OMACOR
1000 mg soft capsules
Omega-3-acid ethyl esters 90
ferrer

1. NAME OF THE MEDICINAL PRODUCT

Omacor®, 1000mg, soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains:
1000 mg Omega-3-acid ethyl esters 90, containing eicosapentaenoic acid (EPA) ethyl ester (460mg) and docosahexaenoic acid (DHA) ethyl ester (380mg).
The total content of Omega-3-acids ethyl esters is about 90%, including also as antioxidant 4 mg d-alpha-tocopherol (mixed with a vegetable oil e.g. soya oil).

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, soft.
Soft, oblong, transparent gelatine capsules containing pale yellow oil.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertriglyceridaemia
Endogenous hypertriglyceridaemia: as a supplement to diet when dietary measures alone are insufficient to produce an adequate response.
- type IV in monotherapy,
- type IIb in combination with statins, when control of triglycerides is insufficient.

Omacor is not indicated in exogenous hypertriglyceridaemia (type 1 hyperchylomicronaemia). There is only limited experience in secondary endogenous hypertriglyceridaemia (especially uncontrolled diabetes).

4.2 Posology and method of administration

Hypertriglyceridaemia
The daily dose is 4 grams per day taken as a single 4-gram dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily).

The capsules should be taken with food to avoid gastrointestinal disturbances.

There is limited clinical data regarding the use of Omacor in elderly patients over 70 years of age and patients with renal impairment (see section 4.4). There is no information regarding the use of Omacor in children and adolescents or in patients with hepatic impairment (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance, to soya or to any of the excipients listed in section 6.1.

Omacor contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product.

4.4 Special warnings and precautions for use

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

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

Clinical data regarding the use of Omacor in elderly patients over 70 years of age are limited.
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 (eg., acetylsalicylic acid, warfarin, coumarin) should be monitored periodically, see section 4.5.

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 4d/day, 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.

Precautions for use

Regular monitoring of hepatic function (especially ALT and AST) is required in patients with hepatic impairment, in particular with the higher dosage of 4 g per day.

4.5 Interaction with other medicinal products and other forms of interaction

Increased bleeding time has been seen when Omacor is given in conjunction with acetylsalicylic acid and warfarin, but without haemorrhagic complications (see section 4.4)

Acetylsalicylic acid:
Patients should be informed about potential increased bleeding time.

Warfarin and coumarin:
The prothrombin time/intemational normalized ratio (PT/INR) must be monitored during combination treatment with Omacor among patients receiving blood-thinning therapy, and when treatment with Omacor is discontinued.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breastfeeding There are no data on the excretion of Omacor in human milk. Omacor should not be used during lactation.

Fertility
There are no adequate data on the effect of Omacor on fertility.

4.7 Effects on ability to drive and use machines

Effects on ability to drive and use machines have not been studied. Nevertheless, Omacor is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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); not known

Immune system disorders:
Rare: 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

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

Hepatobiliary disorders:

Rare: liver disorders (including transaminases increased, alanine aminotransferase increased and aspartate aminotransferase increased)

Skin and subcutaneous tissue disorders:
Uncommon: rash
Rare: urticaria
Not known: pruritis

4.9 Overdose
There are no special recommendations. Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Omega-3-triglycerides including other esters and acids,
ATC code: C10AX06

The omega-3 series polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential fatty acids.
Omacor acts on plasma lipids by lowering triglyceride levels resulting in a fall in VLDL (very low density lipoprotein), and the substance is also active on haemostasis and blood pressure.

Omacor reduces the synthesis of triglycerides in the liver because EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis and they inhibit esterification of other fatty acids.

The increase in peroxisomes of β-oxidation of fatty acids in the liver also contributes to the fall in triglycerides, by reducing the quantity of free fatty acids available for their synthesis. The inhibition of this synthesis lowers VLDL.

Omacor increases LDL-Cholesterol in some patients with hypertriglyceridaemia. Rises in HDL-Cholesterol are only small, significantly smaller than seen after administration of fibrates, and occur inconsistently.

The long-term lipid-lowering effect (after more than one year) is not known. Furthermore, there is no strong evidence that lowering triglycerides reduces the risk of ischaemic heart disease.

During treatment with Omacor, there is a fall in thromboxane A2 production and a slight increase in bleeding time. No significant effect has been observed on the other coagulation factors.

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 1: 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 2: 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 3 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 3: 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	
Absolute change (mg/dL, mmol/L)	-89.2	-1.01	3.6	0.04	<0.0001
Relative change (%)	-27.0		0.9		<0.0001
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	
Absolute change (mg/dL, mmol/L)	-433.6	-4.90	11.8	0.19	0.0001
Relative change (%)	-39.4		2.8		<0.0001

[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.

5.2 Pharmacokinetic properties

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 lipid 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.

Animal pharmacokinetic studies have shown that there is a complete hydrolysis of the ethyl ester accompanied by satisfactory absorption and incorporation of EPA and DHA into the plasma phospholipids and cholesterol esters.

5.3 Preclinical safety data

No safety issues have been identified relevant to human use at the recommended daily intake. Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. In addition non-clinical literature data on safety pharmacology indicate that there is no hazard to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell:
Gelatine, glycerol, purified water, medium-chain triglycerides, lecithin (soya)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30ºC. Do not freeze.

6.5 Nature and contents of container

High density polyethylene bottle and screw cap with desiccant.
1 x 28 capsules, 1 x 100 capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Date of Information

February 2020

Manufacturer:
Patheon Softgels B.V.
De Posthoornstraat 7
5048 AS Tilburg
The Netherlands

Batch Released by:
Ferrer Internacional, S.A.
Joan Buscallà, 1-9
08173 Sant Cugat del Vallès (Barcelona)
Spain

Imported and Distributed by:
DCH Auriga Singapore
10 Raeburn Park, #01-33,
Singapore 088702