary Heart Disease (CHD) which make omega-3 acids attractive in the prophylaxis and treatment of cardiovascular diseases.

Omacor® increases low density lipoproteins (LDL) cholesterol in some patients with hypertriglyceridaemia. A small rise in high- density lipoproteins (HDL) cholesterol has also been observed however it is significantly smaller than seen after fibrates, and is not consistent across this population subset.

There is no strong evidence that lowering the triglycerides reduces the risk of ischaemic heart disease.

During treatment with Omacor® a decrease in thromboxane A2 production has been observed and a slight increase in bleeding time (particularly with the higher doses, 4 g per day). No significant effect has been observed on the other coagulation factors (see section Precautions).

Omacor® has been shown to cause a significant reduction in blood pressure.

Pharmacokinetics

The hydrolysis of omega-3 ethyl esters by esterases in the intestine is complete and rapid. After absorption, OFA are metabolised by multiple pathways that are not highly predictable. Animal pharmacokinetic studies have shown that there is no systemic exposure of the ethyl esters. Due to this complicated process, it is not possible to conduct standard bioavailability studies, and consequently, to measure meaningful values for Cmax, Tmax, AUC, etc. for Omacor®.

The levels of EPA and DHA do increase on ingestion of Omacor®, although in a less than dose-proportional manner.

The absorption of Omacor® has been determined by measuring the increase of EPA and DHA in plasma or serum phospholipids after dosing. Significant, dose-dependent increases in serum phospholipid EPA content were seen, while increases in DHA incorporation were less marked and not dose dependent. Uptake of EPA and DHA into plasma/serum phospholipids in subjects treated with Omacor® was also independent of gender, age, and hypertensive status. Concomitant ingestion of another unsaturated fatty acid, olive oil, did not affect absorption of omega-3 fatty acids from Omacor®.

During and after absorption there are three main pathways for the metabolism of the omega-3 fatty acids:

- The fatty acids are first transported to the liver where they are incorporated into various categories of lipoproteins and then channelled to the peripheral lipids stores.
- The cell membrane phospholipids are replaced by lipoprotein phospholipids and the fatty acids can then act as precursors for various eicosanoids.
- The majority is oxidised to meet energy requirements.

The concentration of omega-3 fatty acids, EPA and DHA, in the plasma phospholipids corresponds to the EPA and DHA incorporated into the cell membranes.

CLINICAL TRIALS

Post Myocardial Infarction (MI):

GISSI-Prevenzione study: A multi-centre, randomised, open-label study performed in Italy, enrolled 11324 patients, with recent MI (< 3 months; [50% within 16 days and 72% within 30 days]) and receiving recommended preventive treatments associated with a Mediterranean diet: antiplatelet drugs, mainly aspirin (overall 82.8% at 42 months), beta-blockers (38.5% at 42 months) and ACE inhibitors (39.0% at 42 months). Since statins were not supported by definitive data on efficacy when the GISSI-Prevenzione trial was started in 1993, only 4.7% of the patients received a statin at baseline. Most of the patients were normolipidaemic (mean value of total cholesterol (TC) was 211.6 mg/dL (5.459 mmol/L), mean value of serum TG was 161.9 mg/dL (1.846 mmol/L) at baseline).

A relatively large proportion of the patients were aged > 70 years. The only exclusion criterion was any condition associated with a poor short-term prognosis (including, but not limited to, severe congestive heart failure and cancer). Patients were randomised to Omacor® (N = 2,836), vitamin E (N = 2,830), Omacor® and Vitamin E (N = 2,830) or no treatment (N = 2,828). The dose of Omacor® was 1g daily, and vitamin E was 300 mg daily. Mean duration of treatment was 3.5 years.

The analysis in the GISSI-Prevenzione trial was performed for the intention-to-treat (ITT) sample and according to two strategies defined in the protocol:

1. An analysis of efficacy of the combined two Omacor® treated groups compared to the combined two treatment groups without Omacor®, and efficacy of the combined two vitamin E supplements treated groups compared with the combination of the two treatment groups with no vitamin E. This is the two-way analysis.
2. An analysis of efficacy of each of the treatment groups: Omacor®, vitamin E supplements, and the combination versus the control group, as well as comparisons between the combination versus the Omacor® only group and the vitamin E only group. This is the four-way analysis.

The data were analysed by Kaplan-Meier-survival curves and the log-rank test. In order to further quantify treatment effects, the relative risks and associated confidence intervals were assessed using Cox's proportional hazards models adjusted for the confounding effects of relevant prognostic indicators.

In Table 1 hereafter the main results of two-way analysis are summarised for the main endpoints and selected secondary endpoints. Results of the log-rank test as well as the relative risk together with the 95% confidence interval are presented for the Omacor® group and the control group.

For this two-way analysis a 10% relative decrease in risk and a 1.3% absolute decrease in risk are observed for the combined endpoint of death, non-fatal MI and nonfatal stroke (Number Needed to Treat NNT = 77). The log-rank test was significant with a p-value of 0.048.

The relative and absolute risk decreases for the second combined endpoint cardiovascular death, nonfatal MI and nonfatal stroke were respectively 11% and 1.1% (Number Needed to Treat NNT = 91). The log-rank test result of p=0.053 was comparable to the p-value of the first combined endpoint, however, it was not significant.

Analyses of the individual components of the main endpoint showed significant differences between the two treatment groups for total mortality (p=0.016), cardiovascular death (p=0.019), coronary death (p=0.016) and sudden death (p=0.011). There was no difference across the treatment groups for non-fatal cardiovascular events and other deaths.

Table 1: Primary endpoints and selected secondary endpoints of GISSI Prevenzione

Two-way analysis					
	All (n=11324)	2 Omacor® groups with and without vitamin E (n=5666)	Log rank	2 Control groups without Omacor® (n=5668)	Relative risk (95% CI)
Main endpoints					
Death + nonfatal MI + nonfatal stroke	1500 (13.3%)	715 (12.6%)	P=0.048	785 (13.9%)	0.90 (0.82-0.99)
Cardiovascular death + nonfatal MI + nonfatal stroke	1155 (10.2%)	547 (9.7%)	P=0.053	608 (10.7%)	0.89 (0.80-1.01)
Secondary analyses					
Total mortality	1017 (9.0%)	472 (8.3%)	P=0.016	545 (9.6%)	0.86 (0.76-0.97)
Cardiovascular death	639 (5.5%)	291 (5.1%)	P=0.019	348 (6.2%)	0.83 (0.71-0.97)
Cardiac death	520 (4.6%)	228 (4.0%)	Not available	292 (5.2%)	0.78 (0.65-0.92)
Coronary death	479 (4.2%)	214 (3.8%)	P=0.016	265 (4.7%)	0.80 (0.67-0.96)
Sudden death	286 (2.5%)	122 (2.2%)	P=0.011	164 (2.9%)	0.74 (0.58-0.93)
Other death	378 (3.3%)	181 (3.2%)	Not available	197 (3.5%)	0.91 (0.74-1.11)
Nonfatal CV events	578 (5.1%)	287 (5.1%)	Not available	291 (5.1%)	0.98 (0.83-1.15)

In Table 2 hereafter the results of the four-way analysis are presented for the main endpoints and selected secondary endpoints. Results of the log-rank test as well as the relative risk together with the 95% confidence interval are presented for only the Omacor® group and the control group.

For this four-way analysis a 15% relative decrease in risk and a 2.3% absolute decrease in risk are observed for the combined endpoint of death, non-fatal MI and nonfatal stroke (Number Needed to Treat NNT = 43). The log-rank test was significant with a p-value of 0.023.

The relative and absolute risk decreases for the second combined endpoint cardiovascular death, nonfatal MI and nonfatal stroke were respectively 20% and 1.2% (Number Needed to Treat NNT = 83). The log-rank test result was highly significant with a p-value of 0.008.

Analyses of the individual components of the main endpoint showed significant differences between the two treatment groups for total mortality (p=0.009), cardiovascular death (p=0.001), coronary death (p=0.001) and sudden death (p=0.0004). There was no difference across the treatment groups for non-fatal cardiovascular events (relative risk of 0.96 and 95% CI of 0.76-1.21) and other deaths with a relative risk of 0.99 and 95% CI of 0.75-1.30.

Table 2: Primary endpoints and selected secondary endpoints of GISSI Prevenzione

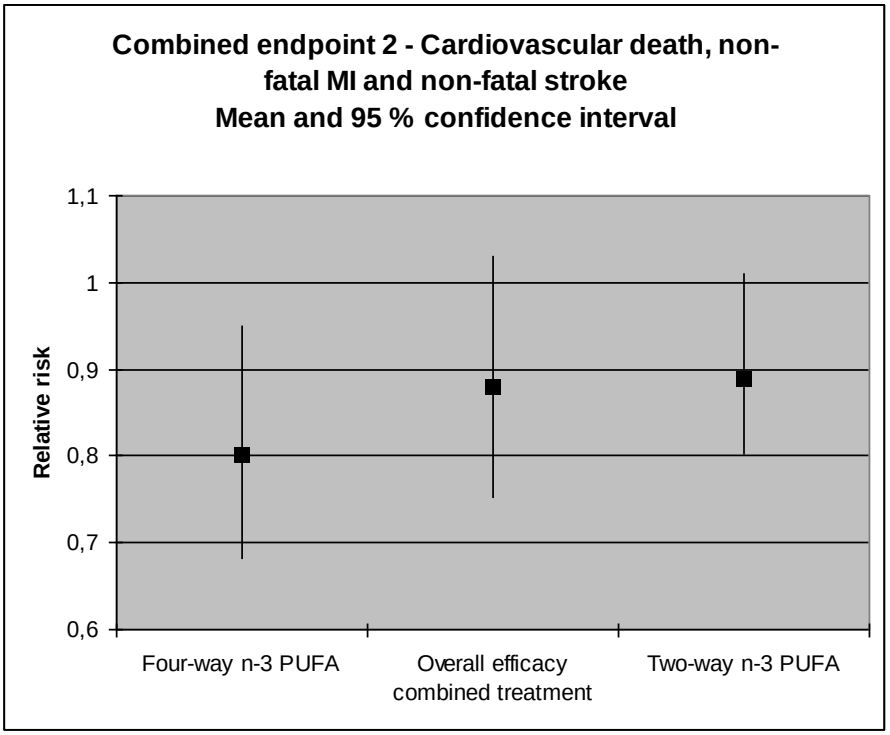
Four-way analysis					
	All (n=11324)	Omacor® (n=2836)	Log rank	Control (n=2828)	Relative risk (95% CI)
Main endpoints					
Death + nonfatal MI + nonfatal stroke	1500 (13.3%)	356 (12.3%)	P=0.023	414 (14.6%)	0.85 (0.74-0.98)
Cardiovascular death + nonfatal MI + nonfatal stroke	1155 (10.2%)	262 (9.2%)	P=0.008	322 (11.4%)	0.80 (0.68-0.95)
Secondary analyses					
Total mortality	1017 (9.0%)	236 (8.3%)	P=0.009	293 (10.4%)	0.80 (0.67-0.94)
Cardiovascular death	639 (5.5%)	136 (4.8%)	P=0.001	193 (6.8%)	0.70 (0.56-0.87)
Cardiac death	520 (4.6%)	108 (3.8%)	Not Available	165 (5.8%)	0.65 (0.51-0.82)
Coronary death	479 (4.2%)	100 (3.5%)	P=0.001	151 (5.3%)	0.65 (0.51-0.84)
Sudden death	286 (2.5%)	55 (1.9%)	P=0.0004	99 (3.5%)	0.55 (0.40-0.76)
Other death	378 (3.3%)	100 (3.5%)	Not Significant	100 (3.5%)	0.99 (0.75-1.30)
Nonfatal CV events	578 (5.1%)	140 (4.9%)	Not Significant	144 (5.1%)	0.96 (0.76-1.21)

Referring to the Lancet publication of the GISSI-Prevenzione study (1999), the first primary combined endpoint (death, non-fatal MI and non-fatal stroke) reached statistical significance for the overall efficacy of Omacor® plus vitamin E.

For the second primary combined endpoint (cardiovascular death, non-fatal MI and non-fatal stroke), neither the two-way analysis for the Omacor® effect (Table 3 in the publication) nor the overall efficacy profile of Omacor® plus vitamin E treatment (Table 5 in the publication) reached statistical significance, even so the risk reduction trend is clear.

The risk reductions for the Omacor® treatment group were 20 % in the four-way analysis (statistically significant) and 11 % in the two-way analysis (non-significant), accordingly. For the combined Omacor® plus vitamin E treatment group, the analysis showed a risk reduction of 12 %, thus demonstrating a small additional risk reduction of the combined treatment compared to the two-way analysis of the n-3 PUFA group (see the graph below).

In the analysis of this latter overall efficacy profile, the investigators compared the large Omacor® group (5666 patients), including those taking a combination of Omacor® and vitamin E, to the small “clean” control group of 2828 patients, resulting in a broader confidence interval than the two-way analysis where the control group also included the vitamin E-group (N=5658).



n-3 PUFA = omega-3 polyunsaturated fatty acids

At the end of the study 28.5% of the patients receiving Omacor® and 26.2% of the patients receiving vitamin E had discontinued treatment. Thirteen patients were lost to follow-up.

The investigators also assessed the time course of the benefit of Omacor®. Patients allocated to Omacor® had a significantly lower mortality even after 3 months of treatment (1.1% versus 1.6%, relative risk [RR] 0.59, confidence interval [CI] 0.36 to 0.97; p=0.037). The reduction in sudden cardiac death was almost significant at only 3 months, accounting for up to 57% of the overall mortality benefit (0.5% versus 0.7%; RR 0.44; P=0.048). The benefit on sudden cardiac death became significant at 4 months (2.0% versus 2.7%; RR 0.55, 95% CI 0.39 to 0.77; p=0.0006).

Hypertriglyceridaemia:

There have been eight double-blind, parallel group, placebo-controlled studies in hypertriglyceridaemia, using Omacor® 4 g per day. These eight studies are the pivotal studies. These studies included seven individual studies and one part of a study that evaluated Omacor® 2 g, 4 g, 8 g, and placebo treatment arms.

The duration of the eight pivotal studies was short term (maximum 12 weeks).

Numerous studies in patients with hypertriglyceridemia have been conducted with Omacor®, with variable designs: double-blind studies, placebo-controlled studies, randomised studies, open studies and long term studies (up to 24 months). Omacor® at doses of 4 g per day consistently and significantly reduced triglycerides levels compared to placebo. The studies have shown that the reductions were maintained for up to 24 months after treatment.

Table 3: Omacor® has been documented to have the following effects on the lipid profile.

Lipid	Effect
TG levels	Omacor® 2–4 g per day consistently and significantly reduced TG levels compared with placebo. These reductions were maintained for up to 20 months after treatment. Reductions in TG levels were observed across age, gender, and baseline TG. When Omacor® was used in conjunction with statins, an additive effect was observed.
Very-low-density lipoprotein (VLDL) cholesterol (VLDL-C) levels	Omacor® 2–4 g daily produced reductions in VLDL-C levels that were consistent with reductions in TG levels.
TC levels	Omacor® 2–4 g daily had no effect on TC levels in patients with hyperlipidaemia type IIb.
HDL-C levels	Omacor® 2–4 g daily produced small, significant increases in HDL-C levels, especially in patients with low HDL-C at baseline.
LDL-C levels	Omacor® 2–4 g daily increased LDL-C levels, especially in patients with low LDL-C at baseline (HTG type IV). The increase was probably due to cholesterol enrichment of LDL particles with a shift from small, dense LDL particles to larger, more buoyant LDL particles.

The following table summarises the median percent changes in lipid parameters from baseline in the overall population, and in patients with Types IIb, IV and V dyslipidaemia.

Table 4: Summary of median percent changes from baseline for lipids parameters by dyslipidaemia classification

	TG		TC		HDL-C		LDL-C		VLDL-C		Non-HDL-C	
	Omacor	Pbo	Omacor	Pbo	Omacor	Pbo	Omacor	Pbo	Omacor	Pbo	Omacor	Pbo
Overall (%)	-28.0	+2.5	-2.9	-0.5	+8.9	+3.5	+16.8	+0.7	-25.2	+8.0	-3.9	-1.0
Type IIb (%)	-26.3	+0.8	-2.3	-1.5	+5.5	+4.6	+1.4	-3.9	-10.9	+13.7	-3.2	-2.1
Type IV (%)	-25.5	+4.5	+2.0	+1.1	+11.1	+2.9	+33.8	+2.2	-34.3	+6.7	+1.4	+1.0
Type V (%)	-39.4	+2.8	-16.5	+0.5	+18.1	-4.6	+42.8	+19.9	-31.9	+2.2	-18.9	+0.7

Remarks:

- The documented number of patients enrolled in clinical trials with Type III dyslipidaemia is very limited, and no studies were designed to especially investigate the effect of Omacor® in these patients. Type III dyslipidaemic patients are homozygotes for ApoE, and genotyping of patients was only performed in one study (K85-95011). More Type III dyslipidaemic patients may have been therefore enrolled in clinical studies without being verified as such. There is no reason to believe that Type III dyslipidaemic patients do not respond to Omacor®.
- One of the pivotal clinical trials in patients with type IV and V dyslipidaemia (K85-95009 study) demonstrated a mean LDL-C increase of 42.6% with Omacor® 4 g/day. 67% of the patients in the study experienced increases in LDL-C, and the increases observed were in the range of 6%-110%. However, mean LDL-C concentrations at the end of the study were still only equal to 2.69 mmol/L (104 mg/dL). For the majority of these patients (40 of 42 with no history of coronary disease) this is still below their target LDL-C levels.

In clinical trials on patients with Type IIb dyslipidaemia mean LDL-C is unchanged or slightly increased (maximum 8.6%) with Omacor® treatment. In studies with concomitant treatment of Omacor® and a statin no significant increase in LDL-C has been observed with Omacor®.

The cholesterol enrichment of LDL particles appears to happen in conjunction with a marked reduction in VLDL-C. Studies also demonstrate a shift from small, dense LDL particles to larger, more buoyant LDL particles, indicating a shift towards less atherogenic lipoprotein particles.

Consistent with the overall population (see Table 5 hereafter), subjects in each baseline triglycerides level category in the Omacor® 4 g treatment group had significantly larger mean absolute and relative changes in triglycerides levels compared with those in the placebo treatment group.

For the subjects who received Omacor® 4 g per day, those with higher baseline levels (TG = 500-749 mg/dL and ≥750 mg/dL [5.65–8.46 mmol/L, and ≥8.47 mmol/L])) had greater reductions in triglycerides levels, and therefore were more likely to exhibit a better response to Omacor®.

Table 5. Mean change from baseline in TG levels at endpoint, overall and by baseline TG level - Integrated analysis of the 8 Category I studies.

	Omacor 4 g		Placebo		P-value[a]
	Mean Value		Mean Value		
Overall					
	(n = 206)		(n = 204)		
Baseline value (mg/dL, mmol/L)	422.8	4.77	404.0	4.56	
Endpoint value (mg/dL, mmol/L)	285.7	3.23	410.3	4.63	
Absolute change (mg/dL, mmol/L)	-137.0	-1.55	6.3	0.07	<0.0001
Relative change (%)	-28.0		2.5		<0.0001
≤ 250 mg/dL (≤ 2.82 mmol/L)					
	(n = 63)		(n = 67)		
Baseline value (mg/dL, mmol/L)	215.1	2.43	207.1	2.34	
Endpoint value (mg/dL, mmol/L)	172.6	1.95	216.9	2.45	
Absolute change (mg/dL, mmol/L)	-42.6	-0.48	9.8	0.11	<0.0001
Relative change (%)	-19.8		4.9		<0.0001
251-499 mg/dL (2.83-5.64 mmol/L)					
	(n = 90)		(n =88)		
Baseline value (mg/dL, mmol/L)	332.7	3.76	334.8	3.78	
Endpoint value (mg/dL, mmol/L)	243.5	2.75	338.4	3.82	<0.0001
Absolute change (mg/dL, mmol/L)	-89.2	-1.01	3.6	0.04	<0.0001
Relative change (%)	-27.0		0.9		
500-749 mg/dL (5.65-8.46 mmol/L)					
	(n = 28)		(n = 26)		
Baseline value (mg/dL, mmol/L)	599.3	6.77	597.1	6.74	
Endpoint value (mg/dL, mmol/L)	360.3	4.07	598.6	6.76	
Absolute change (mg/dL, mmol/L)	-239	-2.70	1.5	0.02	<0.0001
Relative change (%)	-39.5		1.5		<0.0001
≥ 750 mg/dL (≥ 8.47 mmol/L)					
	(n = 25)		(n = 23)		
Baseline value (mg/dL, mmol/L)	1072.4	12.11	1024.1	11.56	
Endpoint value (mg/dL, mmol/L)	638.8	7.21	1035.9	11.70	0.0001
Absolute change (mg/dL, mmol/L)	-433.6	-4.90	11.8	0.19	<0.0001
Relative change (%)	-39.4		2.8		

[a] P-values were computed using analysis of variance (ANOVA)

A number of studies have been conducted to evaluate the effect of concomitant use of Omacor® with widely used statins (simvastatin, atorvastatin). The studies have been carried out in patients with elevated serum triglycerides receiving statin therapy. The results of the studies demonstrate that the combined treatment increases the efficacy in lowering triglycerides. In these studies, little or no effect on LDL-C has been observed and no significant safety issues have been raised.

INDICATIONS

- Post Myocardial Infarction: Adjuvant treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (e.g., statins, antiplatelet medicinal products, beta- blockers, ACE inhibitors).
- Hypertriglyceridaemia: Endogenous hypertriglyceridaemia as a supplement to diet when dietary measures alone are insufficient to produce an adequate response. Treatment is indicated for the following types of dyslipidaemia (Fredrickson classification) only:
  - Type IV & V as monotherapy and with close monitoring of LDL-C levels
  - Type IIb as add-on therapy to statins, when control of triglycerides with statins has been shown to be insufficient.

Patients with higher baseline levels of triglycerides are more likely to exhibit a better response to Omacor®. Omacor® is not indicated in exogenous hypertriglyceridaemia (Type 1 hyperchylomicronaemia). There are insufficient data to support the use in patients with secondary endogenous hypertriglyceridaemia including patients with diabetes mellitus).

CONTRAINDICATIONS

Hypersensitivity to the active substance, to soya (including soya milk, soya beans) or to any of the excipients.

PRECAUTIONS

During treatment with Omacor® there is a fall in thromboxane A2 production. No significant effect has been observed on the other coagulation factors. Some studies with omega-3-acids demonstrated a prolongation of bleeding time, but the 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 combined effect of Omacor® and concomitant anticoagulants. Patients receiving treatment with Omacor® and an anticoagulant or other drug affecting coagulation (e.g., acetylsalicylic acid, warfarin, and coumarin) should be monitored periodically, and the dosage of anticoagulant therapy adjusted if necessary. (see INTERACTIONS WITH OTHER MEDICINES).

It is recommended that routine monitoring of the entire lipid profile is undertaken.

As a possible rise in LDL-C has been shown in some studies with intake of Omacor® 4g/day (see CLINICAL TRIALS), LDL-C should therefore be monitored on a regular basis, especially in patients with type IV and V dyslipidaemia.

Omacor® is not recommended as monotherapy in Type IIb dyslipidaemia. Statins are to be used as first line treatment with Omacor® indicated as add-on therapy when control of the triglyceride levels is required.

Effects on Fertility

No adverse effects on fertility were observed in a rat fertility study at oral doses of up to 2,000 mg/kg/day (35 times the human dose of 4 g/day on a mg/kg basis).

Use in Pregnancy: Category B1

There are no adequate data from the use of Omacor® in pregnant women. The potential risk for humans is unknown. Therefore Omacor® should not be used during pregnancy unless clearly necessary.

In female rats given oral gavage doses of up to 2,000 mg/kg/day (35 times the human dose of 4 g/day on a mg/kg basis) beginning two weeks prior to mating and continuing during gestation and lactation, no adverse effects were observed). In pregnant rats given oral gavage doses of up to 6,000 mg/kg/day (105 times the human dose of 4 g/day on a mg/kg basis) over gestation days 6 to 15, no adverse effects were observed. In pregnant rats given oral gavage doses of up to 2,000 mg/kg/day (35 times the human dose of 4 g/day on a mg/kg basis), from gestation day 14 to the end of lactation, no adverse effects were observed.

In rabbits given oral gavage doses over gestation days 7 to 19, no adverse effects were observed at 375 mg/kg/day (ca. 7 times the human dose of 4 g/day on a mg/kg basis), but reduced foetal weights were observed at ≥750 mg/kg/day (ca.13 times the human dose of 4 g/day on a mg/kg basis) and increased post implantation loss was observed at 1500 mg/kg/day (ca. 26 times the human dose of 4 g/day on a mg/kg basis). Doses of ≥750 mg/kg/day were maternotoxic. Overall there is no preclinical evidence for a potential risk in pregnant humans.

Use in Lactation

There are no data on the excretion of Omacor® components 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.

Paediatric Use

In the absence of efficacy and safety data, the use of this medication in children is not recommended.

Hepatic Impairment:

In some patients a small but significant increase (within normal values) in ASAT and ALAT have been reported (see ADVERSE EFFECTS). ALAT and ASAT levels should be monitored in patients with hepatic impairment, in particular with the higher dosage of 4 capsules.

Carcinogenicity

There was no evidence of a carcinogenic effect of Omacor® from the carcinogenicity studies in rats and mice at oral doses of up to 2,000 mg/kg/day (35 times the human dose of 4 g/day on a mg/kg basis).

Genotoxicity

There was no clear evidence of a genotoxic effect of Omacor® from the genotoxicity studies conducted (Ames test in Salmonella typhinurium, gene mutation at the HGPRT locus in Chinese hamster V79 cells, chromosome aberration study in cultured human lymphocytes and in vivo mouse micronucleus test).

INTERACTIONS WITH OTHER DRUGS

Increased bleeding time has been seen when Omacor® is given in conjunction with acetylsalicylic acid and warfarin, but without haemorrhagic complications (see section PRECAUTIONS).

Acetylsalicylic acid

Patients should be informed about potential increased bleeding time.

Warfarin and coumarin

The prothrombin time/international normalised ratio (PT/INR) must be monitored during combination treatment with Omacor® among patients receiving blood-thinning therapy, and when treatment with Omacor® is discontinued.

Statins

Omacor® 4 g has been administered with simvastatin 80 mg under fasting conditions to 24 healthy volunteers in a two 14-days period drug-drug interaction study. Results of this study demonstrated that at steady state, the co-administration of Omacor® capsules with simvastatin did not appear to affect the pharmacokinetics of simvastatin tablets. The combination appeared to be well tolerated.

ADVERSE EFFECTS

Post Myocardial Infarction: From the GISSI- Prevenzione study.

Adverse effects were reported as a reason for discontinuation of the therapy for 3.8% of the patients in the Omacor® groups, and in 2.1% in the vitamin E-groups. Overall, gastrointestinal disturbances and nausea were the most reported adverse effects, 4.9% and 1.4% of the Omacor® recipients, and 2.9% and 0.4% of vitamin E recipients.

Hypertriglyceridaemia:

In all subjects (655) treated with Omacor® for hypertriglyceridaemia, the following results were seen:

- Adverse events (AEs) occurred in approximately 30% of subjects,
- Only 11 specific AEs occurred at a rate greater than 1%,
- The most common treatment-emergent AEs were eructation (4.4%) and taste perversion (4.1%),
- Treatment emergent serious adverse events occurred in 2.4% of subjects,
- Four subjects (0.6%) died.

The 8 pivotal trials showed similar safety profiles.

The only potentially drug-related laboratory abnormality was mild elevation in alanine aminotransferase (ALT) levels, without concurrent elevation in aspartate aminotransferase (AST) levels.

A slight, but significant, prolongation of bleeding time has been observed without any reports of bleeding problems during clinical trials with Omacor® alone.

The following table summarises the treatment-emergent adverse events experienced by subjects from the 8 double-blind, parallel group, placebo-controlled studies in hypertriglyceridaemia, using Omacor® 4 g per day (see section Clinical Trials).

Table 6: Summary of treatment-emergent adverse events that were experienced by at least 1% of subjects in either treatment group by system organ class and preferred term (all subjects from the 8 pivotal studies)

	Omacor® 4 g per day (N = 226)		Placebo (N = 228)		P-Value[b]
SOC/Preferred Term	n	(%)	n	(%)	
Subjects with at least 1adverse event	80	(35.4)	63	(27.6)	0.0859
Infections and infestations					
Infection	10	(4.4)	5	(2.2)	0.2010
Influenza	8	(3.5)	3	(1.3)	0.1398
Nervous system disorders					
Dysgeusia	6	(2.7)	0	(0.0)	0.0147
Headache	3	(1.3)	3	(1.3)	1.0000
Cardiac disorders					
Angina pectoris	3	(1.3)	2	(0.9)	0.6847
Gastrointestinal disorders					
Eructation	11	(4.9)	5	(2.2)	0.1351
Diarrhoea	8	(3.5)	8	(3.5)	1.0000
Nausea	7	(3.1)	7	(3.1)	1.0000
Dyspepsia	7	(3.1)	6	(2.6)	0.7868
Flatulence	4	(1.8)	9	(3.9)	0.2599
Abdominal pain	2	(0.9)	3	(1.3)	1.0000
Skin and subcutaneous tissue disorders					
Rash	4	(1.8)	1	(0.4)	0.2146
Musculoskeletal and connective tissue disorders					
Back pain	5	(2.2)	3	(1.3)	0.5025
General disorders and administration site conditions					
Pain	4	(1.8)	3	(1.3)	0.7235

Adverse events were coded using MedDRA version 13.0. Subjects were counted only once for each body system and for each preferred term.

[b]: P-values were computed using Fisher's exact test.

Adverse events according to System Organ Class:

The following list presents the frequencies of study related adverse events, observed both in post-myocardial infarction and in hypertriglyceridaemia.

The frequencies of adverse reactions are ranked according to the following: Very common (≥1/10); common (≥ 1/100 to < 1/10); uncommon (≥1/1000 to < 1/100); rare (≥1/10000 to < 1/1000); very rare (< 1/10000)

Immune system disorders

Uncommon: hypersensitivity

Metabolism and nutrition disorders

Uncommon: hyperglycaemia, gout

Nervous System disorders:

Uncommon: dizziness, dysgeusia, headache

Vascular disorders:

Uncommon: hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: Epistaxis

Very rare: nasal dryness

Gastrointestinal disorders:

Common: gastrointestinal disorders (including abdominal pain, dyspepsia, gastro-oesophageal reflux disease, eructation, nausea or vomiting, abdominal distension, flatulence, diarrhoea or constipation)

Uncommon: gastrointestinal haemorrhage

Hepatobiliary disorders:

Uncommon: liver disorders – including transaminases increased (alanine aminotransferase increased and aspartate aminotransferase increased)

Skin and subcutaneous tissue disorders:

Uncommon: rash

Rare: urticaria, acne,

Investigations:

Very rare: White blood cell count increased, blood lactate dehydrogenase increased.

The following adverse event has been reported spontaneously during postmarketing use of Omacor® (frequency unknown):

Blood and lymphatic system disorders:

Haemorrhagic diathesis

DOSAGE AND ADMINISTRATION

Adults:

Post Myocardial Infarction: One capsule per day taken with a glass of water.

Hypertriglyceridaemia: Four capsules per day taken with a glass of water.

Omacor® must be taken with food to avoid gastrointestinal disturbances.

Omacor® has been given in clinical trials in doses of up to 8 g per day and has been found to be well tolerated.

OVERDOSAGE

There are no special recommendations for overdosage with Omacor®. Treatment should be symptomatic.

Contact the Poisons Information Centre on 131126 for management of overdose.

PRESENTATION AND STORAGE CONDITIONS

1000 mg; Soft, oblong, transparent capsule containing pale yellow oil.

Omacor® capsules are packed in white tamper-evident high density polyethylene (HDPE) bottles with desiccant closed with an inner seal and a screw cap.

Pack size: 28 or 100* capsules.

Store below 30 degrees C. Protect from light. Do not refrigerate. Do not freeze.

* Not currently marketed

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POISON SCHEDULE OF THE MEDICINE

Schedule 4.

NAME AND ADDRESS OF THE SPONSOR

BGP Products Pty Ltd
299 Lane Cove Road
Macquarie Park NSW 2113
Australia

DATE OF FIRST INCLUSION IN THE ARTG

28 July 2010

DATE OF MOST RECENT AMENDMENT

31 March 2015