Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Omega-3-acid ethyl esters 90

Proprietary Product Name: Omacor

Sponsor: Abbott Products Pty Ltd (formerly Solvay Pharmaceuticals Pty Ltd)

October 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	28 July 2010
Active ingredient(s):	Omega-3-acid ethyl esters 90
Product Name(s):	Omacor
Sponsor's Name and Address:	Abbott Products Pty Ltd Locked Bag 1070, Pymble, NSW, 2073
Dose form(s):	Capsules – soft
Strength(s):	1000 mg
Container(s):	HDPE Bottle, desiccant and HDPE closure with an exterior security ring that provides tamper-evident closure of the bottle
Pack size(s):	28 and 100 capsules
Approved Therapeutic use:	Post Myocardial Infarction: Adjuvant treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (for example, 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: -Types 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 I hyperchylomicronaemia). There are insufficient data to support the use in patients with secondary endogenous hypertriglyceridaemia including patients with diabetes mellitus.
Route(s) of administration:	Oral (PO)
Dosage:	**Adults:** Post Myocardial Infarction: One capsule/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.
ARTG number(s):	155717

Product Background

Omacor capsules are manufactured, licensed and supplied to Abbott Products (formerly Solvay) by the innovator company, Pronova BioPharma of Norway. The active pharmaceutical ingredient (API) of Omacor, omega-3-acid ethyl esters 90, is chemically different from the original biological substances- fatty acid (FA) glycerol esters (triglycerides) obtained by extraction from crude fish oil. Chemically changed and different from the source biological material and then highly purified, omega-3-acid ethyl esters 90 are well characterised with their own monograph in the British Pharmacopoeia. However, this active ingredient has not been previously registered in Australia as a prescription medicine and is therefore considered as a new chemical entity for registration purposes.
One of the best natural sources of omega-3FA is fish, especially mackerel, herring, salmon and tuna. The innovator company is based in a country (Norway) where fish forms a significant part of the diet. EPA and DHA are the main constituents of fish oil. EPA and DHA are essential polyunsaturated fatty acids and cannot be synthesised from omega-6 FA found in vegetable oils (for example, linoleic acid). Alpha-linolenic acid (ALA) is also an omega-3FA predominantly found in plant derived products such as soybeans, canola oil and flaxseed oil; ALA is converted to EPA in the body to a certain extent. Triglycerides (TGs) contain 3 long chain FA molecules attached to a glycerol backbone.
The Australian Register of Therapeutic Goods (ARTG) is replete with hundreds of products derived from fish oil and these are listed under Fish Oil and Omega – 3. The ARTG listed Fish Oils typically contain 30% EPA/DHA in triglyceride form. A number of products are formulated as capsules of 1g which contain lower amounts of EPA and DHA. Omacor is a highly purified omega -3FA product, the first omega-3 application as a prescription medicine. The proposed administration of fewer capsules compared with other listed fish oil capsules would be more convenient for patients, resulting in improved compliance.

A presubmission meeting for Omacor was held at the TGA in May 2006. Discussion centred upon the proposed indication especially secondary prevention after myocardial infarction (MI) and a pivotal trial, GISSI-Prevenzione (Gruppo Italiano per Studio della Sopravvivenza nell'Infarto Miocardico) published in the Lancet in 1999. In this meeting, the sponsor was advised to provide further data to support the secondary prevention indication and has subsequently submitted a hybrid submission of internal reports and published studies for both indications.

Omacor is proposed for patients with hypertriglyceridaemia, (Type IV, IIb, and III). Elevated TG levels are described as an independent risk factor for coronary heart disease (CHD) in a number of large epidemiological studies. This is the rationale for Omacor treatment of hypertriglyceridaemia (HTG), especially in patients whose TG levels have remained elevated despite a low fat diet and other medications known to have a significant effect on TG levels, that is, fibrates such as gemfibrozil, and nicotinic acid.

In patients with extremely high TG levels (>1000mg/dL or≥ 12 mmol/L) t here is an increased risk of acute pancreatitis (Fredrickson Type IV/V HTG). Although the Fredrickson classification of hyperlipidaemia (synonyms dyslipidaemia, hyperlipoproteinaemia) is considered dated, it does provide a relevant separation of lipid disorders based on the predominant elevated lipoprotein(s). Fredrickson Type II and IV hyperlipidaemia are common whereas I, III, V are rare. Only the more severe forms are approved indications in the USA (TG>500mg/dL: > 5.7mmol/L).

There is no information pertaining to Omacor dosing in children or in patients over 70 years of age.

Table 1 lists some currently available hypolipidaemic agents for the treatment of HTG in Australia.

Table 1 Hypolipidaemic Agents for Hypertriglyceridaemia in Australia (MIMS).
· Gemfibrozil –adjunct to diet & other therapeutic measures for severe hypertriglyceridaemia types IV and V with pancreatitis risk unresponsive to diet control; diabetic dyslipidaemia; coronary heart disease risk reduction in Type IIa and IIb hypercholesterolaemia.
· Fenofibrate – adjunct to diet in hypercholesterolaemia, dyslipidaemia types II, III, IV, V and dyslipidaemia associated with Type 2 diabetes mellitus.
· Nicotinic acid- hyperlipidaemia, hypertriglyceridaemia, Fredrickson-Lees Levy hyperlipoproteinaemia Type II, IIb, III, IV, V (adjunctive therapy).

Regulatory Status

Regulatory Status

The sponsor provided a list of countries with known regulatory status of Omacor to February 2008 (see abbreviated list in Table 2). The product Omacor was approved for marketing in 48 countries although it had been submitted in 64. The first approval was in Norway in September 1994. Similar applications (for the treatment of hypertriglyceridaemia and post myocardial infarction, MI) have been submitted in the following countries:

Table 2.

Date of marketing authorisation	Country	Trade name
1996-07-16/2006-06-xx	Austria	Omacor/ Zodin
2003-06-16	Belgium	Omacor
2006-01-xx	Finland	Omacor
1995-10-02/2003-06-11	France	Omacor/ Zodin
1996-09-12/2005-05-17	Germany	Omacor/ Zodin
1996-11-21/2005-11-xx	Greece	Omacor/ Zodin
2003-07-03	Ireland	Omacor
2006-05-xx	Israel	Omacor
2003-08-15	Netherlands	Omacor
1994-09-27	Norway	Omacor
2003-07-22	Spain	Omacor
1996-07-23/2005-12-xx	United Kingdom	Omacor/ Zodin
2004-11-11	USA	Lovaza[1]

[1]Not for the indication of "Post-MI" in the USA.

At the time of the sponsor's submission, 22 EU member states had Omacor approved by the mutual recognition procedure (MRP). The submission approved in the UK (July 1996) and the Netherlands (August 2003) was said to be identical to the current TGA submission (excluding the additional data requested by the TGA).

The European Summary of Product Characteristics (SPC) lists the indications as intended in Australia (November 2007 update). The therapeutic indications as approved in the EU are

almost the same as those sought in this application except that in the EU, Omacor is not indicated in exogenous hypertriglyceridaemia (Type 1 hypertriglyceridaemia).

Omacor was approved in the USA in November 2004 as a prescription medicine and is traded as Lovaza (the name being changed because of another US product called Amicar). Abbott Products (formerly Solvay) is not the marketing authorisation holder in the USA.

The US prescribing information only lists the hypertriglyceridaemia (HTG) indication which is more restricted than that proposed for the Australian PI. It reads:

> *Very High Triglycerides. Lovaza is indicated as an adjunct to reduce triglyceride (TG) levels in adult patients with very high (≥500mg/dl) triglyceride levels.*

The approved indications in the US Full Prescribing Information are as follows:

> *Lovaza (omega-3-acid ethyl esters) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL [1]) hypertriglyceridaemia.*
>
> ***Usage Considerations:*** *Patients should be placed on an appropriate lipid-lowering diet before receiving Lovaza and should continue this diet during treatment with Lovaza.*
>
> *Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting Lovaza therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridaemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.*
>
> ***Limitations of Use:*** *The effect of Lovaza on cardiovascular mortality and morbidity in patients with elevated triglycerides has not been determined.*

The FDA website only contains information on the hypertriglyceridaemia indication.

Less severe forms of HTG were not approved in the US because of associated rises in LDL – cholesterol (LDL-C) compared with placebo in pivotal trials. The FDA statistical reviewer found significant rises in LDL-C in patients with less severe HTG (≥ 177mg/dl and < 500mg/dl)[2] and greater falls in TG in the more severe group. "The changes in LDL-C, Apo-B and LDL-C/HDL – C could negate the potential cardio protective effect of Omacor." Very severe HTG could be equated with Fredrickson Type IV/V, hyperlipoproteinaemia (dyslipidaemia).

In the USA, the PI was revised in 2007 to include additional clinical trial data in patients with TG levels of 200 to 499 mg/dL (2.26-5.63 mmol/L).

Abbott Products (formerly Solvay) acquired the rights to Omacor from Pronova (Norway) in 2003.

[1] 500 mg/dL = 5.7 mmol/L

[2] NB Conversion mg/dLTG X 0.01129 = mmol/L

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

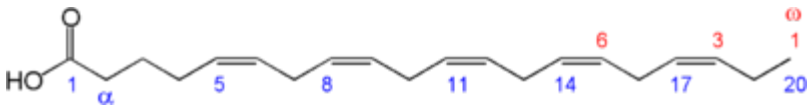
Drug Substance (active ingredient)

The drug substance is derived from natural fish oil. The process involves chemical reaction and purification to give a final product where the levels of the 2 major components 'eicosapentaenoic acid (EPA) ethyl ester' and 'docosahexaenoic acid (DHA) ethyl ester' (see structures below in Figure 1) are greatly enhanced. It is then stabilised by addition of the anti-oxidant (d-alpha tocopherol).

The specifications include tests and limits for other omega-3-acid ethyl esters, other fatty acid ethyl esters, cholesterol, Vitamins A and D, and environmental impurities such as specified heavy metals and pesticides. The advice of the Medicines Toxicology Evaluation Section (MTES at TGA) has been sought as to whether these limits are qualified.

Figure 1: Structure of the main omega – 3 fatty acid components.

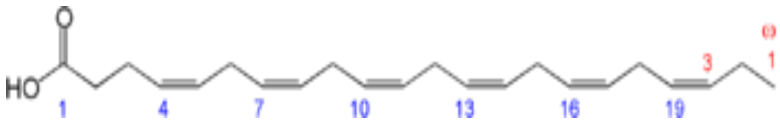
EPA



20:5 n-3

$C_{22}H_{34}O_2$, relative molecular mass 330.51.n-3 refers to first double bond at carbon 3 from the terminal methyl.

DHA



22:6 n-3

$C_{24}H_{36}O_2$, relative molecular mass 356.55. All double bonds are in the cis configuration.

Drug Product

Formulation and manufacture

Simply the drug substance (which is an oil) encapsulated in a soft gelatin capsule.

More particularly, Omacor is a concentrate of ethyl esters of long-chained polyunsaturated omega-3 fatty acids (minimum content of 90%) in soft gelatine capsules, each containing 1 g of the concentrate, corresponding to 840 mg eicosapentaenoic acid (EPA) ethyl ester/docosahexaenoic acid (DHA) ethyl ester. Each capsule contains d-alpha-tocopherol, added as an antioxidant. The active ingredient's main components, EPA and DHA ethyl esters, are essential nutrients that are metabolized in the same way as other long-chained fatty acids.

Specifications

The use of a disintegration test rather than a dissolution test was justified. Oxidation of the drug substance may occur. This is controlled by an anisidine value test (present in the British Pharmacopeia (BP) monograph for the drug substance). Questions were raised with the sponsor about the appropriateness of the test and the proposed expiry limit.

Stability

A number of stability studies were provided using the proposed capsules and the European packaging. A new stability section with more recent data was supplied. For hot and humid conditions the inclusion of a desiccant was shown to give better stability and is therefore the packaging presentation that should be applied for this product. The company has given a commitment to perform an appropriate in-use stability study. The inclusion of label statements 'Protect from light', "Do not refrigerate" and "Do not freeze" have also been applied.

Bioavailability

During absorption of the ethyl esters, they are rapidly hydrolysed to free fatty acids and these are rapidly incorporated into phospholipids, cholesterol esters and triglycerides. It is therefore not possible to determine the bioavailability of the ethyl esters or the free fatty acids.

The submission did not include any cross-over bioavailability studies, but did include parallel group studies comparing different products containing various purities of omega-3-acid ethyl esters and omega-3-acid triglycerides and a study comparing the product with and without olive oil (as a food).

Quality Summary and Conclusions

The quality evaluator concluded that the levels of (derivatised) EPA and DHA increased on multiple dosing of the products, but that it was not possible to conclude that this increase was greater with the proposed product over other products or that olive oil (or food) will not affect these levels.

III. Nonclinical Findings

Introduction

This was a hybrid format submission made up of company-sponsored studies and published studies. The published studies, as expected, were a disparate collection, rarely relating to the specific product in question. Additional reasons that the data from these studies were often difficult to extrapolate to the clinical situation included difficulty in estimating the dose of omega-3 fatty acid(s) and/or the experimental model was not relevant. Further, the extent to which the submitted published papers reflect the broader literature had not been assessed. However, although lacking the focus of company sponsored studies, the literature studies provided useful back-up information.

Only one company-sponsored primary pharmacology study investigating the lipid lowering activity of the drug was submitted. However, data on plasma lipids from the repeat dose toxicity studies confirmed the lipid lowering activity of the product at high doses. The remaining primary pharmacology data were from published studies. It was disappointing that the sponsor did not submit a study to support the postmyocardial infarction indication, however, studies published in the literature (rats and dogs) provided evidence of a role for fish oil omega-3 fatty acids in the prevention of ventricular arrhythmias.

Secondary or safety pharmacology data were derived solely from the published literature, although some of the repeat dose toxicity studies included electrocardiogram (ECG) data. These data, although limited, are considered sufficient, given the nature of the product. No nonclinical data on drug interactions were submitted and therefore clinical data will need to be relied upon with respect to drug interactions.

The sponsor submitted three pharmacokinetic (PK) studies, an absorption study, a distribution study and a study examining faecal excretion, as well as backup literature data. Once absorbed and hydrolysed, the EPA and DHA released from Omacor will enter the body

lipid pool and will be distributed, stored and metabolised and used as an energy source, like any other dietary fat. Given this, it is considered that the pharmacokinetic data submitted by the sponsor were sufficient, particularly in light of the fact that the sponsor provided toxicokinetic data (serum/plasma lipid composition) from repeat dose studies.

Acute toxicity studies were not conducted, given the low toxicity of the product. The lack of such studies is considered acceptable, particularly given that adequate repeat dose studies were conducted (28-day, 90-day and 52-week studies in both rats and dogs), with the 52 week studies being Good Laboratory Practice (GLP)-compliant.

Submitted genotoxicity studies (bacterial reverse gene mutation, forward gene mutation at the HGPRT (hypoxanthine-guanine phosphoribosyltransferase) locus, chromosomal aberrations in cultured lymphocytes and an *in vivo* mouse micronucleus test) and carcinogenicity studies (80-88 week mouse and 101 week rat studies) and reproductive toxicity studies (fertility and early embryo development study in rats, embryofetal development studies in rat and rabbit, and peri-postnatal development study in rats) were generally in accordance with International Conference on Harmonisation (ICH) requirements and all were GLP compliant.

Additional studies such as local tolerance were not submitted and this is acceptable for this type of product.

NB. Published references cited in the nonclinical sections of this document are listed in Appendix 1.

Pharmacology

Primary pharmacodynamics

Omega-3 fatty acids are essential fatty acids as they are not synthesised by the body in sufficient quantities for requirements. EPA and DHA occur naturally in fish, particularly oily fish such as mackerel. Thus, the pharmacodynamic (PD) effects of Omacor will essentially relate to the inherent biochemical properties of naturally occurring EPA and DHA.

Postmyocardial infarction indication

Although all data relating to this indication were from published studies, these studies, which used ischaemia-induced arrhythmia models (mainly *in vivo*), provided evidence for the cardioprotective, anti-arrhythmic activity of omega-3 fatty acids. The *in vivo* studies submitted were from two research groups, with one group (McLennan *et al*. 1996) studying rats in which DHA rather than EPA appeared to be effective, and the second group (Billman *et al*. 1997) studying dogs in which both EPA and DHA appeared to be effective.

In the *in vivo* rat study, the diet was supplemented with EPA ethyl ester, DHA ethyl ester or a mixture of omega-3 fatty acid ethyl esters and animals were fed *ad lib*, achieving doses of up to 450 mg/kg/day test fatty acid. On a mg/kg basis, this dose is considerably higher than the 1 g/day proposed clinical dose of Omacor for the postmyocardial infarction (post-MI) indication (1 g/day corresponds to 14.3 mg/kg/day for a 70 kg person).

The dog model used intravenous (IV) infusions of either fatty acid mixtures or individual fatty acids, which may not reflect the clinical situation in which plasma fatty acids would mainly be in the form of triglycerides, although it is not clear whether this difference would influence the cardiovascular primary pharmacological effect. When EPA and DHA (as individual fatty acids) were infused in the dog, plasma concentrations of 323 and 546 nmol/mL EPA and DHA, respectively, were achieved. In a clinical pharmacokinetic study reported in the literature (Marsen *et al*., 1992), a mixture of fish oils (3 g/day, formulated in capsules as either ‘Ameu’ or ‘MaxEPA’) was given to healthy volunteers for 4 weeks. The fish oil mixture included daily doses of EPA (510-600 mg) and DHA (330-510 mg), that is,

only slightly higher than the doses of EPA and DHA that patients given 1g Omacor/day would receive (about 460 mg EPA/day and about 380 mg DHA/day). In that study, fatty acid analysis revealed maximum plasma concentrations of EPA of 5.5-7.7 mg/dL (≈170-230 µM), depending on the formulation administered, and of DHA of 8.9-9.8 mg/dL (≈ 250-270 µM). Although comparisons are not based on free fatty acid concentrations, these values for maximum EPA/DHA plasma concentrations in humans are about half the plasma concentrations obtained in the dog study which resulted in protection from ventricular fibrillation in >70% of dogs.

In vitro studies provided some insight into the mechanisms underlying the anti-arrhythmic effects of the omega-3 fatty acids. Both EPA and DPA were found to be blockers of several cardiac ion channels, including the depolarizing sodium (Na^+) current, the repolarising transient outward potassium (K^+) current and the L-type calcium (Ca^{2+}) current. In addition, EPA and DHA (5 µM) increased sarcoplasmic Ca^{2+} content but Ca^{2+} release from the sarcoplasmic reticulum was reduced by EPA (>10 µM). Concentrations of free EPA and DHA required for these effects on ion currents and sarcoplasmic reticulum Ca^{2+} content and release were in the low micromolar range. Data from the above-mentioned clinical study indicated that plasma concentrations above this level are reached clinically at a dose similar to the proposed clinical dose for the antiarrhythmia indication. Further, higher concentrations of the omega-3 fatty acids are thought to be achieved locally within the cell membrane than are found free in plasma.

Other effects of omega-3 fatty acids that are discussed under '*Secondary Pharmacology'*, although not always consistently observed, may also contribute to the antiarrhythmic effects. These include antithrombotic effects, antihypertensive effects and anti-atherosclerotic effects.

Hypertriglyceridaemia indication

The sponsor submitted one primary pharmacology study, a 3-week study in rats which, although Omacor was given by the dietary rather than the gavage route, demonstrated a dose related reduction in plasma triglycerides, total cholesterol and phospholipids. In the majority of the repeat dose studies, dose related reductions in serum/plasma total lipids, triglycerides, total cholesterol and phospholipids were also observed. There is also evidence from published studies that repeated administration of fish oil or the individual omega-3 fatty acids, EPA and DHA (or their ethyl esters) from fish oil (either in the diet or by gavage) will reduce plasma triglycerides and cholesterol. The study that most closely mimicked the proposed use of Omacor in humans is that of Demoz *et al*. (1994) in which EPA or DHA were administered PO to rats at 1000 mg/kg/day for 3 months. Both EPA and DHA reduced plasma cholesterol concentrations and EPA reduced plasma triglycerides.

Effects on the lipoprotein fractions were less extensively investigated and results were more variable, but in some studies reductions in Very Low Density Lipoproteins **(**VLDL**),** Low Density Lipoproteins **(**LDL**)** and/or High Density Lipoproteins **(**HDL) were observed. In isolated hepatocytes from various species it was found that, compared to oleic acid, EPA (and in some instances DHA) reduced the secretion of VLDL triglyceride and/or apoB proteins (Lang and Davis, 1990, Benner *et al*., 1990, Wang *et al*., 1993 and Lin *et al*., 1995). Studies in isolated perfused rat liver also showed that EPA or EPA+DHA reduced the secretion of VLDL triglyceride compared with oleic acid (Zhang *et al*., 1991 and Wong and Marsh, 1988). Reductions in plasma VLDL levels were observed in some *in vivo* studies (Froyland *et al*. 1997 and Adan *et al*. 1999a). The sponsor's Clinical Overview reported reductions in VLDL and increases in HDL in patients given Omacor 4 g daily.

In the sponsor's 3-week primary pharmacology study in rats, significant reductions in plasma lipid parameters were observed at an Omacor dose of 1.3 g/100 g diet which corresponded to 900-1300 mg/kg/day. In the 52 week rat toxicity study, significant reductions in both triglycerides and cholesterol were observed at 2000 mg/kg/day. In the 52 week dog study (no analysis of statistical differences conducted), reductions in triglycerides (females only) and cholesterol were observed at 1000 mg/kg/day. Plasma cholesterol and triglycerides were reduced in the study by Demoz *et al*. (1994) at EPA or DHA doses of 1000 mg/kg/day. The proposed dose of Omacor for the hypertriglyceridaemia indication is 2 g/day which corresponds to 29 mg/kg/day for a 70 kg person, but can be increased to 4 g/day or 57 mg/kg/day for a 70 kg person. The lowest dose tested in the sponsor's primary pharmacology rat study was 0.6 g/100g diet which corresponded to 400-600 mg/kg/day. Reductions in triglycerides at this dose were not significant (18% reduction). Lower doses were tested in the rat repeat dose toxicity studies, with 100 mg/kg/day being the lowest dose tested (52 week study); at this dose, reductions in mean plasma triglycerides were not significant, but were still sizeable (25% in males and 27% in females). Lower doses were tested in dogs, with the lowest dose being 50 mg/kg/day (28 and 90 day studies and the 52 week study). At this dose, no consistent reductions in plasma triglycerides or cholesterol were observed. Exposure ratios (ER) achieved at these doses, calculated on both a mg/kg and mg/m^2 basis, are shown in the following table (Table 3).

Table 3.

	Primary pharmacology study (D30)	**Rat 52 week study**	**Dog 52 week study**
Dose for significant ↓ in TG &/or cholesterol (mg/kg/day)	900-1300	2000	1000
ER (mg/kg) at above dose*	16-23	35	18
ER (mg/m^2) at above dose^	3-4	6	9
Low dose (LD; mg/kg/day)	400-600	100	50
ER (mg/kg) at LD	7-11	2	nr
ER (mg/m^2) at LD	1-2	0.3	nr

* ER (animal: human) calculated based on a dose of 57 mg/kg/day; ^ER calculated based on a dose of 2109 mg/m^2/day; nr - no consistent reductions in plasma triglycerides were observed, sig=significant.

In conclusion, significant reductions in plasma triglycerides were only achieved at doses of omega-3 fatty acids that were in excess of those proposed for clinical use (considerably in excess for a calculation based on mg/kg). Lower doses (see above table) achieved exposures closer to expected clinical exposures, but only elicited small, non significant reductions in plasma triglycerides. Thus, a lipid lowering effect in experimental animals has not been demonstrated at the doses proposed clinically. It will be necessary to rely on clinical data for confirmation of efficacy for the triglyceride lowering indication.

In vitro studies have investigated possible mechanisms of the lipid lowering activity of the omega-3 fatty acids which include inhibition of the activity of diacylglycerol acyltransferase (the enzyme catalysing the final step in triglyceride synthesis), interference with the assembly and/or secretion of VLDL lipoproteins, increased hepatic mitochondrial beta oxidation of

fatty acids and consequent reduction in the availability of fatty acids for triglyceride synthesis, increased intracellular degradation of apolipoproteins and reduced lipogenesis in the liver.

Safety and secondary pharmacology

Safety pharmacology

Although specific safety pharmacology studies were not conducted by the sponsor, there were no data from either the company-sponsored toxicity studies or from the literature that would suggest that dosing with Omacor might have adverse effects on the functions of the vital organ systems. The organ system for which there were some pertinent data is the cardiovascular system. Thus, heart rate and electrocardiogram (ECG) parameters were measured in the 28 day, 90 day and 52 week dog studies, and in all studies, these were unaffected by treatment. Further, in a published study using a dog model of ischaemia-induced cardiac arrhythmias, Billman *et al*. (1999) found that following IV infusion of EPA to achieve a plasma concentration of 323 nmol/mL, or DHA to achieve a concentration of 546 nmol/mL, 5 of 7 dogs (EPA) or 6 of 8 dogs (DHA) were protected from ventricular fibrillation without significant changes in heart rate, PR interval or QTc interval.

Secondary pharmacology

Cyclooxygenase converts arachidonic acid to prostaglandins (PG), prostacyclins (PGI) and thromboxanes (TX) of the 2 series and EPA to the 3 series. Similarly, lipoxygenase converts arachidonic acid to leukotrienes (LT) of the 4 series and EPA to the 5 series. Kulkarni and Srinivasan (1986) demonstrated this for EPA *in vitro*, while Knapp and Salem (1989) demonstrated the production of PGI_3 in rats fed fish oil. EPA inhibits arachidonate metabolism in the cyclooxygenase pathway and this inhibition has been reported to be competitive (Obata *et al*., 1999).

Given that the eicosanoids of the different series have different biological activities, the intake of Omacor might be expected to influence biological activities in which the eicosanoids play a role. For example, changes in eicosanoid patterns might affect blood coagulation through changes in the regulation of platelet function. Thus, Kramer *et al*. (1996) showed that EPA and DHA competed with arachidonic acid to reduce thromboxane A_2 production (an eicosanoid formed from arachidonic acid which stimulates platelet aggregation and vasoconstriction) in washed human platelets. Thromboxane A_3 (a weak aggregating agent) was formed from EPA. Reductions in platelet thromboxane A_2 (or B_2, the stable metabolite of thromboxane A_2) and platelet aggregation were demonstrated in rats fed EPA and DHA ethyl esters (Nieuwenhuys and Hornstra, 1998; Adan *et al*., 1999a). However, there were no consistent findings with respect to platelet aggregation in the repeat dose toxicity studies in which they were investigated (the 28 day rat and dog studies). Further, reductions in thromboxane B_2 and platelet aggregation observed by Nieuwenhuys and Hornstra (1998) did not result in an antithrombotic effect in the aortic loop model, possibly because of the complex homeostatic mechanisms involved in controlling blood coagulation. Thus, prostacyclin opposes the action of thromboxane, and reductions in this eicosanoid may maintain constant platelet aggregation in circumstances of reduced thromboxane. A reduction in aortic prostacyclin levels following dietary supplementation with EPA or DHA ethyl ester has been observed in rats (Adan *et al*., 1999a).

In conclusion, effects on platelet aggregation and antithrombotic effects of EPA and DHA have not been consistently observed, although increased bleeding times were noted in dogs and monkeys (two published papers-Boerbom *et al.,* 1997 and Casali *et al*., 1986).

Fish oil/omega-3 fatty acids have shown some potential in preventing atherosclerotic lesions in different species, including rats (Adan *et al*., 1999a), dogs (Casali *et al*, 1986) and pigs (Weiner *et al*., 1986) but not mice (Adan *et al*., 1999b). Reductions in plasma lipids and effects on platelet function and on the endothelium may contribute to the anti-atherosclerotic effect. However, results have varied depending on the animal model, dose and other experimental conditions, with DHA lacking efficacy in a mouse model of severe hypercholesterolemia (Adan *et al*., 1999b) and EPA + DHA ethyl esters lacking efficacy in a study investigating atherosclerosis in cephalic vein grafts in cynomolgus monkeys (Boerboom *et al*., 1997).

In various rat models of hypertension, fish oil/omega-3 fatty acids have shown moderate, antihypertensive activity (Yin *et al*., 1990; Chiang *et al*., 1990; Bellenger-Germain *et al*., 2002; Bond *et al*., 1989; Rousseau *et al*., 2003). Reductions in serum and aortic levels of thromboxane A_2, a potent vasoconstrictor, may contribute to this effect. Effects in normotensive rats were generally not investigated, but Chiang *et al*. (1990) did not observe an effect of dietary supplementation with EPA on systolic blood pressure in normotensive rats.

Fish oil/omega-3 fatty acids generally resulted in improvements in various parameters relating to blood glucose levels in rat and mouse models of Type 2 diabetes mellitus (Kusunoki *et* al., 2003; Nobukata *et* al., 2000; Shimura *et al*., 1997) but were ineffective in models of insulin insufficiency (Shimura *et al*., 1997), and in one study (Hammes *et al*., 1996), diabetic retinopathy was increased in this model by fish oil supplementation. Mechanisms that might contribute to the improvements observed in the Type 2 diabetes models include increased glucose stimulated insulin secretion and endothelium-dependent vasorelaxation.

The eicosanoids are known to play a role in the regulation of inflammation and therefore effects of fish oil/omega-3 fatty acids on the synthesis/levels of inflammatory mediators (such as nitric oxide (NO), as seen by Komatsu *et al*. (2003) and tumour necrosis factor α (TNFα) and interleukin 1α **(**IL-1α**)** as seen by Curtis *et al*. (2002) might be expected, as might an effect on the process of inflammation, such as the reduction in renal disease seen in a murine systemic lupus erythrematosis model by Robinson *et al*. (1993).

The eicosanoids are also known to play a role in the regulation of immune function and therefore effects of fish oil/omega-3 fatty acids on immune function (for example, increased IL-2 production and proliferative responses to T-cell mitogens as seen by Wu *et al*.,1996) might be expected.

A number of *in vitro* and *in vivo* studies investigating a variety of tumour types suggested anti-tumour activity of omega-3 fatty acids (Palakurthi *et al*., 2000; Maehle *et al*., 1999; Sakaguchi *et al*., 1990; Rose *et al*., 1999; Boudreau *et al*., 2001; Hansen Petrik *et al*., 2000; Calviello *et al*., 2000). One study (Salem *et* al., 2000) showed the opposite effect, a stimulation of melanoma growth in mice, but this study utilized the unusual subcutaneous (SC) route rather than the dietary/oral route of administration. Possible mechanisms for these effects on tumour growth are not clear, but may involve changes in prostanoids (particularly those with angiogenic activity), lipid peroxidation, immune function and intracellular Ca^{2+}.

Given the role of prostaglandin E_2 (PGE_2) in bone resorption, effects of fish oil/omega-3 fatty acids on bone metabolism might be expected. Indeed, studies both *in vitro* and *in vivo* demonstrated favourable effects on calcium and/or phosphorus homeostasis, bone resorption, bone mass, bone density and/or susceptibility to breaks (Raisz *et al*., 1989; Haag *et al*., 2003, Sakaguchi *et al*., 1994; Sun *et al*., 2003; Yamada *et al*., 1995). However, it should be noted that the *in vivo* models were models of oestrogen deficiency or diabetic osteopenia and in one

of the studies (Sakaguchi *et al*., 1994) a beneficial effect was only observed in animals fed a low calcium diet.

Pharmacokinetics

All pharmacokinetic (PK) studies, both company sponsored and literature studies were conducted in rats, but toxicokinetic data were collected from dogs and rabbits, in addition to rats. The metabolism of fats is likely to be similar across species and the literature data for rats and the information provided in the sponsor's Clinical Overview relating to the pharmacokinetics of omega-3 fatty acids and their esters are consistent with this. Due to the nature of the product and its metabolism, it was not possible to measure meaningful values for standard pharmacokinetic parameters such as area under the concentration versus time curve (AUC) and maximum serum or plasma concentration (C_{max}).

Broadly, dietary fats are absorbed in the form of chylomicrons (large lipoproteins) which are formed in the enterocytes and released into the lymph, and then into the blood when the thoracic duct connects with the systemic circulation. Newly formed chylomicrons are generally composed largely of triglycerides (about 85%), as well as cholesterol and cholesteryl esters. The enzyme, lipoprotein lipase, found on capillary endothelial cells in adipose tissue, skeletal and cardiac muscle, and liver releases the triglycerides, and the remaining chylomicron remnant is transported to the liver where it is degraded.

Consistent with our knowledge of fat absorption, EPA and DHA were absorbed largely via the lymph. It is apparent that EPA and DHA ethyl esters were hydrolysed during absorption from the small intestine (Ishiguro *et al*., 1988) and re-esterified mainly into triglycerides for transport in the chylomicrons in lymph (Chen *et al*., 1985 and Ishiguro *et al*., 1988).

Absorption of fish oil fatty acids given orally to rats was shown to be efficient (De Schrijver *et al*., 1991; Chen *et al*., 1985), and there was further evidence of high oral bioavailability from an excretion study in which less than 10% of the dose of radioactive carbon (^{14}C)-labelled EPA ethyl ester or DHA ethyl ester was excreted in faeces over 7 days.

From a sponsor study and a published paper (Babcock *et al*. 1976), it was apparent that a substantial proportion of the absorbed radioactivity (^{14}C-EPA, ^{14}C-DHA and metabolites) was present in the liver within the first 24 h post dose. In *in vivo* studies, phospholipids were the major radiolabelled liver lipid fraction following administration of radiolabelled EPA or DHA to rats (Babcock *et* al., 1976; Ishiguro *et al*., 1988). In the post-absorptive state, VLDL produced by the liver from free fatty acids is the major source of plasma triglycerides.

De Schrijver *et al*. (1991) concluded that once polyunsaturated omega-3 fatty acids are absorbed, their effect on lipid metabolism is not determined by dietary source. Thus, once absorbed and hydrolysed, the EPA and DHA released from Omacor would enter the body lipid pool and will be distributed, stored and metabolised and used as an energy source, like any other dietary fat.

As noted above, lipoprotein lipase releases the triglycerides from circulating chylomicrons. Indeed, EPA was found to be rapidly taken up by tissues, with Chen *et* al. (1987) demonstrating that within 240 min of administration of chylomicrons enriched with ^{14}C-EPA to the jugular vein of rats, 98% of radioactivity had been cleared from the circulation.

As normal dietary fat constituents, EPA, DHA and the other omega-3 fatty acids comprising Omacor would be expected to mainly undergo oxidation, normally in the mitochondria and peroxisomes, to provide energy for the cell, but some will function as substrates for the production of the eicosanoids (Kulkarni and Srinivasan, 1986) and some will form structural components of membranes (in the form of phospholipids). Indeed when ^{14}C-EPA-Co-enzyme

A (CoA) was incubated with rat liver mitochondrial fraction (Ishiguro *et al*. 1988), it was metabolised by beta oxidation which generates acetyl-CoA, the entry molecule for the Krebs cycle. Kubo *et al*. (1988) observed that activities of purified acetyl-CoA-dehydrogenase from rat liver for EPA were 139 U/g for peroxisomal β-oxidation and 549 U/g for mitochondrial β-oxidation suggesting that hepatic peroxisomes have a quantitatively significant role in β-oxidation of EPA, together with mitochondria.

Given the physiological roles of fatty acids in the body, they would not be expected to be rapidly eliminated. Data from the faecal excretion study support this expectation (£ 11% excreted after one week). Also, given their metabolism, little fatty acid would be expected to be eliminated from the body unchanged.

Toxicokinetic data from several toxicity studies (52 week rat, and 28 and 90 day dog studies, mouse carcinogenicity study, and rabbit embryofetal development range finding study (13 days) showed that following repeated administration of Omacor, plasma concentrations of EPA and DHA (presumably largely in the form of triglycerides) increased dose dependently, while concentrations of arachidonic acid decreased dose dependently. Small dose dependent increases in docosapentaenoic acid (a metabolite of EPA and DHA) were also observed when this fatty acid was measured (dog studies). When the concentrations of groups of fatty acids were measured (mouse and rat studies), dose related increases in concentrations of the polyunsaturated n-3 fatty acids, and reductions in the concentrations of the monounsaturated fatty acids and the polyunsaturated n-6 fatty acids were observed. Some EPA and DHA would be expected to be present in the body of all species from dietary sources, with levels depending on the composition of the diet. Indeed, fatty acid analysis revealed low levels of these in the plasma of control animals in the toxicity studies.

Comparative exposures

Toxicokinetic data were provided for some of the repeat dose toxicity studies in rats and dogs, from the mouse carcinogenicity study and from the rabbit embryofetal dose-range finding study. Data for the individual fatty acids in serum or plasma were generally given as percentages of total fatty acids, although the data for mice was as mg/L. These data were not directly comparable with the pharmacokinetic data from clinical studies that were presented in the sponsor's Summary of Clinical Pharmacology Studies. These were in the form of increases in EPA and DHA concentrations in serum phospholipids above baseline values or percentage increases in EPA and DHA in serum phospholipids. Given the lack of equivalent data for pharmacokinetic comparisons between humans and the experimental animal species, the simplest approach is to make interspecies comparisons based on dose. Although interspecies exposure comparisons for most drugs are based on mg/m^2 it is not clear in the case of Omacor, whether mg/m^2 or mg/kg is the most appropriate comparator. Allometric scaling (mg/m^2 comparisons) is based on metabolic considerations, and as the omega-3 fatty acids are not metabolised like standard pharmaceuticals (but are incorporated into cell membranes, eicosanoids and into the body lipid stores), mg/m^2 may not be the most appropriate comparator. However, the omega-3 fatty acids are also not confined to the vascular space and are not strictly confined to a particular body compartment, so mg/kg is also not definitively the most appropriate comparator. Animal: human exposure ratio calculations have been done using both mg/kg and mg/m^2, although mg/kg may be the more appropriate choice of the two if adipose tissue (where the majority of Omacor components will be stored) is considered a compartment (Table 4).

Table 4.

Study details Species Study duration		**Dose** (mg/kg/day, mg/m^2/day)	**ER** (based on mg/kg)* **MI indication**	**ER** (based on mg/m^2)* **MI indication**	**ER** (based on mg/kg)^ **TG indication**	**ER** (based on mg/m^2)^ **TG indication**
Rat 52 weeks	**HD & NOAEL**	2000, 12000	140	23	35	6
Dog 52 weeks	**HD & NOAEL**	1000, 20000	70	38	17	9

ER exposure ratio (animal: human); *calculation based on a human dose of 1 g/day (14.3 mg/kg/day or 529 mg/m^2/day for a 70 kg person) for the myocardial infarction (MI) indication; ^ calculation based on a maximum human dose of 4 g/day (57 mg/kg/day or 2109 mg/m^2/day for a 70 kg person) for the triglyceride (TG) reduction indication. HD=high dose. NOAEL=No adverse effect level.

Exposure ratios were adequate in long term PO studies in both rats and dogs.

Drug interactions

Although it is proposed to use Omacor together with other standard therapy (for example, statins, antiplatelet medicinal products, beta-blockers and angiotensin-converting enzyme (ACE) inhibitors) for the post myocardial infarction indication, and in combination with statins for Type IIb/III hypertriglyceridaemia, no data on pharmacological or pharmacokinetic drug interactions were submitted. Given the nature of the product, some of the drug interactions that might occur with standard pharmaceuticals would not be expected with Omacor treatment. Nevertheless, some forms of interaction might be possible and it will be necessary to rely on clinical data to determine the safety of use of Omacor with other drugs, particularly drugs that reduce clotting.

Toxicology

General toxicity

Repeat dose toxicity studies were adequate in terms of species, duration, dose levels and parameters measured, although dose levels in the main dog studies could possibly have been a little higher. The lack of, or limited, analysis of variance in many studies was disappointing.

Reductions in plasma lipids were a consistent finding in the toxicity studies. These reductions are considered to reflect the pharmacological activity of the product and are discussed under '*Primary pharmacodynamics*'.

Fur staining was a consistent finding, being observed in high dose (HD) males and females in every toxicity study in both rats and dogs (that is, at 4000 mg/kg/day in the 28 and 90 day rat studies, at 2000 mg/kg/day in the 52 week rat study and at 1000 mg/kg/day in the 28 day, 90 day and 52 week dog studies). It was also observed in HD males (2000 mg/kg/day) in the rat carcinogenicity study and in rabbits (anal and tail fur) in the embryofetal development study at $\geq$ 750 mg/kg/day), but was not observed in mice (in either the 13 week or carcinogenicity studies).

Skin lesions were the dose-limiting finding in both rats and dogs. In the 90 day rat study, desquamation of the tail and/or feet/legs was observed as a clinical sign in all high dose males and females and the tail became necrotic in a number of animals. Due to the severity of the tail lesions, HD males (4000 mg/kg/day) euthanised in Week 9. Dose levels were halved (or approximately halved) in the 52 week study in which tail lesions were again observed at the HD (2000 mg/kg/day) but not at high incidence or severity (incidence of tail lesions in the rat carcinogenicity study at the same dose was little changed from control incidence). In the 90 day rat study, histological examination of the tail and foot/leg lesions revealed increased incidences of dermatitis, folliculitis (tail only) and hyperkeratosis/acanthosis, and in some

instances, a necrotic tail tip. Skin lesions were also observed in the 7 day pilot dog study in which one male and one female dog were dosed at 5000 mg/kg/day, with both dogs developing skin irritation. The severity of erythema, oedema, fissuring and desquamation required the female to be euthanised even when dosing was ceased 3 days earlier. The HD used in all three main dog studies (28 days, 90 days and 52 weeks) was 1000 mg/kg/day and at this dose, there was little evidence of skin pathology (dermatitis was observed in HD males in the 28 day study, but not in the longer studies using the same dose levels).

Skin changes (specifically to the skin of the mouth) were also observed in rabbits (in the embryofetal development study) at≥ 750 mg/kg/day.

These skin lesions may result from a lack of omega-6 unsaturated fatty acids, such as linoleic acid, which like the omega-3 fatty acids, are essential fatty acids. There is evidence in the literature that deficiency of linoleic acid results in skin lesions in rats and dogs. Thus, Ziboh *et al*. (2002) reported that deficiency of linoleic acid in rats results in a characteristic scaly skin disorder, and Wiese *et al*. (1966) reported skin lesions in puppies fed a low fat diet (<0.01% linoleic acid), with findings of desquamation, thickened and oedematous epidermis, and deranged keratinisation.

There was little evidence of gastrointestinal disturbance. Soft faeces were observed in all treated males and in HD females throughout the treatment period in the 28 day dog study, but similar observations were not made in any of the other dog studies (at the same dose levels) or in rats.

Reductions in body weight gain were observed in some studies (most notably, the 28 and 90 day rat studies and the 90 day dog study). However, such reductions were not consistently observed. In the 90 day rat study, they were only observed in HD males, presumably associated with morbidity due to the tail/feet lesions. These reductions were generally not associated with a reduction in food consumption.

In some studies (most notably the 28 day dog study and rabbit embryofetal development range-finding study), animals developed sores in the urogenital area and on the hind limbs. These parts of the body are likely to be contaminated with the animal's own urine. These may reflect a local irritant effect of the metabolic products of the omega-3 fatty acids excreted in urine and/or changes in the skin.

Neurological clinical signs were occasionally observed, but were not consistent findings. Thus, paddling and high stepping gait, occurring immediately after dosing and lasting about 10 min, were observed in mid-dose (MD) and HD males and females between Weeks 22 and 39 in the 52 week rat study. Dilated pupils were observed for about 1h post dosing from Day 2 to Day 6-7 in both dogs (given 5000 mg/kg/day) in the 7 day pilot dog study.

There were no major changes in haematological parameters. Small reductions in platelet numbers and increases in white blood cell (WBC) counts (generally due to neutrophils) were observed in some studies, but were not consistent findings. There were no consistent increases in prothrombin time (PT) or activated partial thromboplastin time (APTT) in either the rat or dog studies. Time to clotting was measured in the 28 day rat and dogs studies. There was no evidence of an effect in dogs, but in rats, time to clotting was increased at the HD in both males and females. Some blood samples taken for analysis of HDL, LDL and VLDL cholesterol in the 7 day pilot dog study failed to clot, but the dose was high in this study and animal numbers were low (5000 mg/kg/day; n=2). Prolonged bleeding times have been observed in published studies on dogs fed mackerel fish (Casali *et al*., 1986) and in cynomolgus monkeys given EPA/DHA supplementation (Boerboom *et al*., 1997). In

conclusion, there is some evidence from nonclinical studies of an effect on blood clotting, but mainly at high doses.

There was little evidence of target organ toxicity. In the 28 day and 90 day rat studies, small increases in aminotransferase activity (and in alkaline phosphatase (AP) in the 90 day study) were observed in HD males and females, and there were small increases in liver weight in the 28 day rat study in HD females. These findings were not associated with any histological changes in the liver in these studies, but increases in the incidence of biliary proliferation were observed in the 52 week rat study (in HD males) and the rat carcinogenicity study (mainly at the HD, in both males and females), but severity was graded as minimal to slight in most animals. Hepatocyte vacuolation was increased in severity (not incidence) in the 52 week rat study at the HD (both sexes) and Oil Red O staining of the liver showed greater fat present at the HD compared to controls. There was a small increase in the incidence of hepatocyte vacuolation (minimal to slight in severity) in HD males and females in the 13 week mouse study, and there was also a small increase in liver weight (up to 6%, in HD males and MD and HD females). However, no hepatic changes were observed at the lower doses in the mouse carcinogenicity study. The only evidence of a toxic effect in the liver in dogs was the observation of mottled/dark liver at necropsy in the 7 day pilot study (no histology was conducted in this study and there were only 2 treated animals). In conclusion, minor changes in the liver were observed in rats and mice, mainly at the highest doses tested and high exposure ratios. The hepatocyte vacuolation may have been associated with the fatty nature of the product. The biliary proliferation may have been a consequence of alterations in the composition or amount of bile produced due to the lipid content of the test article.

There were increases in kidney weights (generally <10%) in all the repeat dose rat studies, at the HD (and sometimes MD), and plasma urea was increased in HD males and females in the 52 week rat study. While no histological changes to the kidney were observed in the repeat dose rat studies, there were small increases in incidence of tubular vacuolation in the rat carcinogenicity study (HD females and all treated male groups). Staining with Oil Red O suggested that the kidney tubular vacuolation was due to lipid. Increased pigment in the kidney was also observed in the rat carcinogenicity study and Schmorl's stain revealed this to be due to lipofuscin, a pigment composed of lipid-containing residues of lysosomal digestion. In dogs, the only evidence of an effect on the kidney was the observation of pale kidneys at necropsy in the 7 day pilot study. There was no evidence of a toxic effect on the kidney in mice. In conclusion, minor effects were observed in the kidney in rats, generally at the highest doses tested, and these appeared to be due to the fatty nature of the product.

Although there were occasional findings of gastritis in the forestomach (in 5/20 HD females in the 90 day rat study), possibly due to the stress associated with the tail/feet lesions, and in the rat carcinogenicity study (non dose related increases in incidences in all treated groups), they are not considered of toxicological significance.

Adrenal vacuolation was observed in both rats (in 6/20 HD males in the 52 week study, with concomitant increase in mean adrenal weights) and dogs (in 3/4 HD females in the 52 week study), but appeared to be of minor toxicological incidence (minimal – slight in severity in dogs).

In the mouse carcinogenicity study, there were increases in the incidence of pigment in mesenteric lymph node, adrenals and ovaries, mainly at the HD in females and MD-HD in males, that were shown by Schmorl's stain to contain lipofuscin. The incidence of splenic pigment was increased in HD females in the 52 week dog study, but this finding is not considered of toxicological significance as severity was minimal to slight and there was a sizeable background incidence of this finding in control animals.

Changes in the lung (foamy histiocytes, pigmented histiocytes and cholesterol granulomas) were observed in the rat carcinogenicity study, but not in any of the repeat dose toxicity studies. The observed changes appear to be associated with the fatty nature of the product. In the rabbit embryofetal development studies (main and range finding), changes in the lung were observed at necropsy (no histopathology).

In conclusion, excluding the changes in plasma lipid parameters that can be attributed to the pharmacological activity of the product, the effects of Omacor seen in the toxicity studies were minor, and in most instances were probably associated with the fatty nature of the product and alterations in lipid metabolism. The no observable adverse effect level (NOAEL) in the 52 week rat study was considered to be the high dose of 2000 mg/kg/day and in the 52 week dog study the high dose of 1000 mg/kg/day.

Genotoxicity and carcinogenicity

The package of genotoxicity studies exceeded International Conference on Harmonisation (ICH) requirements. Study designs, including concentrations/doses tested were generally adequate, although concentrations tested in the chromosome aberration study were not optimal (see discussion below) and the HD in the mouse micronucleus study probably could have been slightly higher.

Results of most of the genotoxicity studies were negative. However, there were some equivocal/positive results. The results of the first Ames test (*S. typhimurium* strains TA1535, TA1537, TA98 and TA100) were negative. In a repeat study, which included strain TA102 as recommended in the current guideline (3BS6a)[3], results were again negative for strains TA1535, TA1537, TA98 and TA100, but some statistically significant results were obtained for strain TA102, both in the presence and absence of metabolic activation.

Some positive results were also obtained in the chromosome aberration assay in cultured human lymphocytes, but these results were difficult to interpret.

The difficulties in interpreting the results of the chromosome aberration study are to some extent overcome by the fact that the sponsor also conducted a forward gene mutation study in Chinese hamster V79 cells at the HGPRT locus. However, this genetic locus is considered less sensitive than the *tk* locus for the detection of a wide range of genetic changes, as large scale deletion events or numerical changes often do not give rise to mutant colonies at the HGPRT locus, and an *in vitro* mouse lymphoma *tk* assay is the preferred test (see ICH Topic S2B)[4]. In conclusion, the weight of evidence from all the genotoxicity studies suggests that Omacor is not genotoxic.

The carcinogenicity studies conducted in rats and mice were generally adequate in terms of study design, including, dose, duration and animal numbers, except that it was disappointing that histology was only conducted on animals that died or were killed during the study and on gross lesions and masses, and the liver for all rats. The guideline (CPMP/SWP/2877/00[5]) states that 'Listed tissues …from all animals in all groups killed during or at termination of the study should be examined microscopically.'

[3] This note for guidance concerns the application of Part 3, section D of the Annex to Directive 75/318/EEC as amended: 3BS6a Guideline Title: *Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.* The document provides guidance for the testing of pharmaceuticals for genetic toxicity. **[**EU guideline adopted by TGA.]

[4] CPMP/ICH/174/95: Note for Guidance on *Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals*.

[5] CPMP/SWP/2877/00: *Note for guidance on carcinogenic potential*. Dated 25 July 2002.

In rats, at doses up to 2000 mg/kg/day, there were no changes in the incidence of neoplastic lesions that are considered of toxicological significance. In mice, there was a significant increase in uterine smooth muscle tumours in the HD group (2000 mg/kg/day) compared with the combined control groups. The underlying cause of these uterine tumours may be treatment-related as such tumours may be promoted via cyclooxygenase (COX)-prostaglandin pathway(s) (Jabbour *et al*., 2006)[6]. Uterine smooth muscle tumours are not an uncommon tumour type in mice of this strain and age, but no historical control data for the laboratory in which the study was conducted were provided. Crl:CD-1(ICR)BR strain mice from Charles River Ltd were used in the study. Published data from Charles River Laboratories (March, 2005) on the spontaneous incidence of neoplastic lesions in this strain of mice indicate that the highest percentage incidence observed for leiomyoma was 7.50% and for leiomyosarcoma was 6.00%. The incidence of leiomyosarcoma in the Omacor HD group was 3.9% (2/51) which is lower than the Charles River historical control value of 6.00%, but the incidence of leiomyoma in the Omacor HD group was 13.7% (7/51) which is higher than the Charles River historical control value of 7.50%. However, one of the two control groups had an incidence of leiomyoma of 9.8% (5/51) which is also above the Charles River historical control value of 7.50%. Further, there was no evidence of a dose response, with no leiomyomas being found at the low dose (LD) or MD. For leiomyosarcomas, with the low numbers of tumours observed, there was also no clear evidence of a dose response. There was also no evidence of an effect of Omacor on the reproductive system in the repeat dose toxicity studies and there was no increase in the incidence of these tumour types in rats. Overall, the weight of evidence suggests that the increase in incidence of uterine smooth muscle tumours at the HD of Omacor was not likely to have been treatment related. The dose of 2000 mg/kg/day (6000 mg/m^2/day) in the mouse gives an ER (for a human dose of 4 g Omacor/day) of 35 based on a mg/kg comparison and 3 based on a mg/m^2 comparison.

Reproductive toxicity

A full complement of reproductive toxicity studies was conducted, although a peri-postnatal rather than a pre-postnatal study was done. Relevant studies were preceded by dose-range finding studies and study designs including dose levels were adequate. The fertility and early embryofetal development study had a Caesarean section group as well as a littering group.

In the fertility and early embryonic development study in rats, no effects on reproductive parameters of the F_0 generation[7] or on fetuses or pups were observed at doses up to 2000 mg/kg/day. This high dose was appropriate, given that total litter loss was observed in 3/10 litters at 3000 mg/kg/day and 2/10 litters at 6000 mg/kg/day in a dose-range finding study.

In the rat embryofetal development study, no effects on reproductive parameters of the F_0 generation or on fetuses were observed at doses up to 6000 mg/kg/day. In the rabbit embryofetal development study, a HD of 1500 mg/kg/day was selected, which was appropriate given that 3/5 does receiving 3000 mg/kg/day in the dose-range finding study were anorexic and were euthanised. Abortions were observed following Omacor administration at 1500 mg/kg/day (1/5 does in the dose-range finding study and 1/16 does in the main study). In the main study, the MD and HD were maternotoxic (reduced food intake and mean body weight gain, and in some individual animals, body weight loss) and at the HD dose, post implantation loss was increased, with a corresponding reduction in number of fetuses/doe. At the MD and HD, fetal weights were reduced and there were increases in the incidences of incomplete or absent ossification in certain bones, a common finding in low

[6] Jabbour HN *et al.* (2006). Prostaglandin receptors are mediators of vascular function in endometrial pathologies. *Mol Cell Endocrinol* 252:191-200.

[7] The initial parent generation in a multi-generation reproduction study.

birth weight fetuses. The small increases in incidences of total skeletal variations and of total external/visceral variations in the treated groups are not considered of biological significance, as the magnitude of the increases was small and there was no dose relationship. The NOAEL of Omacor for maternotoxicity and for embryofetal development in rabbits was 375 mg/kg/day. For the maximum human dose of 4 g/day, the dose of 375 mg/kg/day gives an exposure ratio of 6.6 (based on mg/kg) or 2.7 (based on mg/m^2) for a 70 kg person.

In the peri-postnatal study in rats, there were no remarkable findings at doses up to 2000 mg/kg/day.

No data were provided on excretion of Omacor into milk, although it might be expected that some EPA and DHA would be incorporated into milk triglycerides.

Nonclinical Summary and Conclusions

- Omega-3-acids ethyl esters 90 (Omacor) is a product derived from fish oil and presented in a capsule for oral administration. It contains a minimum of 90% omega-3-ethyl esters. The main components are EPA ethyl ester and DHA ethyl ester (approx. 460 and 380 mg/capsule, respectively). Omega-3 fatty acids are essential fatty acids.

- Primary pharmacology data were mainly in the form of publications and there were difficulties in extrapolating the data to the clinical situation. Published studies which used ischaemia-induced arrhythmia models provided evidence for the cardioprotective, anti-arrhythmic activity of omega-3 fatty acids, although doses employed in the animal studies were higher than the proposed clinical dose.

- While there was consistent evidence in nonclinical studies that the omega-3 fatty acids lower the levels of blood lipids, most notably, triglycerides and cholesterol, significant reductions were generally only achieved at doses in excess (*ca* 20-40-fold) of that proposed clinically for the hypertriglyceridaemia indication.

- Possible mechanisms involved in the cardioprotective activity include blocking of several cardiac ion channels (Na^+, K^+ and L-type Ca^{2+} currents) and increased sarcoplasmic Ca^{2+} content. Possible mechanisms involved in the lipid lowering activity include inhibition of the activity of diacylglycerol acyltransferase, interference with the assembly and/or secretion of VLDL lipoproteins, increased hepatic mitochondrial beta oxidation of fatty acids, increased intracellular degradation of apolipoproteins and reduced lipogenesis in the liver.

- Although specific safety pharmacology studies were not conducted by the sponsor, there were no data to suggest that dosing with Omacor might have adverse effects on the function of the vital organ systems. ECG parameters measured in the 28 day, 90 day and 52 week dog studies were unaffected by treatment. Literature data revealed that dogs were protected from ventricular fibrillation by EPA or DHA without significant changes in heart rate, PR interval or QTc interval.

- Secondary pharmacology data were literature publications only. Omega-3 and omega-6 fatty acids are converted to eicosanoids of different series and eicosanoids of the different series have different biological activities. Thus, the intake of Omacor might be expected to influence biological activities in which the eicosanoids play a role, in particular, blood coagulation. However, although fish oil/omega-3 fatty acids generally reduced thromboxane A_2 production and platelet aggregation, an effect on blood clotting in nonclinical studies was generally only observed at high doses.

- Published studies revealed generally favourable effects of fish oil/omega-3 fatty acids on atherosclerosis, blood pressure, insulin secretion and diabetes, inflammation, immune responses, anti-tumour activity and bone metabolism. Although not always consistently observed, anti-thrombotic, antihypertensive and anti-atherosclerotic effects may contribute to the anti-arrhythmic effects.

- EPA and DHA ethyl esters are hydrolysed during absorption from the small intestine. Absorption is largely via the lymph. EPA and DHA, which are transported in lymph and plasma mainly as triglycerides in chylomicrons and VLDL, are rapidly taken up by tissues. As normal dietary fat constituents, small amounts would be expected to form structural components of membranes and function as substrates for the production of the eicosanoids, with the majority being taken up into the pool of body lipids to eventually undergo oxidation, normally in the mitochondria and peroxisomes, to provide energy for the cell.

- Toxicokinetic data in rats, dogs and rabbits showed that following repeated administration of Omacor, plasma concentrations of EPA and DHA (as triglycerides) increased dose-dependently, while concentrations of arachidonic acid decreased dose-dependently.

- As no data on drug interactions were submitted, it will be necessary to rely on clinical data to determine the safety of use of Omacor with other drugs.

- Repeat-dose oral toxicity studies of up to 52 weeks duration were conducted in rats and dogs and a 13 week oral dose-range finding study was conducted in mice. Effects on lipid parameters were due to the primary pharmacological activity of the product. There was no evidence of any important target organ toxicity. The major toxic effect was skin changes that were probably due to a lack of omega-6 fatty acids. There were some minor changes in the toxicity studies/carcinogenicity studies that appeared to be related to the lipid nature of the product: increased incidences of hepatocyte vacuolation, kidney tubular vacuolation, pigment in some organs, and foamy and/or pigmented histiocytes and cholesterol granulomas in lungs. Other findings included biliary proliferation and adrenocortical vacuolation, but were of minor severity. ‘No effect’ doses in the rat and dog 52 week studies were 2000 and 1000 mg/kg/day, respectively. Acceptable exposure margins were achieved at these doses.

- The weight of evidence from genotoxicity studies (bacterial reverse gene mutation, forward gene mutation at the HGPRT locus, chromosomal aberrations in cultured lymphocytes and an *in vivo* mouse micronucleus test) suggested that Omacor is not genotoxic.

- There was no clear evidence of a carcinogenic effect in either mice or rats at oral doses up to 2000 mg/kg/day in both species.

- No effects on reproductive performance were observed in reproductive toxicity studies in rats (fertility and early embryonic development study, embryofetal development study and peri-postnatal study) at oral doses up to 2000 mg/kg/day, 6000 mg/kg/day and 2000 mg/kg/day, respectively. In a rabbit embryofetal development study, the MD and HD (750 and 1500 mg/kg/day) were maternotoxic. At these doses, there was a reduction in fetal weight and an increase in the incidence of incomplete or absence of ossification in certain bones. Additionally, at the HD dose, there was an increase in post-implantation

loss and a decrease in number of fetuses/doe. There was no evidence of a teratogenic effect in either rats or rabbits.

Recommendations

Issues addressable from the nonclinical data

The nonclinical evaluation has not raised any significant safety issues relating to the proposed use of Omacor. The submitted toxicity studies were considered adequate for this product and included repeat dose toxicity studies in rats and dogs of up to 52 weeks, genotoxicity studies, carcinogenicity studies in mice and rats and a full package of reproductive toxicity studies. The main toxicity findings were skin lesions that appeared to be due to deficiency of omega-6 fatty acids. There were also some minor changes in variety of organs, mainly relating to the fatty nature of the product. There was some evidence of an effect on blood clotting from nonclinical studies, but only at high doses.

Issues likely to be addressable from the clinical data

Assessment of efficacy for both indications will need to rely on clinical data. Nonclinical studies provided evidence for the cardioprotective, anti-arrhythmic activity of omega-3 fatty acids, although doses employed in the animal studies were higher than the proposed clinical dose. Similarly, while there was consistent evidence in nonclinical studies that the omega-3 fatty acids lower the levels of blood triglycerides, significant reductions were generally only achieved at doses in excess of that proposed clinically for this indication.

As no data on drug interactions were submitted, it will be necessary to rely on clinical data to determine the safety of use of Omacor with other drugs.

There are no objections on nonclinical grounds to the registration of Omacor for the proposed indications.

IV. Clinical Findings

Introduction

The following clinical studies were included with the current Australian submission:

(i) Bioequivalence/bioavailability studies:

CK85-002, 006, 007, 027, K85-91003, 92006. All in healthy subjects.

(ii) Dose finding studies PK:

CK85-001, K85-98023 (not available)

(iii) Pooled analysis of dose proportionality across hypertriglyceridaemia

Studies (listed with respect to daily dose and study number):

2g: CK85-013, K85-92004;

4g: CK85-013, 014, 017, 019, 022,023, K85-95014 and 95012;

6g: CK85-012;

8g: CK85-013.

This list excludes the dose finding study CK85-001 (4, 8 +14g daily) in healthy subjects.

(iv)* Pharmacokinetics /TG and fatty acid levels:*

11 randomised double-blind (DB), placebo (corn oil) controlled trials in patients with HTG. This overlaps with (iii) above – 9 studies as well as CK85-95009 and 94010 (the latter two studies in patients with severe Type IV hypertriglyceridaemia). PK was also investigated in

studies K85-95015 (patients with 1gA nephropathy) and C85-003 (in patients with hypertension)

(v) Pharmacodynamic studies:

CK85-020: leukotrienes in healthy men;

CK85-025: osmotic fragility and membrane fluidity in human erythrocytes of healthy females;

CK85-003: effect on BP in hypertensives;

CK85-004: effect on bleeding time in patients with coronary heart disease;

CK85-005: effect haemostatic variables in post MI; CK85015c: physical properties and metabolism of LDL particles in patients with psoriasis and atopic dermatitis;

CK85015d: T lymphocytes in psoriasis/atopic dermatitis;

K85-97026: endothelial function in patients with hypercholesterolaemia;

K85-97027: apolipoprotein – B100 kinetics in obese men with insulin resistance;

K85-92007: endothelial function and BP in heart transplant recipients;

K85-02025: plaque effects in patients undergoing endarterectomy (ongoing).

The literature contained a large number of studies investigating just about every aspect of the physiology of omega-3 fatty acids.

(vi) Hypertriglyceridaemia, efficacy + safety: Trials were divided into 4 categories, the first being pivotal trials.

8 double-blind (DB), parallel placebo (corn oil) – controlled studies in patients with HTG of varying severity. All were provided as internal reports.

- CK 85-013: n = 69, 8 weeks, Omacor dose (2) 4 or (8)g daily
- CK 85-014: n= 112, 12 weeks, Omacor dose 4g daily (1g X 4)
- CK 85-017: n = 55, 12 weeks, 4g daily
- CK 85-019: n = 53, 12 weeks, 4g daily
- CK85-022: n= 60, 12 weeks, 4g daily
- CK 85-023: n = 57, 12 weeks, 4g daily
- K 85-94010: n = 41, 6 weeks, 4g daily, severe HTG Type IV, USA
- K 85-94010: n = 43, 4 months, 4g daily, severe HTG Type IV, USA

All reports included ethical statements and statements of Good Clinical Practice (GCP; Categories 1 to 3). Case report forms (CRFs) were used to record data.

9 controlled trials in patients with HTG using doses other than 4g daily and/or designs different from Category 1:

- K85-95014: n = 59, DB randomised placebo-controlled (RPC) on simvastatin, 6 + 6 months, 4g daily, Type 11*b* (elevated cholesterol and TG)
- CK85-012: n= 40, DB randomised placebo controlled, 16 weeks, 6g daily
- K85-92004: n = 136, DB randomised placebo controlled, 3 months, 2g daily
- K85-97018: n = 49, DB, randomized controlled trial **(**RCT), 3 months, 3g daily
- K85-98019: n= 48, DB RCT, 3 months, 3g daily
- K85-95012: n = 21, DB RCT, 6 weeks, 4g daily, TG secondary endpoint
- K85-95013: n= 14, DB RCT crossover, 16 weeks, 4g daily, combined familial hyperlipidaemia (classified differently by sponsor)

- K85-95011: n = 98, DB randomised versus gemfibrozil, 3 months, Omacor 6g daily
- K85-95109/95210: n = 36/29, open, 5/6 months, 2 versus 4g daily

5 uncontrolled extension studies or uncontrolled parts of HTG trials:

- CK85-112: n = 35, open extension of CK85-012, 1 year, 4g daily
- CK85-113: n = 32, open extension of CK85-013*, 1 year, 4g daily
- K85-92004 extension: n = 133, open, 4 weeks only, 3g daily (2g daily in DB study)
- K85-94110: n = 38, open extension of K85-94010*, 1 year, 4g daily
- K85-95014 extension: n = 46, open, 6 months, 4g daily

* = Category 1

Other investigator initiated trials not monitored by Pronova where TG was measured:

- CK85-009: n = 20, DB RCT, 5-6 months, 6g daily, coronary-artery bypass graft (CABG) patients
- Pharmacia 3: n = 41 DB RCT, 5 weeks, 4g daily, combined hyperlipidaemia on a background of simvastatin 20mg.
- Pharmacia 5: n = 42, DB RCT add atorvastatin 10mg, 5 weeks, 2g daily in combined hyperlipidaemia. Placebo-corn oil in Pharmacia studies.
- Pharmacia 6: n = 20, DB RCT, 12 weeks, 4g daily in patients with severe HTG.
- CK85-018: n = 15, DB crossover 3 treatments 6 daily versus 6g + 40mg lovastatin versus lovastatin alone, 6 weeks per treatment in patients with Type IIa hypercholesterolaemia.
- K85-90001: n = 207, open Omacor 4g/day versus control, 9 months, after CABG/HTG.

(vii) Secondary Prevention following Myocardial Infarction

- GISSI – Prevenzione, prospective randomised open comparative trial with blinded evaluation of endpoints in 11,324 patients followed up for an average of 3.5 years. Four groups: Omacor 1g/day; Vitamin E; Omacor + Vitamin E; or control-usual treatment.
- Nilsen *et al* (also called Pharmacia 4), DB placebo (corn oil) controlled trial in 300 patients following acute myocardial infarction. The Omacor dose was 2g twice daily (bd).

The literature search by the sponsor yielded a number of systematic reviews/meta-analysis of studies employing fish or fish oil supplements in patients with known coronary heart disease. Individual studies included von Schacky *et al* (1999), Singh *et al* (1997; both fish oil supplements containing EPA and DHA), Burr *et al* (the Diet and Reinfarction Trial (DART); fish advice)

Prof Von Schacky wrote the sponsor's expert opinion for the additional literature submitted.

(viii) Other sponsored studies

(CK or K numbers) in patients with non – indicated conditions not mentioned above (safety only evaluated).

- CK85-008: n = 67, DB randomised placebo controlled, 16 weeks, 7g daily in patients with rheumatoid arthritis.
- CK85-010: n = 204, DB randomised placebo controlled, 1 year, 6g daily in patients with Crohns disease.
- CK85-011: n = 64, DB randomised placebo controlled, 2 years, 6g daily in patients with ulcerative colitis.

- CK85-015a/015b: n = 145 patients with either psoriasis or atopic dermatitis (some of the cohort employed in a PD evaluation 015c/015d), DB randomised placebo controlled, 4 months, 6g daily.
- CK85-016: n = 32, DB randomised placebo controlled (RCT), 6 weeks, 6g daily in patients with immunoglobulin A (IgA) nephropathy.
- CK85-026: n = 8, open K85 versus 30% EPA/DHA in Max EPA, 6 weeks, n-3: 3g/day in 8 patients with chronic glomerular disease.
- K85-91002: n = 500 (388 evaluable), DB RCT, 2 weeks, then 6 months, 6g daily in patients undergoing coronary angioplasty.
- K85-95015: n = 73, open randomised, 2 years, 4 versus 8 capsules daily in patients with IgA nephropathy.
- K85-98020: n = 45, DB RCT, 1 year, 4g daily in heart transplant patients.
- K85-98022: n = 20, versus Vitamin E, 12 weeks, 4g daily in patients with chronic hepatitis C.
- CK85-021: n = 31, DB RCT, 22 weeks, 6g/day in psoriatic patients.
- CK85-024: n = 22, DB RCT, 24 weeks, 6g/day in hypertensive patients.
- K85-97017: n = 24, DB RCT, 6 months – No report submitted. Conducted in heart transplant patients.
- Pharmacia 2: n = 156, DB RCT, 10 weeks, 6g daily in patients with systolic hypertension.
- Pharmacia 7: n = 339 renal transplant patients. Only a summary of the report was submitted.

Most of these trials were available as publications or preliminary reports.

There were also 3 ongoing trials (no reports submitted):

- K85-95016; n = 90, DB RCT, 2 years, 6g daily, in patients with IgA nephropathy.
- K85-98021; n = 50, DB RCT crossover, 1 month, 6g daily in patients with congestive heart failure.
- K85-02024; n = 200, DB RCT, 2 years, 2g daily in patients with renal disease and CHD.

Submitted published literature

The literature submitted pertains to the secondary prevention indication and the effect of supplement omega-3 FA on cardiovascular outcomes including mortality. Some 35 unique studies reported on mortality or cardiovascular (CV) outcomes (in patients on qualified fish intake or omega-3 fatty acid supplements). Safety was evaluated in 18 publications.

The 35 papers were part of a 315 page full text retrieval. The papers are divided according to the National Health & Medical Research Council (NHMRC) classification of evidence. An extended summary of the report is provided, derived from the submitted material.

These publications extend to December 2007.

(i) Level I Systematic Review of Relevant Randomised Controlled Trials (RCTs)

- Bucher 2002; meta-analysis of 11 dietary intervention studies and 9 studies using n-3FA: 7951 intervention, 7855 controls.
  Conclusion: reduction in overall mortality, mortality due to MI, sudden death in CAD.
- Yzebe 2004; similar to above, a meta-analysis of studies between 1966 and 2003. Results suggested a reduction in mortality due to MI but the studies did not include statin data and authors did not recommend routine addition of fish oils or fish.

- Harper 2005; systematic review of n- 3FA interventions on cardiovascular outcomes (1966-2004) and Cochrane Library. Heterogeneous studies using fish oil, plant based n-3 and diet.
  Conclusion: evidence supports a role for fish oil (EPA/DHA) or fish in secondary prevention with trials showing reduction in total mortality, CHD death and sudden death. The suggested dose was 0.5 to 1.8g/day EPA plus DHA.
- Von Schacky 2006; systematic review of EPA and /or DHA ethyl esters in cardiovascular disease (CVD) including Omacor found in studies of a Medline search as well as a Cochrane review and the author's personal database. The author concluded that DHA and EPA benefited MI survivors and that triglycerides, platelet aggregation, haemostatic factors, BP and endothelial function were favourably influenced by DHA/EPA. Further studies are required to better define anti-arrhythmic effect. Studies included the GISSI-Prevenzione and Nilsen (Pharmacia 4).
- Robinson 2006; a systematic review of randomised epidemiological and clinical trials of n-3 FA in humans (fish + plant sources) – through to July 2005. The epidemiological studies were more convincing with respect to reduction in incidence of non-fatal MI and stroke. Overall there was a potential to reduce coronary death. [The efficacy to reduce TG was greater in those with higher baseline levels – This was also evident in submitted sponsor trials.] The author found some effect on lowering BP and endothelial function but inconsistent effects on other haemostatic and inflammatory parameters and glucose metabolism.
- Hooper 2004 and 2006; Cochrane review. This included 48 RCTs (n = 36, 913) and 41 cohort analyses of 6 months or more. The data were heterogeneous and overall there was no reduction in total mortality or combined cardiovascular (CV) events in those taking additional n-3 FA. Removal of the DART 2 study (Burr 2003) resulted in a risk reduction of death of 0.83 (95%CI 0.75-0.91).

(ii) Level 2 Evidence – at least one well designed RCT

- GISSI – Prevenzione investigators 1999, Stone 2000, Marchioli 2001, Marchioli on behalf of GISSI-P investigators 2002. This trial report was also submitted in the original submission. The study enrolled 11,325 Italians post MI (within 3 months) treated openly with either Omacor 1g daily, Omacor + 300mg Vitamin E, Vitamin E alone, control-usual management for an average of 3.5 years. There were two composite endpoints both incorporating total mortality. Statin use was 5% at baseline and 47% by study end. Marchioli *et al* (2007) ruled out statins as confounder as well as the relatively healthy Mediterranean diet. They conducted an "ad hoc" analysis of the time course of effect – The positive effect on total mortality was evident at 3 months and the effect on reducing sudden death was nearly significant at 3 months and this improved with time (p = 0.0006 at 42 months).
- Nilsen 2001: This was submitted originally. It was a DB RCT of 2g twice a day (Omacor) versus corn oil placebo in 300 patients post MI for 12 to 24 months. This was a negative trial with Omacor making no difference on CV events. The author in a subsequent letter to the American Journal of Clinical Nutrition attributed the failure to a high fish diet.
- Singh 1997: This RCT compared three treatments in 404 patients with suspected acute MI: EPA/DHA 1.08/0.72g daily or 20g/day mustard oil (ALA 2.9g/day) or placebo capsules containing aluminium hydroxide for 12 months. At one year, cardiac events were significantly lower in both the fish oil and the mustard oil groups compared with placebo. The effect was evident within 28 days.

These three trials are discussed in more detail below (see *Efficacy*).

(iii) Level III Evidence in studies examining relationship between dietary fat and CV disease.

Hundreds of observational and clinical trials have been performed with fish and plant oils (mainly EPA, DHA and ALA). The literature search yielded many studies investigating the effects of n-3 FA on "risk factors" for CVD namely: serum lipids, glucose metabolism, inflammatory markers/cytokines, homocysteine, haemostatic markers, arrhythmias and HR variability, plaques, ventricular systolic dysfunction, restenosis after CABG.

- Serum lipids:
  Durrington 2001 (submitted as study K85-95014); Swahn 1998 (submitted as study CK85-019); Davidson 2007: DB, RCT in 254 HTG patients given Lovaza 4g daily or placebo for 8 weeks on a background of simvastatin 40mg daily. A significant reduction in non-HDL cholesterol and TG levels and an increase in HDL-C ($p<0.001$ versus placebo) were noted in the Lovaza group. Fatati 1996: very small study (n = 20). Giasi 1993: Open trial in 37 patients with Type II b and IV hyperlipoproteinaemia, given 3g daily for 45 days.
- Effect on Glucose Metabolism:
  Patel 2007: A pilot study in 37 post MI males given 1g Omacor daily for 3 months. A slight increase in insulin, but not glucose, compared with 'usual care' patients was noted.
- Effect on Inflammatory Markers/cytokines:
  Grundt 2003: 60 patients from post-MI study (Nielsen/Pharmacia 4). Results showed modest increase in lipid peroxidation in the Omacor group measured by TBA-MDA (thiobarbituric acid–malondialdehyde complex) at 12 months. Chan 2002: This is pharmacodynamic (PD) study number K85-97027. The authors concluded that visceral obesity is associated with increased high sensitivity C reactive protein (hs-CRP) and interleukin 6 (1L-6). Reduction in markers was attributed to concomitant atorvastatin 40mg. Madsen 2003: 60 healthy subjects were enrolled. No significant effect on hs-CRP was noted.
- Effect on Homocysteine:
  Grundt 2003: Significant decrease in homocysteine in the n-3 PVFA group compared with the corn oil group after 1 year.

  Effect on Haemostatic Markers:

  Lee 2006: Open label study in 77-post MI patients given 1g Omacor per day versus usual care. There was improvement in coagulation indices, endothelial function, platelet reactivity or inflammation in Omacor treated patients. Grundt *et al* 2003: Nilsen study cohort (60 patients) as above. No significant change in tissue factor, factor XIIa and fibrin monomer after 12 months of treatment. Prisco 1994:, DB RCT in 20 normolipaemic subjects given 4g Esapent (Omacor) or olive oil for 4 months. No significant change in fibrinolytic parameters was noted. Smith 1989: 40 post MI patients received 4g/day of K85 in addition to usual oral anticoagulants in an open study of 4 weeks duration. There was an increase in Ivy bleeding time[8] and fibrinogen with K85 treatment (these patients were stable when on anticoagulants alone).

Effect on Arrhythmia and heart rate (HR) variability (HRV):

[8] A quantitative coagulation assay based on a standardized skin wound, which measures platelet and vascular responses to injury.

Christensen 1996 and 1997: 55 patients with acute MI (AMI) received either n-3FA (8 caps = 5.2g of n-3) or placebo capsules (olive oil) in a DB randomised manner for 12 weeks. There was a minor increase in HRV, that is, RR interval from 807 to 823 ms in the n-3 group (p=0.07) with no change noted in patients on placebo. The authors concluded that the increase in HRV was favourable with respect to survival. The preparation was Pikasol (a TG concentrate).

Christensen 1998: Similar to the study described above but in 29 patients with chronic renal failure (CRF). In the former study there was no difference in ventricular ectopics. Hamaad 2006: 39 patients with AMI received either Omacor 1g/day (850-882mg EPA/DHA) or usual care in an open-label randomised single-blind manner over 3 months. There was no significant difference between groups with respect to HRV parameters. Marchioli 2005: The authors re-analysed GISSI – Prevenzione primary combined endpoints and attributed the benefit over control to a reduction in overall mortality (−20%), cardiovascular death (−30%) and sudden death (−45%). Calo 2005: The authors studied atrial fibrillation (AF) before and after CABG in 160 patients, (79 n-3 polyunsaturated fatty acids (PUFA), Omacor 2g/day versus usual care) in an open randomised manner. The incidence of AF was 33.3% in the control group and 15.2% in the omega-3 group (p=0.013).

- Effect in patients with Implantable Cardioverter Defibrillator (ICD):
  Singer 2004: In a randomised, DB study, 65 patients with cardiac arrhythmia but not CHD were given 3g/day fish oil (not Omacor but containing 1g n-3 PUFA) or olive oil capsules. The treatment duration was 6 months. The author concluded that Holter monitoring showed a decrease in atrial and ventricular premature complexes as well as positive effects on serum lipids. Brouwer 2006: This DB randomised placebo controlled trial in 546 ICD patients with documented malignant ventricular arrhythmias compared 2g/day of fish oil (= 961mg n-3 FA) and oleic acid (sunflower oil) for almost a year. There was no difference between treatments for the main outcome measures – ventricular tachycardia (VT)/ventricular fibrillation (VF) or all cause death. Leaf 2005: In this randomised DB study, the investigators compared 4g/day n-3 PUFA (65% EPA/DHA – not Omacor) with 4g olive oil over one year in 402 patients with ICD for prevention of fatal ventricular arrhythmias. There was a trend towards a prolonged time to first ICD event or death from any cause (p = 0.057) in the primary analysis (intent to treat (ITT)).

- Effect on Plaques:
  Studies by Macchi 1993, Grundt 2004 and Aarsetoy 2006. The Grundt paper concerns the 300 patients enrolled in the Nilsen secondary prevention trial which showed no difference in primary variables during the treatment period and following prolonged washout. The Macchi trial (1993) was small, only 20 patients were enrolled. Aarsetoy (2006) investigated plaque parameters in patients from the Nilsen/Pharmacia 4 trial and concluded there were no differences between Omacor and corn oil.

· Effect in Patients with Ventricular Systolic Dysfunction

Macchia 2005: analysed data from the GISSI – Prevenzione study (9630 patients) in order to assess the effect of Omacor on mortality and sudden death in patients with left ventricular systolic dysfunction (LVSD). As expected, mortality was higher in patients with ejection fractions (EF) at < 50% (12.3% versus 6.0%). The sudden death rates were 3.4% and 1.4% in patients with EF < 50% and > 50% respectively. Omacor decreased risk of death in both populations (relative risk (RR) 0.81 when EF > 50% or 0.76 when EF < 50%). The effect on sudden death was greater in those with LVSD (RR 0.42 compared with RR 0.89 in patients without LVSD).

· Effect on Restenosis after CABG

Maresta 1999 and 2002, Johansen 1999 and Eritsland 1996.

The Maresta paper concluded a small but significant reduction in restenosis at 6 months following angioplasty: 339 patients were initially given 6g Esapent or olive oil. After 1 month the Esapent dose was reduced to 3g/day. The Johansen study compared Omacor 3g bd with corn oil in 500 patients undergoing elective percutaneous transluminal angioplasty (PCTA). There was no difference in the restenosis rate after 6 months. The paper by Eritsland compared graft restenosis rates in 610 patients undergoing CABG following usual care or treatment with 4g Omacor. The conclusion was that there was a trend in favour of Omacor after one year.

· Sponsor Review of Consensus Guidelines

- The World Health Organization (WHO) recommends an intake of 1-2 servings of fish per week (1 serving = 200-500mg/week DHA and EPA) as protection against CHD and stroke.
- The American Heart Association and the European Society of Cardiology recommend for:
(i) non-documented CHD: fish, especially oily fish at least twice a week.

(ii) documented CHD: 1g of EPA/DHA per day preferably from oily fish; EPA/DHA supplements could be considered on physician consultation.

The National Health and Medical Research Council recommends in all people:

(i) ALA: 1.3g/day and 0.8g/day in men and women respectively.

(ii) DHA + EPA + DPA: 160mg/day and 90mg/day respectively.

(iii) Upper limit of (ii) of 3g/day for children adolescents and adults.

- The National Heart Foundation of Australia also recommends oily fish (2-3 serves a week at 150g per serve) or fish oil capsules or liquid in adults and food or drinks enriched in n-3 PUFA in all adults.

- Health professionals are encouraged to advise Australians with documented heart disease to consume 1000mg/day of DHA/EPA via oily fish, fish oil preparation or foods/drink enhanced with n-3FA. There is also advice to consume 2g/day of alpha-linolenic acid. Patients with elevated TG are advised as first line therapy to take 1200mg/day EPA/DHA and if appropriate, up to 4g/day.

The sponsor's current Australian submission contained 6 bioavailability (BA)/bioequivalence (BE) trials of varying design including 2 composite trials: 3 RCT DB and parallel; 3 open, randomised parallel (2) and one crossover study. There were 245 subjects (243 males) enrolled and most trials lasted 14 to 49 days. All 6 BA/BE studies employed Omacor and a comparator drug (triglyceride, other ethyl ester (EE) formulation or placebo (corn oil, olive oil)).

The rise in the EPA fraction of phospholipid was dose-dependent following FA ethyl ester doses of 4-14g (in CK85-001/002). The TG dose ranged from 12 to 24g over 14 days (30% n-3FA). The investigators (in one publication) concluded that omega-3-fatty acids (given over a 7-week period) were equally well absorbed from the TG dose and Omacor (CK85-007). The 30% TG preparation contained 18% EPA and 12% DHA.

Very large doses of Omacor were used in the crossover study, CK85-006. The composite study K859-91003/92006 compared three formulations of n-3FA ethyl esters: 62.5%, 80%, and 85%. The 85% formulation produced the highest phospholipid EPA content (equivalent to a 5.1g EPA/DHA daily dose). The PK study K85-98023, although listed in the sponsor's tabular summary of all studies, was not provided. It was described as an Italian study investigating EPA and DHA uptake in plasma, platelets and mononuclear cells following Omacor 1, 2 and 4g over 12 weeks.

There was a pooled analysis of dose proportionality across HTG studies: 2g (2 studies), 4g (9 studies), 6g (1 study), and 8g (1 study). The levels of EPA/DHA were expressed in mg/dL although the original studies used mmol/L (SI system). Most patients received 2-4g daily doses. The uptake of EPA appeared to be dose-dependent and rises in EPA and DHA were comparable to those following equivalent doses of TG preparations. An open extension of study K85-94010 showed that the increases in EPA and DHA were maintained for 1 year (K85-94110).

Incorporation of EPA and DHA was also studied in patients with HTG. Eleven trials of DB randomised, placebo-controlled design enrolled 317 evaluable subjects who received 4g Omacor daily over a period of 6-24 weeks; the mean percent increase in EPA incorporation in phospholipids ranged from 139% (CK85-023) to 361% (CK85-95011): mean DHA increased by 11 to 77% in 9 trials and decreased by 10% in one (CK85-95009).

Pharmacokinetics was also investigated in patients with IgA nephropathy (K85-95015) and hypertension (CK85-003). In 2000, the sponsor withdrew an application to the FDA for the IgA nephropathy indication.

The current Australian submission included 11 PD trials (in published form) incorporating 30 healthy volunteers (CK85-020 and 025) and patients with hypertension (n=234 in CK85-003, K85-92005), men with coronary heart disease (n=22 in CK85-004), 40 post MI patients (in CK85 -005), 23 patients with psoriasis and atopic dermatitis (in CK85-015c), 30 patients with hypercholesterolaemia (in K85-97026), 48 insulin-resistant obese men (in K85-97027) and 30 heart transplant patients (in K85-020). Patients received either 4-7g Omacor daily or a comparator drug. The following main parameters were evaluated: formation of leukotrienes in granulocytes (in CK85-020; 14 males); osmotic fragility and membrane fluidity of erythrocytes (in CK85-025; 16 females); blood pressure (in CK-003); bleeding time (in K85-004:CHD); haemostasis (in CK85-005-post MI); physical proportion and metabolism of LDL particles (in CK85-015c); endothelial function (in K85-92026); apolioprotein B-100 kinetics (in K85-97027); glucose metabolism (in K85-02025).

All PD studies showed significant fall in serum triglycerides. Where it was measured, most trials showed a slight prolongation of bleeding time (BT), but there was no consistent effect on coagulation factors noted. In study CK85-005, BT and fibrinogen were significantly increased but no significant interaction of warfarin with Omacor was noted.

The proposed mechanism of action of omega-3 fatty acids (at daily intake 2-3g/day) is a decrease in the hepatic synthesis of triglycerides. EPA is stated to affect the enzyme responsible for the last step of TG synthesis. In animals, increased peroxisomal beta oxidation has been demonstrated following n-3FA administration which in turn would reduce

the availability of free fatty acids for TG synthesis. The exact mechanism of action in post myocardial infarction (MI) patients has not been established. Several studies suggest the following protective effects may play a role: anti-arrhythmic effect, heart rate variability, reduction in blood viscosity as well as effects on fibrinolysis and platelet aggregation. Several publications claimed HR variability to be an independent risk factor for cardiovascular deaths after MI.

Literature Review updated from December 2007 to December 2008 (as requested by TGA).

Most of the publications were reviews or supplements to trials carried out prior to 2007. Significant papers included:

- Jenkins *et al*, 2008[9]. Trials in patients with implantable cardiovascular defibrillators were reviewed (from papers by Leaf *et al*, Brouwer *et al*, Raitt: all previously submitted).
- Jung *et al*, 2008[10]: stated evidence pertaining to benefits of n-3 FA in CVD (and potential underlying physiological and molecular mechanisms).
- **GISSI-HF (heart failure) trial completed in 2008:** published in Lancet online August 2008. The design was DB, RCT and compared Omacor 1g daily to placebo in 7046 patients for a median follow up of 3.9 years (interquartile range (IQR) 3-4.5). Analysis of the co-primary composite parameters revealed survival curve separation at 2 years, with a trend in favour of n-3 FA. Cardiovascular deaths occurred in 20.4% on n-3FA and 22% on placebo (adjusted HR 0.9, probability (p) = 0.045). Sudden cardiac deaths occurred in 8.8% on n-3FA and 9.3% on placebo, respectively (adjusted hazard ratio 0.93, p not statistically significant (ns)). First hospitalisation for ventricular arrhythmia numbered 3% on n-3FA and 4% on placebo, respectively, (adjusted HR 0.72, p = 0.013) There was little effect on atherothrombotic events. The incidence of stroke (fatal and non-fatal) was 3.5% in patients given n-3 PUFA and 3% placebo patients (HR 1.16, p= 0.271). All cause mortality in the per-protocol (PP) population was 26% (of those given n-3) and 29% (of those given placebo); adjusted HR 0.86, p = 0.004.
- Rauch *et al*, 2006 (OMEGA trial) described an ongoing study of omega-3FA ethyl esters in post-MI patients. This DB, RCT compared Zodin (n-3 PUFA, ethyl esters) and placebo (olive oil) in 3,827 patients within 3 to 14 days of presenting with acute MI. The main investigator was Dr Jochen Senges. The patients received optimal care for AMI. At the end of the first year there was no improvement in the incidence of sudden death and secondary endpoints. The study was described as underpowered (50%). The source of this information was Cardiology Today newsletter (30 March 2009), and not a formal trial report.
- Independent source: Lavie *et al* (2009[11]) reviewed omega-3 PUFA and cardiovascular disease and pointed out the "potential beneficial effects" of n-3PUFA in primary prevention, CHD and post-MI, sudden cardiac death, heart failure (HF),

[9] Jenkins DJ *et al* (2008). Fish-oil supplementation in patients with implantable cardioverter defibrillators: a meta-analysis. *CMAJ* 78(2): 157-164 2008

[10] Jung UJ *et al* (2008). Beyond Cholesterol: Prevention and Treatment of Coronary Heart Disease with n–3 Fatty Acids. n–3 Fatty acids and cardiovascular disease: mechanisms underlying beneficial effects. *Am J Clin Nutr* 87 (6):2003S-2009S

[11] Lavie *et al* (2009). Omega-3 polyunsaturated fatty acids and cardiovascular diseases *J Am Coll Cardiol*. 54: 585-594.

atherosclerosis and atrial fibrillation. The authors described the DART (Diet and Reinfarction Trial) results favouring fish or fish oil supplements with respect to all cause mortality and the GISSI-Prevenzione study and the JELIS trial (latter was not submitted). The JELIS trial (Japan EPA Lipid Intervention Study) enrolled 14,981 patients in primary (1º) prevention and 3,664 in secondary (2º) prevention. The patients had hypercholesterolaemia and were randomised to statin alone or statin together with highly purified EPA (1.8g daily). The study ran for 5 years. There was a 19% reduction in CV events but no reduction in sudden cardiac death (which was considered low in absolute terms).

Comment on the Submitted Publications

All publications included in this hybrid application were reviewed. Those considered relevant are described in this evaluation report. 'Relevant studies' included epidemiological studies employing a fish or fish oil arm among comparator groups as well as comparative trials and systematic reviews / meta-analyses. Some studies (both company sponsored trials and published studies) were evaluated for safety only when Omacor was used in patients with medical conditions not included in the proposed indications in the PI.

The submission included 22 studies of Omacor (of differing design) in patients with HTG, 8 of which can be considered pivotal. Pronova allowed individual investigators to perform studies according to their "specific suggestions and expertise". The eight randomised placebo-controlled double-blind pivotal trials employed 4g Omacor daily in comparison with corn oil placebo. Patients in some non-pivotal trials carried out in the USA employed patients with severe HTG. The duration of treatment in pivotal trials (provided as internal reports) ranged from 6 weeks (in one), to 12 weeks (in 5) or more (in 2). These trials showed consistent and significant reductions in serum TG and VLDL-C, and smaller increases in LDL-C. There were no significant changes in total cholesterol. Non- pivotal HTG trials included Omacor as an add-on to statins in patients with mixed/ combined hyperlipidaemia (simvastatin, atorvastatin, lovastatin) and a single DB trial comparing 6g Omacor daily with gemfibrozil in 98 patients over 3 months (published paper).

Overall the HTG package divided 30 trials into 4 categories:

1. Eight double-blind (DB), randomised (R), placebo-controlled trials using Omacor 4g daily as 1g capsules. These 'pivotal' studies, as well as those of Category 2 and 3, were conducted according to Good Clinical Practice (GCP) and patient data were recorded on case report forms (CRF).
2. Nine controlled trials of various designs and/or using doses other than 4g.
3. Five uncontrolled extension studies or uncontrolled parts of studies in HTG (extension of Category 1 & 2 studies).
4. Eight published studies including 'add on to statin' trials employing low patient numbers.

The pooled conclusions of pivotal studies are in the Clinical Trials section of the Product Information (PI), however there are no figures (means or medians) pertaining to the various lipid/lipoprotein fractions. The pivotal trials received ethical committee approval and patients were required to provide written informed consent. These trials enrolled 490 patients. Overall, there were 655 patients included in HTG trials receiving Omacor treatment.

The secondary prevention indication approved in Europe for patients following MI is accompanied by data from two main trials; GISSI-Prevenzione (documented in an internal report and publication) which enrolled 11,324 patients and Pharmacia 4 (by Nilsen *et al*) which enrolled 300 patients. Since the 1970s, evidence has been collected regarding the role of omega -3 fatty acids in the prevention and management of cardiovascular disease, both FA

derived from fish oil (EPA, DHA) and plant sources (α-linolenic acid, ALA). The published literature abounds in studies investigating biological mechanisms that might explain the reported association between omega -3 FA intake and cardiovascular outcomes. These include *in vivo* and *in vitro* studies on antiarrhythmic mechanisms, platelet aggregation inhibition and increased bleeding time.

The current submission contained a wealth of literature on individual studies (experimental and clinical) as well as systematic reviews and meta-analysis of clinical studies employing either fish diets or omega -3 fatty acids in patients with coronary heart disease. Many of these papers referred to the GISSI-Prevenzione study.

Wang *et al* (2006) carried out such a review of the health effects of n-3FA on cardiovascular (CV) outcomes in patients, including both randomised controlled trials and observational studies (that is, in patients on a diet of fish or n-3 supplements). A presentation (summarised in an abstract) from the European study of Cardiology Congress of 2008 also revealed results from a clinical trial (run by the GISSI group) investigating the effects of n-3 FA in patients with symptomatic heart failure.

The Health Professionals Study and the US Physician's Health Study (by Ascherio, 1995) showed a significant association between omega-3 FA intake and the lower incidence of sudden death. The DART study (Burr *et al* 1999) was the first study to investigate the effects of omega-3 FA intake (not Omacor) in men following MI: it showed a 29% decrease in all cause mortality over a 2 year period. Many studies have shown the positive effect of statins in secondary prevention. The GISSI-Prevenzione study and the Nilsen study employed omega-3FA ethyl ester formulations in order to evaluate cardiovascular outcome, both mortality and non-fatal cardiovascular events.

The GISSI-Prevenzione study was open and patients were randomised to one of four groups: Omacor, Omacor + Vitamin E, Vitamin E and control (usual care). Those on the test medications also received usual care. The trial was designed to represent "normal clinical practice" and covered a broad spectrum of patients. A placebo arm was not employed as the sponsor considered that no real 'inert' Omacor placebo exists. However corn oil placebo was used in pivotal HTG clinical trials. In GISSI-P, deaths and events covered in primary endpoints were blindly evaluated by an expert committee. The selection of the 1g Omacor daily dose was based on the previous DART study. The primary endpoints were composite including all cause mortality and cardiovascular deaths. When the study commenced, a relatively small number received statins, however by the end, concomitant statin intake had increased following the results of the 4S (Scandinavian Simvastatin Survival Study) and CARE (Cholesterol and Recurrent Events study) studies to 42.2% in the Omacor group. Overall GISSI-P showed a 15% risk reduction for the first composite endpoint (death, non fatal MI, non-fatal stroke). There was no significant reduction in non-fatal CV events in a population accustomed to a Mediterranean diet. The greatest effect was on sudden death. A sub-analysis carried out by the sponsor revealed that the mortality rate was not influenced by statin intake. The effect of the 1g dose on triglycerides was minimal (mean 3.4% decrease). It was extraordinary that only 13 patients were lost to follow-up. A large number of publications were submitted with experimental evidence to support the risk reduction in mortality and sudden death following omega-3 FA intake.

The Pharmacia 4 (Nilsen *et al*), a randomised DB trial study, which compared Omacor 4g daily with corn oil placebo in 300 post MI patients, showed no difference on endpoints, despite the significant decrease in triglycerides over an 18 month period and a slight increase in the HDL-C. The population generally ate a high fish diet and lived in coastal areas. The ratio of EPA to DHA was 1.2:1.

The DART trial mentioned above was a dietary advice trial conducted in 1989.

The clinician that provided the sponsor's expert opinion also conducted a trial comparing omega-3FA and non-marine fatty acids in 223 patients (half had recent MI). Although this trial showed no significant reduction in cardiovascular events (although a trend was noted), the author did support the marketing of Omacor for the proposed indications in Australia.

Omacor was well tolerated in trials carried out to investigate secondary prevention, especially in the GISSI-Prevenzione trial. In this trial 3.8% discontinued use because of adverse events (AE) following Omacor compared with 2.1% following Vitamin E. A total of 376 (6.6%) experienced 452 AE attributed to omega-3FA, most commonly dyspepsia, nausea (1.4%) and gastrointestinal disturbances (0.5%). Dyspepsia was also common (1.8%) among those on Vitamin E. Patients receiving Vitamin E ± ω-3FA experienced 234 AE (in 207 patients or 3.7%). There was no difference between groups with respect to arrhythmias and gastrointestinal haemorrhage.

In the pivotal HTG trials where patients received 4 g daily, gastrointestinal (GI) events were reported in 15.9% on Omacor versus 13.6% on corn oil. Taste perversion occurred in 6% of patients on Omacor compared with 0 patients given placebo corn oil; rash was reported in 1.8% and 0.4% respectively. In HTG trials combined, 655 patients received Omacor treatment. The most common treatment-emergent AE were eructation (44%) and taste perversion (4.1%). Serious AE were recorded in 2.5% of patients and four of these patients died (integrated analysis by the sponsor). Some clinical trials (internal reports and publications) reported slight increases in bleeding times that were sometimes statistically significant. However there were no clinical bleeding episodes attributed to Omacor treatment. The proposed Australian PI contains the safety data presented above and includes recommendations for monitoring of both coagulation (if on high doses or other anticoagulants) and liver function (mild deviations of alanine transaminase (ALT) seen in some trials). The Omacor exposure was less than 6 months in most trials, however the GISSI-P trial (the largest) followed patients for up to 3.5 years.

Drug batches used in clinical studies

Many of the publications provided background material and non-clinical data. These were mentioned and referenced in the sponsor's clinical expert report (CER) where relevant. Irrelevant material was excluded.

The summary data state omega – 3 – acid ethyl esters as above and α – tocopherol 2.4 to 4.6 mg in 5 batches used in clinical trials. The capsule shell contained gelatin, glycerol, water purified, and colourants. The 5 batches were only used in some of the clinical trials called pivotal, CK85-013a ; CK85 – 014 ; CK85 – 019 ; CK85 – 022 ; CK85 – 023 ; CK85 – 017 ; K85 – 94010 ; K85 – 95009 (all in patients with hypertriglyceridaemia).

The pivotal secondary prevention trial GISSI – Prevenzione employed an "Omacor" product (called Seacor and Esapent in Italy). The 1g soft gelatin capsule contained a minimum of 850mg EPA + DHA ethyl esters.

The ratio of EPA to DHA in the proposed market formulation is 1.2:1. Some of the studies described in publications used ethyl ester preparations which had slight variation in the proportion of EPA and DHA (considered the active moiety) compared with 'Omacor". These variations would probably not impact on the efficacy results. Most of the internal reports and published trials provided compositional details of the ethyl ester preparations employed.

Pharmacokinetics

EPA and DHA are hydrolysed in the intestine, absorbed and then re-esterified and carried in chylomicrons. Lipoprotein lipase hydrolyses the TG core resulting in release of fatty acids for uptake into the cells. Fatty acids are incorporated into cell membranes including those of erythrocytes. The sponsor elected to measure plasma phospholipids before and after EPA/DHA ingestion.

The increase in EPA/DHA content of plasma or serum phospholipids (PL) was considered to correlate with total body stores of omega -3FA and EPA and DHA were measured as percent change from baseline. Blood samples from subjects in pharmacokinetic trials sponsored by Pronova, and also in various published studies, were assayed for serum or plasma EPA, DHA and other fatty acids levels. In general EPA was absorbed in a dose-dependent manner whereas the change in DHA was non-linear. Fatty acid composition was measured in healthy or HTG subjects by five different methods in five different laboratories in Norway (n=1), USA (n=3) and Italy (n=1).

1. Norway: 17 trials (CK85-12; K85-5 trials) using capillary gas chromatography (mg/L serum or relative amount to total).
2. Kansas City: 4 trials, CK85-006, K85-95009, K85-97018 and 98019 using gas liquid chromatography (serum PL/ FA composition and concentration).
3. Italy: 1 trial –K85-98023. PL separated by thin layer chromatography in plasma, platelets and mononuclear cells, and then assayed using gas chromatography for individual free fatty acid ethyl esters.
4. Houston: K85-94010 and 94110 using high performance liquid chromatography (HPLC) with fluorimetric detection.
5. Minnesota: using capillary gas-liquid chromatography.

Fatty Acid Incorporation in Healthy Volunteers

The application contained six bioavailability studies in healthy male subjects which investigated the uptake of EPA and DHA into plasma/serum phospholipids as a maker of absorption rather than the traditional AUC. The sponsor considered this incorporation (into plasma, red cells and platelets) as a reflection of "whole body omega-3 status". Incorporation of these long-chained fatty acids was also investigated in clinical efficacy trials of patients with HTG as a marker of compliance along with capsule count. The sponsor also used this incorporation in their analysis of dose proportionality and comparison with the absorption of triglyceride formulations of EPA/DHA.

Six trials were provided as internal reports and publications; CK85-001/002, CK85-007, CK85-027, CK85-006, K85-91003 and K85-91003/92006. These are discussed below.

Studies 001 and 002 were carried out in the UK and Norway, respectively, using similar protocols except for the dose: 12 or 24g/day in 001 and 4, 8 or 14g/day for 2 weeks in 002. Study 002 employed a 30% n-3FA triglyceride preparation only at very high doses. Study 001 employed Omacor manufactured by Norsk Hydro AS in the late 1980s. Subjects took 1g tablets of K85 ethyl esters as 2 divided doses (3 groups of 8).

The plasma was assayed before dosing and 0.5, 1, 2, 4, 6 and 10 hours after dosing on Days 1 and 15. The capsules were taken after an overnight fast and 15 minutes before breakfast. Platelet function was also investigated (by determining ADP and thrombin-induced aggregation). The following table (Table 5) shows EPA and DHA percent incorporation (showing the combined results for studies 001 and 002). The long chained FAs are incorporated in the phospholipid fraction of the plasma.

Table 5.

Mean ± SD EPA Incorporation DHA Incorporation

Daily Dose	Baseline	Day 15	Baseline	Day 15
K85 4g	0.8 ± 0.2	5.4 ± 1.2	1.7 ± 0.3	4.4 ± 0.5
K85 8g	0.9 ± 0.5	9.1 ± 1.1	2.3 ± 0.7	5.3 ± 0.7
K85 14g	0.8 ± 0.4	9.7 ± 2.7	1.8 ± 0.3	4.5 ± 0.6
TG 12g	0.9 ± 0.5	6.0 ± 1.5	2.4 ± 1.2	4.7 ± 1.5
TG 24g	1.1 ± 0.8	8.6 ± 1.5	3.0 ± 1.4	5.3 ± 0.5

The EPA, but not DHA, incorporation tended to increase with dose in Study 002. The serum was also assayed for ethyl esters but the levels were undetectable (assay detection limit was 2ug/mL). The sponsor concluded that Omacor is hydrolysed prior to absorption in the gut.

The plasma TG decreased in the 2 and 4g twice daily groups. It should however be noted that the baseline was higher than the mean baseline of the 7g twice a day (bd) group (0.61 ± 0.20mmol/L versus 1.47 and 1.32 in the lower dose groups).

There were no consistent trends in the platelet aggregation tests. The 3 groups were not matched for age or weight (mean ages were 32, 25, 25 years in the 2, 4 and 7g bd groups, respectively). Two weeks after cessation of treatment, the DHA and EPA incorporation had declined but were still significantly higher than mean baseline levels. In 6 subjects there were minor increases in prothrombin time on Day 15 but this had declined post treatment. The bleeding time doubled in one subject. The results of the haemostatic tests were inconsistent.

Study CK85-007 (Hansen *et al*, Norway) compared DHA/EPA as ethyl esters (4g: EPA 2.2g, DHA 1.4g) with DHA/EPA as triglycerides (12g: EPA 2.2g, DHA 1.4g) and placebo (4g corn oil) in 31 healthy subjects aged 21-47 years. The 1g capsules were administered daily for 7 weeks with blood sampling at baseline, and 1, 3 and 7 weeks after an overnight fast. Plasma was assayed for fatty acid incorporation into phospholipids (DHA, EPA, arachidonic acid (AA) or ALA)

Repeated measures analysis of variance (ANOVA) showed a significant reduction in ALA (by 26-27% following K85 and 'Active – EPA' versus corn oil, $p<0.001$) and a significant reduction in AA in the K85 group ($p = 0.007$). Both DHA and EPA increased significantly in the treated groups (by approximately 1.5 and 3 times, respectively) after 7 weeks treatment. The authors of this paper concluded that there was no difference between the treated groups with respect to DHA and EPA incorporation. Both treatments significantly reduced thromboxane A_2 (TxA_2) and inhibited collagen-induced platelet aggregation compared with corn oil. There was a slight reduction in plasma fibrinogen (by 16% with K85 and by 12% with corn oil).

Study CK85-027 (Wieland and Grünwala, 1990) was a study comparing two ethyl ester omega-3 FA preparations containing 54% n-3 and 85% n-3 (Omacor) with a triglyceride formulation (1g capsules of Ameu−32% EPA/DHA, 2g three times a day (tds)) The doses of 54% n-3 and 85% n-3 were 1g tds and 1g bd, respectively. The study enrolled 30 healthy men aged 22 to 28 years. Serum was analysed on Day 0, 3, 7, 14, 21 and 28 of treatment. The "Omacor" capsule contained 53% EPA and 32% DHA (ratio 1.65:1) giving a daily dose of 1.06 and 0.64g, respectively, compared with 1.11g and 0.51g/day of the 54% EE formulation and 1.26g and 0.66g/day of the TG preparation. With all formulations the EPA and DHA (expressed as % of serum FA) increased gradually over the 28 days. Only graphs were provided in the report (that is, no raw data were included).

The EPA level increased 5 to 6 times above baseline (visually higher with 85% EE compared to the other two). The DHA level increased by a factor of 2x in both 85% EE and TG groups, less so with 54% EE (1.7x) In all groups there was a fall in TG (by 9% for K85 and by 14% for 54% EE) and serum fibrinogen (by 8 – 9% approx).

Overall there was no real difference between the preparations.

Study CK85-006 enrolled only 5 normolipaemic subjects (2 females and 3 males aged 32-54 years) who received four treatments as single doses in crossover fashion: 40g n-3TG (EPAX), 28g n-3EE (K85 Norsk Hydro) plus 12g olive oil, 28g n-3EE alone and olive oil alone. The n-3FA were equally well absorbed from TG and EE preparations (measured as TG and the FA content of cholesteryl esters, phospholipids for up to 24 hours post dose).

Study K85-91003 compared 3 formulations of ethyl esters containing n-3 at 85%, 80% and 62.5%, respectively. The daily dose in all groups was 5.1g n-3 in "liquid form" for 14 days in 36 healthy men aged 23 to 56 years. The trial was DB randomised and parallel in design. The 85% concentrate was called Omacor by the sponsor. The following table (Table 6) shows the results for plasma EPA and DHA percentage increase from the study.

Table 6.

DHA / EPA incorporation Day 0-14	**Formulation**		
Mean ± SD (%) change	**85%**	**80%**	**62.5%**
EPA % ↑	9 ± 215	7 ± 275	4 ± 183
DHA % ↑	33.9 ± 30.3	40.6 ± 38.9	32.8 ± 35.6

There was a slight trend towards greater EPA incorporation with the higher n-3 content formulations. There was a significant reduction in TG with the 80% and 85% formulations of ethyl esters.

There was no separate report for study K85-92006, which was of similar design except that subjects were also evaluated on Day 28 (14 days after last dose), and enrolled 65 males. The two studies were combined in a separate but relatively small report. The analysis was based on the ITT principle and statistical results were expressed as mean changes from baseline for EPA and DHA. The table (Table 7) below shows change from baseline on Day 14 (as mg/L). Medians were similar across groups and there was no significant change in HDL-C.

Table 7.

Analyte	**Percentage Omega-3 FA in Formulations**		
	62.5%	**80%**	**85%**
EPA	+44.0	+43.9	+55.3
P=0.044 K85 versus 62.5, all sign ↑ from BL ANOVA			
DHA	+26.7	+23.6	+26.0
NS between treatments, sign↑ from baseline			
TG	-0.04mmol/L	-0.22mmol/L	-0.24mmol/L
	P NS versus baseline	P = 0.012	P = 0.007
Total Cholesterol	-0.27mmol/L	-0.21mmol/L	-0.20mmol/L
	P = 0.018	P = 0.002	P = 0.049

A summary of study K85-98023 was provided. It was an open trial in 36 normolipidaemic volunteers (18 males and 18 females, aged 21 to 51 years). They received 1, 2 or 4g daily for 12 weeks in randomised manner. The increase in plasma EPA incorporation from baseline remained stable over the treatment period and a similar pattern was described in platelets and mononuclear cells. The increase in EPA was dose-dependent between the 2 and 4g daily doses.

The increase in DHA was more gradual and not as marked. There was an increase in the ratio of n-3 to n-6 fatty acids and a relative reduction in AA in plasma, platelets and mononuclear cells.

Dose Proportionality and Studies in Patients with HTG

Apart from normal volunteer studies previously described, the sponsor analysed dose proportionality concerning EPA and DHA 'concentrations' in patients with hypertriglyceridaemia where doses ranged from 2 to 8g of K85 (Omacor) daily for 8 – 12 weeks in most of the trials analysed:

2g (2 studies: 013 and 92004)

4g (9 studies: 013, 014, 017, 019, 022, 023, 95014, 95011, 95012)

6g (1 study: 012)

8g (1 study: 013)

Table 8. Baseline and change from baseline (at the end of treatment) are expressed in mg/dL (mean ± standard deviation (SD)).

Omega-3 Fatty acid Levels					
Daily Dose	**N**	**Baseline EPA**	**Change EPA**	**Baseline DHA**	**Change DHA**
2g	78	24.64 ± 17.83	27.59 ± 15.50	93.79 ± 32.56	22.24 ± 20.43
4g	246	25.36 ± 17.85	57.45 ± 30.33	101.95 ± 38.18	36.45 ± 33.12
6g	19	49.92 ± 33.33	54.89 ± 45.70	144.27 ± 69.98	14.48 ± 38.59
8g	18	24.38 ± 13.23	92.66 ± 36.97	93.68 ± 31.66	30.27 ± 26.55

A 1g/day dose was not used in HTG trials. The rise in EPA was approximately dose proportional for the 2, 4 and 8g doses, however DHA increases were relatively small and not dose proportional. One subject, given 6g daily, exhibited high baseline EPA and DHA levels. All of these trials were DB randomised in design and Omacor was compared with placebo in all but one of them. The following table (Table 9) shows the percentage increase in EPA and DHA following 4g Omacor daily in patients with HTG. This is the maximum recommended daily dose for HTG in the proposed Australian PI. Changes on placebo (corn oil) were not significant.

Table 9.

Mean% Change in DPA and EPA				
Study	**Patients***	**Treatment Duration (wk)**	**Increase in EPA Mean %**	**Increase in DHA Mean %**
CK85-013	17	8	276	34
CK85-014	54	12	300	50
CK85-017	29	12	300	50
CK85-019	26	12	200	29
CK85-022	30	12	233	23
CK85023	28	12	139	11
CK85-95014	30	24	260	54
CK85-95009	22	16	173	-10
CK85-94010	20	6	202	77
CK85-95011	49	12	361	59
CK85-95012	6	6	156	40

Other Studies – Omega-3 Fatty Acid Disposition

Studies in patients with IgA nephropathy (K85-95015) and hypertension (C85-003) confirmed increases in EPA and DHA incorporation into plasma phospholipids. Study K85-95015 enrolled 73 patients (60M & 13F) who were randomised to receive 4g or 8g daily in open fashion for 2 years. Following 4g, the EPA incorporation at 6 months was 3.1% (from baseline (BL) of 0.8%); following 8g, the corresponding figures were 0.9% and 5.2%. The DHA incorporation increased from 3.7% to 6.5% in the 4g group and from 3.5% to 7.7% in the 8g group. In all the patient trials, fatty acid incorporation was monitored as an indicator of compliance in addition to capsule count.

In hypertensive patients (156 subjects randomised blindly to either corn oil or Omacor 6g daily), mean EPA and DHA rose significantly by factors of 2.5 and 1.3 in the Omacor group after 10 weeks ($p < 0.0001$ versus corn oil; Study CK-003).

The sponsor-analysed HTG studies and Study CK85-003 were analysed at a single laboratory (data from a total of 246 Omacor and 192 placebo treated subjects). The mean ± SD% increase in incorporation of EPA into phospholipids was 327 ± 236% following Omacor and 13 ± 72% following placebo. The corresponding DHA figures were 46 ± 42% and 1 ± 22% ($p < 0.001$ between treatments using Wilcoxon rank sum test). Gender, age and BP did not influence % incorporation.

Drug Interactions

Interaction studies are scattered among clinical studies described elsewhere. Some more recent papers (6) were gleaned from the sponsor's literature search; potential drug interactions findings were considered supportive of the studies described elsewhere. According to Bhatnagar and Hussain (2007), the effect of Omacor on cytochrome P450 enzymes has not been investigated. However, EPA and DHA are carried in the circulation in the phospholipids and very little would be free for metabolism. These authors also reviewed

bleeding times (BT) which at higher doses might be increased in those also taking anticoagulants. Alaswad *et al* (2002) did not find an increase in BT in patients receiving 7g of n-3PUFA daily in combination with aspirin and warfarin. An early study by Smith *et al* (1989) demonstrated increase in Ivy bleeding time and a significant increase in fibrinogen following 4g daily (of K85) in 40 post MI patients.

Davidson *et al* (2007) compared Omacor 4g daily plus simvastatin 40mg daily with simvastatin alone over 8 weeks. There was a slight increase in ALT and aspartate transaminase (AST) in the combined group as well a significant increase in fasting glycosylated haemoglobin; the incidence of ALT increases was 1.6% in Omacor & simvastatin treated subjects compared with 0.8% in placebo & simvastatin treated subjects. McKenney *et al* (2007) in a review concluded no significant interaction with coumarin anticoagulants, aspirin and "older" antiplatelet agents but could not make any conclusion about clopidogrel. The proposed Australian PI contains a statement on potential interaction with anticoagulants.

Pharmacodynamics

The literature section of this hybrid submission contained a number of reviews and individual studies. Several of the latter were trials conducted by Pronova with Omacor or related fish oil products. There were additional human trials, nonclinical studies with animals and even culture cell experiments which investigated the effect of fish oils on various physiological functions such as haemostasis/coagulation, endothelial function, heart rhythm, cardiomyocyte automaticity, inflammatory cytokines and other processes involved in inflammation, platelet aggregation, fibrinolysis, blood pressure, glucose metabolism and LDL particles dynamics. Both n-3 and n-6FA are precursors of eicosanoids and further down the line, prostaglandins, thromboxanes and leukotrienes. Omega-3 FA was also investigated for its effects on lipid peroxidation and atherogenesis.

The intended indication of hypertriglyceridaemia is based on numerous investigations (probably hundreds of published articles) into the metabolic, and more specifically, the lipoprotein effects of omega-3FA in fish oils. The sponsor provided a summary of the findings together with supporting publications exploring potential mechanism(s) of action.

Pharmacological action pertaining to lowering of triglyceride and associated effects on lipid metabolism.

Both pharmacological and clinical studies have demonstrated that a daily dose of Omacor of at least 2g daily has a significant effect in reducing triglyceride levels by decreasing the hepatic synthesis of TG.

EPA (a major constituent of Omacor) impairs the activity of the enzyme acyl coenzyme A-diacylglycerol acyltransferase (DGAT) which is involved in the final step of TG synthesis. Animal studies found an increase in perioxisomal beta oxidation following dietary omega-3 fatty acids (FA) resulting in reduced availability of FA for triglyceride synthesis. A significant amount of TG is transported in the VLDL, hence VLDL-C was routinely measured in clinical studies along with LDL-C and HDL-C. Clinical studies demonstrated significant reductions in TG and VLDL-C.

Possible Other Actions of n-3FA

· Both omega-3 and omega-6 fatty acids are incorporated into membranes and plasma phospholipids and will compete with each other for incorporation following a diet containing both omega fatty acid types. The clinical trials showed a relative reduction in n-6FA in the total circulating FA pool following administration of n-3FA (including a reduction in arachidonic acid (n-6, 20:4), the precursor of prostaglandins, prostacyclin,

thromboxanes and leukotrienes). When n-3FAs are ingested, n-6 eicosanoids are partly replaced by n-3 eicosanoids which are generally less biologically active. The n-6 fatty acids slow the synthesis of EPA and DHA from α-linolenic acid which is found in certain plant oils such as flaxseed oil.

It is proposed that n-3FA may result in a dampening of inflammatory processes through their incorporation into the eicosanoid pathway as well as antithrombotic action (reduction in thromboxane A_2 and inhibition of platelet aggregation). Several clinical studies showed an increase in bleeding time, sometimes reaching statistical significance in spite of the individual increases being generally within the normal range (using the Ivy Simplate method). There was no clinical evidence of serious bleeding attributed to Omacor treatment.

· The effect of omega-3 FA on blood pressure was specifically examined in two trials. Although the antihypertensive action is discussed in the literature, the exact mechanism has not been elucidated. An anti-arrhythmic action has also been proposed on the basis of studies *in vitro* (cardio myocyte cultures) *in vivo* animal studies and clinical studies in patient's post- MI (in particular in the GISSI–Prevenzione trial).

Individual Pharmacodynamic Studies

Hypertension

Study CK85-003 employed a cohort of 156 patients from a larger population of 21,826 subjects. The cohort were stratified for gender then randomised in DB fashion to either K85 ethyl esters (6g daily EPA 54.4%, DHA 30.3%) or corn oil (mostly palmitic acid and n-6/n-9 FA). Corn oil is not a true placebo but was chosen in most studies because it lacked n-3 FA. Patients were evaluated at 5 and 10 weeks with respect to blood pressure (BP; automatic device), bleeding time (Simplate II method), plasma fibrinogen levels and platelet counts. Those in the fish oil group exhibited a significant reduction (from baseline) of 4.6mm Hg systolic blood pressure (SBP) and 3.0mm Hg diastolic blood pressure (DBP). The difference between groups was significant after controlling for physical, lifestyle and dietary factors: SBP – 6.4mm, p= 0.0025 and DBP – 2.8mm Hg, p = 0.029. There was a significant correlation between effect on mean BP and concentration of n-3FA in plasma phospholipid. Further trials are required to evaluate omega-3FA as an antihypertensive. There was no significant change in bleeding time, fibrinogen or platelet count. Serum TG decreased from 1.48 to 1.18mmol/L (p = 0.0007 versus baseline) but did not change significantly following placebo oil. At Week 10, plasma EPA incorporation had more than doubled whereas DHA (mean) had only increased by 20%.

A subgroup of patients (50 males and 28 females) was selected to undergo investigation of the effect of n-3FA on glucose and insulin levels (Study K85-92005; see below). The dose of Omacor was 4g daily.

Fish oil in this trial produced a significant fall in mean SBP of 4.1mm Hg (p=0.004 versus baseline; t-test) as well as significant falls in DBP (of 3.3 mmHg, p = 0.0008) and mean arterial pressure (AP: of 3.6 mmHg, p = 0.0003). There was a significant difference between fish oil and placebo treatment. There was a significant reduction and TG and VLDL-C, but no significant change in total and LDL-C, nor in Apo B or Apo A1. Mean EPA and DHA had increased significantly by 2.2 and 1.5 times at Week 16 (compared with baseline). The ratio of n-3 to n-6 FA in plasma increased significantly following fish oil (p = 0.0001). Those with the highest TG at baseline tended to have the greatest reduction (no individual patient data (IPD)).

There was no significant effect on glucose or insulin.

Effect on Haemostatic variables

Eritsland *et al* (1989) carried out a PD interaction study in 22 men with stable coronary heart disease (CHD), aged 37-74 years (CK85-004). The patients were randomised to either Group 1 (aspirin 300mg daily, then 2g n-3FA bd added in Weeks 2-5) or Group 2 (n-3FA for 4 weeks, then aspirin added for 1 week). There were two minor nosebleeds in the aspirin phase of Group 1. The average bleeding times are summarised below (Ivy Simplate method) in seconds.

Group 1: 270s (range of 210-360 s) BL and 360s (range of 300-660 s) aspirin (p = 0.004); 420s (range of 300 – 630s) combined treatment (p: not statistically significant when compared to aspirin alone).

Group 2: 240s (range of 180-270s) BL; 270s (range of 210-400s) n-3FA (p = 0.02); 330s (range of 240-480s) combined (p ns versus n-3FA alone. Increase numerically on combination noted).

There was a significant reduction in platelet count when n-3FA was added to the treatment regimen in Group 1 (median 262 x10^9/L BL compared with 270 $x10^9$/L for aspirin and 192 $x10^9$/L for the combination).

Triglycerides were significantly decreased in Group 1 only. As expected, n-3FA was associated with significant EPA and DHA elevations.

Study CK85-005 (Smith *et al*, 1989) carried out a similar study in 40 post-MI patients (35males (M) and 5 females (F)) who took part in an open secondary prevention trial. They received four 1g capsules of n-3FA (3.4g EPA/DHA) daily for 4 weeks. The mean age was 63 (range 38-76). Eighteen patients received oral anticoagulants. The effect of treatment was analysed by the Wilcoxon rank sum test on medians.

Overall there was a significant increase in EPA and DHA % incorporation ($p<0.001$) and a reduction in linoleic and oleic acid. There was a significant fall in TG (2.0 to 1.5mmol/L, p = 0.02) and a rise in total – C from 7.4 to 7.8 (p = 0.03).

The median LDL-C rose from 5.7 to 6.1 (p = 0.03).

Evaluation of haemostasis revealed significant increases in bleeding time (240 to 270 seconds, $p<0.001$), fibrinogen levels (2.5 to 2.8g/L $p<.001$) and a significant decrease in the thrombotest (114 to 90%, p = 0.014).

The aim of the study was to determine whether warfarin could be given safely with n-3FA. There was some minor nasal bleeding in those taking the oral anticoagulant. There was no change in platelet count, plasminogen activator inhibitor (PAI), factor VII or factor VII phospholipid complex. The 18 patients on warfarin were not analysed separately.

Red Cell Fragility

Study CK85-025 was conducted in 16 females aged 19 to 22 years who received either 6g fish oil or corn oil capsules daily for 28 days in a randomised DB manner. The capsules contained 5.1g EPA/DHA. Corn oil capsules contained 3.4g linoleic acid per dose. There was a significant increase in EPA and DHA within erythrocyte membranes and a relative decrease in linoleic, palmitic acid and oleic acid. The rise in DHA was progressive whereas EPA had reached a plateau after 1 week. The increase in EPA coincided with a fall in osmotic fragility but this effect had recovered somewhat by study end.

There was no significant change in the corn oil group (no p values recorded in study table).

There was no demonstrable effect on membrane fluidity.

Leukotrienes and Inflammation

Study CK85-020 was a small single-blind randomised trial, in 14 healthy males, half of whom received 7g/day of K85. The other subjects received no treatment (Western diet only). The aim of the trial was to study the formation of leukotrienes (LT) in granulocytes *ex vivo* and *in vitro* as previous studies had demonstrated anti-inflammatory effects in patients with rheumatoid arthritis and inflammatory bowel disease but not asthma. The presence of LT4 in urine reflects total formation of arachidonic acid from cysteinyl LT.

In vitro, addition of EPA resulted in an increase in LT series 5. Ingestion of n-3FA resulted in depletion of LT5 and reduction in pro-inflammatory LT4 (unaltered in control). Urinary LT4 had declined by 35% in the fish oil group ($p = 0.05$), but not in the control group, at Week 6.

Study CK85-015d (Soyland *et al*, 1994) investigated human T lymphocyte function in 41 patients with inflammatory skin diseases (psoriasis and/or atopic dermatitis); 21 received K85 6g a day and 20 controls received corn oil for 4 months. Both cytokine production and T cell activation are important in skin inflammation. There was evidence of immunosuppression in the n-3FA group in stimulated isolated T cells. The production of interleukin 2 and 6, tumour necrosis factor α (TNFα), T cell proliferation and CD25 expression[12] were measured in the study. Changes in plasma FA profile were similar to those in other studies.

Endothelial Function

- Goodfellow *et al*, 2000 (CK85-97026) investigated whether n-3FA protected against atheroma and its complications. Thirty patients with hypercholesterolaemia (total-C > 6.5mmol/L after low fat diet for 6 months) were treated with either n-3FA, 2g bd or placebo corn oil for 4 months in a DB randomised manner (15 per group). The capsules of n-3FA contained 85% EPA/DHA.

At baseline and at 4 months, patients underwent brachial artery ultrasound and BP was measured with a finger plethysmograph. Twenty eight patient results were evaluable. There was no difference between groups with respect to peak flow, 1 minute after cuff release and 3 minutes after glyceryl trinitrate (GTN). There was a significant increase in flow mediated dilation with n-3FA in comparison with corn oil (but not GTN-mediated dilation). There was no correlation between flow-mediated dilation and reduction in TG in the n-3FA group. No adverse events were reported and compliance was good (>95% of capsules).

Andreassen *et al*, 1997 (K85-92007) carried out a 'prophylactic' hypertension study in 30 heart transplant patients. The reason for the study was the evaluation the efficacy of n-3FA in prevention of cyclosporin-associated hypertension. Omacor 4g/day was compared in DB manner to corn oil placebo. Treatment commenced 4 days after operation and continued for 6 months. All received cyclosporin, azathioprine and prednisolone. The BP was monitored over 24 hours on Day 12, then at 1, 2, 3 and 6 months. Groups were compared by analysis of variance and the Newman Keuls test for multiple time comparisons. One in each group died from rejection. It was postulated that cyclosporin induces hypertension via an endothelial target. At 6 months, SBP had decreased by 2 ± 4mmHg in the fish oil group and had increased by 17 ± 4mmHg in placebo group ($p<0.01$ between treatments). However, DBP had increased by 10 ± 3 and 21 ± 2mmHg, in the two groups, respectively, ($p< 0.01$). Additional anti hypertensive treatment was required in 5 and 9 patients from the treated and placebo groups, respectively.

The changes in EPA and DHA correlated with decrease in SBP ($p = 0.69$, $p = 0.01$ respectively).

[12] Indicative of IL-2 receptor subunit IL-2Rα expression.

After 6 months of treatment, EPA had increased from 27 ± 6 (mean ± serum) to 100 ± 10mg/L and DHA had increased from 77 ± 7 to 130 ± 7mg/L in the fish oil group. There was a significant increase to total cholesterol in both groups ($p<0.01$) and a significant rise in HDL-C ($p<0.01$for both groups). Triglyceride had decreased from 181 ± 29 to 124 ± 27mg/dL ($p<0.05$ versus placebo and baseline).

Effects on LDL Particles and Apo B-100

- Study CK85-015c (Nenseter *et al*, 1992) was randomised and DB in design and compared 6g/day of K85 (47.1% EPA, 29.6% DHA and 5% of other n-3) and corn oil in 23 patients with psoriasis or atopic dermatitis, aged 23-70 years.
  After 4 months of treatment, there was a significant rise in phospholipid enhancement with n-3FA treatment ($p<0.01$ versus corn oil) and a significant reduction in n-6FA ($p<0.01$ versus corn oil). There was no measureable change in the metabolism of LDL despite some alteration in the lipid component of LDL. There was no difference between groups with respect to LDL size and its susceptibility to lipid peroxidation. Both whole blood and mononuclear cells were collected in the study. The cohort was derived from two larger trials of 145 patients treated for psoriasis (015-a) and atopic dermatitis (015-b). The investigation of the physical properties of LDL was complex using techniques such as circular dichorism spectra of LDL (Apo B α helix), radioactively labelled carbon (^{13}C) nuclear magnetic resonance spectroscopy of Apo B, LDL particle size evaluation with electron microscopy or dynamic light scattering.

- Study 97027 (Chan *et al*, 2002) recruited 48 obese men with insulin resistance who were randomised in DB fashion to one of four groups: Omacor 4g daily (45% EPA, 39% DHA), atorvastatin 40mg daily, both Omacor and atorvastatin or corn oil placebo. The duration was 6 weeks. The study was conducted in Western Australia.
  Visceral obesity and chronic hyperinsulinaemia are associated with increased hepatic Apo B secretion. Marine oils are known to affect lipid metabolism and reduce hepatic TG synthesis. The aim of this study was to investigate the kinetics of Apo B-100 which is the primary apolipoprotein of LDL responsible for carrying cholesterol to the tissues. Apo B acts as a ligand for LDL receptors. Apo B-100 is an isoform which binds to LDL receptors. Apo B-100 is also carried by VLDL and IDL. Apo B-48, the other isoform is carried in chylomicrons. Fish oils have been shown to reduce hepatic VLDL-Apo B secretion in humans and experimental animals. Kinetics were evaluated by injecting IV deuterium [D_3]-leucine at baseline and after 6 weeks.

  Group results were compared (using t-tests) with adjustment for baseline variables using general linear models. Factorial analysis of the Generalized Linear Models (GLM) procedure provides information on main and additive effects of interventions. None had the Apo E2/E2 genotype.

  Omacor enhanced the favourable effects of atorvastatin on TG. However most of the reduction in Apo B, remnant like particle-cholesterol, total cholesterol and LDL-C was due to atorvastatin in the combination group. There was no significant effect on insulin resistance. Atorvastatin reduced VLDL, IDL and LDL-Apo B pool size. Omacor significantly lowered VLDL Apo B pool size only. Atorvastatin did not significantly alter Apo B production or % VLDL-IDL-LDL conversion rates but it did significantly increase fractional catabolic rate. The conclusion was that Omacor did not significantly affect Apo B disposition nor did it interact with atorvastatin.

Other studies have shown that enrichment of VLDL with n-3FA favours conversion of VLDL to LDL which ties in with clinical studies in patients with HTG who have experienced small but sometimes significant increases in LDL-C.

Efficacy

Over 30 years ago, Dyerberg and Berg associated the low prevalence of coronary heart disease in Eskimos with their high fish intake which translates to a diet rich in n-3FA. They also exhibited low TG levels. The literature abounds with studies on fish oils (especially the EPA and DHA components), both clinical trials and epidemiological studies, investigating an association between fish oil/fish intake and the incidence of cardiovascular events and risk factors. Long chained fatty acids are contained within the phospholipid layer of all cell membranes, hence have been the subject of metabolic scrutiny of cellular components, as well as circulating lipids/lipoproteins.

In December 2002, the US National Cholesterol Education Program – Adult treatment panel (NCEP-ATPIII) concluded that elevated triglycerides are an independent risk factor for CHD based on a meta-analyses of prospective population-based studies (Hokanson *et al*, 1996). In an 8 year follow-up study of Danish males (Jeppesen *et al* 1998), there was an association between the risk of CHD and TG level within each HDL-C stratum and after controlling for LDL-C. These studies and the NCEP ATPIII guidelines were provided in the current Australian submission. These guidelines cite a normal TG as < 150mg/dL (1.7mmol/L). The use of the HMG- CoA reductase inhibitors (statins) is well established in the treatment of hypercholesterolaemia and in the secondary prevention of cardiovascular events, however their effectiveness in lowering TG concentrations is relatively less than their efficacy in lowering LDL-C to target levels as indicated in various international guidelines. Omacor is presented as an alternative treatment to fibrates and nicotinic acid in lowering triglycerides in patients whose TG levels have not responded adequately to the lifestyle measures. It is not intended as a treatment of secondary hypertriglyceridaemia.

The Category I, II, and III trials in patients with HTG were described in reports which included reference to conduct of the trials: that is, patients gave written informed consent; the trials received approval by Ethics Committees; there was generally a statement on Good Clinical Practice (GCP) and some reports mentioned the Declaration of Helsinki. The publications did however not always supply ethical statements.

Studies in Patients with Hypertriglyceridaemia: Pivotal Trials Category I

The sponsor divided studies in patients with HTG into 4 categories already described under Contents of Submission. The eight trials under Category 1 were described as pivotal. They all compared Omacor 4g a day with placebo (corn oil) in a double-blind parallel randomised manner.

Study CK85-013 included a 4g/day group, however only the placebo and 4g/day groups were blinded (the 2 g/day and 8 g/day were not blinded). The design of the pivotal trials was very similar hence the sponsor carried out an integrated analysis using the per protocol (PP) approach which included subjects who completed treatment and underwent TG assessment at baseline and endpoint. More than one TG estimation was carried out and the average was taken in the comparative analysis. The following table (Table 10) shows the number of ITT patients. The intended analysis in each trial was ITT "but without last observation carried forward (LOCF)". Medians for 6 of the 8 trials taken from the FDA evaluation (except for 95009 and 94010) are based on smaller patient numbers (completers). The table below (Table 10) shows mean changes expressed as a percentage at endpoint as well as medians. Medians are included as the analyses were non parametric (usually Wilcoxon test for within group

change and Mann Whitney between groups). Except for study 013, the difference between treatments was highly significant.

Table 10 Mean changes from Baseline in TG levels for each of the 8 Category I studies

Study No.	Omacor 4 g		Placebo	
	No. in Study	Relative change (%)	No. in Study	Relative change (%)
CK85-014	(n=55)	-20.4 [a]	(n=57)	10.8
CK85-017	(n=29)	-28.3 [a]	(n=26)	10.1
CK85-019	(n=26)	-23.5 [b]	(n=27)	5.0
K85-022	(n=30)	-24.1 [b]	(n=30)	-4.7
CK85-023	(n=28)	-28 [a b]	(n=29)	-4.3
K85-94010	(n=20)	-38.9 [b]	(n=21)	-7.8
K85-95009	(n=20)	-49.6 [a]	(n=21)	20.8
K85-013[c]	(n=17)	-29.0	(n=17)	-17.0

[a] P<0.0001, compared to placebo, Wilcoxon two-sample test, [b] P<0.05, compared to placebo, Wilcoxon two-sample test, [c] CK85-013 used the Kruskal-Wallis test to evaluate the treatment effect between the Omacor 2g, 4g, 8g, and placebo treatment groups. Since no significant differences between treatment groups were found, no pair wise comparisons were made.

In all studies except CK85-013, the mean reductions (and median reductions) were significantly larger for Omacor compared with corn oil. The largest reduction occurred in patients with severe HTG (Studies K85-94010 and 95009).

The relative change in lipid parameters described as secondary (HDL-C, LDL-C, total-C, VLDL-C, apolipoproteins) were not all measured in every trial. Reduction in VLDL-C tended to parallel reduction in TG in the Omacor group. This is probably due to the TG content of VLDL.

The LDL-C increase was significant compared with placebo in studies CK85-019, K85-94010 and especially in K85-95009. In the latter the mean and median increases were 42.6% and 52.8% respectively. The baseline LDL-C in that study was 79 ± 36 mg/dL (median 78) in the Omacor group and 96 ± 35 (median 93) in the placebo group, both relatively low values (ns between treatments using Mann-Whitney test). Baseline LDL levels were also low in study K85-94010 although total – C was elevated with a large contribution from VLDL-C. LDL-C was not evaluated in studies CK85-017 and 023. In study K85-94010, LDL-C was increased by 27.2% (mean) and 16.7% (median) compared with 4.0 and -4.2% on placebo (p=0.0127 using non-parametric testing). The mean increase in LDL-C in Study 019 was 8.5% compared with corn oil (by 0.4%; p = 0.0484 between treatments).

The increases in LDL-C were not accompanied by significant changes in Apo B in comparison with corn oil. During six studies in which it was measured, Apo B change ranged from (means) -2.6 to 5.39% in the Omacor groups and from -4.0 to 4.62% in the placebo groups. Individual variation was considerable as Apo B is the major lipoprotein of LDL particles but is also found in IDL and VLDL particles. The sponsor provided several publications to support Apo B as an independent risk factor in cardiovascular disease.

Integrated Analysis of Pivotal Trials in Patients with Hypertriglyceridaemia.

A division of Abbott Laboratories carried out analyses which formed part of the NDA (New Drug Application) to the FDA resulting in registration of Omacor for severe HTG (>500mg/dL). The randomised population was 455 in 8 pivotal aforementioned trials including only 34 of 68 patients in study CK85-013 (4g and placebo arms). The dietary run–in ranged from 4 to 10 weeks and was based on either the American Heart Association (AHA) step 1 diet or the recommendations of the European Atherosclerosis Society. The duration of treatment was 6-16 weeks (12 weeks in 5/8 trials). All trials were DB RCT using Omacor 4g daily and TG level as the primary parameter (the primary endpoint was TG change from baseline (BL) to end of study). The BL and endpoint measures were averaged from two or three determinations.

The data were analysed both parametrically (ANOVA) to compare mean and non-parametrically (Wilcoxon two sample test) to compare medians. The latter was primary as the Shapiro-Wilk test showed significant non-normality of distribution in individual studies. However, a parametric approach was chosen for the integrated analysis due to "larger sample size and inclusion of baseline covariates". The LOCF technique was not used and thus only subjects with evaluable measurements were included for the primary endpoint. The secondary parameters used the PP population (excluding patients with protocol violations). The formula for LDL-C depended on TG concentration but not all trials measured LDL-C or other lipid parameters.

There were 443 subjects in the ITT population (223 given Omacor and 220 given placebo) and 410 subjects in the PP population (206 given Omacor and 204 given placebo). The demographic characteristics of the per protocol population are summarised below (Table 11). Nearly 75% were < 60 years old.

Table 11.

Patient Characteristics	Omacor 4g (206)	Placebo (204)	P
Age: mean (SD) median, range	52.0 (10.29) 54 (26-70)	52.0 (10.30) 54 (26-70)	NS
Gender: male female	153 (74.3%) 53 (25.7%)	149 (73.0) 55 (27.0)	NS
Caucasian	198 (96.1%)	192 (94.1%)	NS
BMI (kg/m^2) mean (SD) median (range)	27.4(3.85) 27.1 (19-41)	27.3 (3.21) 27.2 (20 -38)	NS

BMI=body mass index

The groups were matched according to statistical testing: ANOVA for continuous variables and Cochran-Mantel-Haenszel (CMH) chi-square test for categorical variables. The BL triglyceride levels were particularly high in the two American trials (K85-95009 and 94010).

The overall % reduction in the Omacor group was 28% ($p<0.0001$ when compared with the +2.5% change in the corn oil group using ANOVA). The percentage reduction in the Omacor group was greater in those with higher baseline TG levels: at 500-749 mg/dL (5.65 – 8.46 mmol/L) the reduction was -39.5% compared with +1.5% ($p<0.0001$); and at >750 mg/dL (≥ 8.47 mmol/L) the reduction was -39.4% compared with + 2.8% ($p<0.0001$). These concentrations were reported in about 25% of the tested population.

The following demographic subgroups were analysed for change in TG at endpoint: male/females, age <60 / ≥ 60 yrs. The difference between Omacor and placebo remained highly significant for absolute and relative change (p.<0.0001). The following table (Table 12) shows the number of patients with > 20%, >30% and >40% reduction in TG.

Table 12.

Number of patients with X% reduction in TG	Omacor (206)	Placebo (204)	P
>20%	134 (65.0%)	44 (21.6%)	<0.0001
>30%	107 (51.9%)	22 (10.8%)	<0.0001
>40%	56 (27.2%)	13 (6.4%)	<0.0001

With respect to secondary (2°) lipid parameters there were highly significant differences between Omacor and placebo LDL-C and VLDL-C values as shown below (see comments in Table 13 footnote). The percentage changes in HDL-C were relatively small compared with LDL-C and VLDL-C.

Table 13. Secondary Lipid parameters. Absolute and Percent change at endpoint (mean, mmol/L) per protocol (PP) population.

	Omacor		Placebo		
	N	**Mean**	**N**	**Mean**	**P**
Total Cholesterol					
Baseline	206	7.35 mmol/L	204	7.38 mmol/L	
Absolute change	206	-0.33	204	-0.07	0.1388
% change		- 2.9[-4.5]		-0.5 [-0.9]	0.0215
HDLCholesterol					
Baseline	205	0.90 mmol/L	204	0.89 mmol/L	
Absolute change	205	0.06	204	0.03	0.1388
% change		8.9 [6.7]		3.5 [3.4]	0.0215
LDLCholesterol					
Baseline	199	4.31	199	4.46 mmol/L	
Absolute change	197	0.37	191	-0.12	<0.0001
% change		16.8 [8.6]		0.7 [-2.7]	<0.0001
VDLCholesterol					
Baseline	93	2.84mmol/L	94	2.62mmol/L	
Absolute change	93	-0.98		0.02	<0.0001
% change		-25.2 [-34.5]		8.0 [7.6]	<0.0001

NB: The clinical evaluator has included (in brackets) own raw calculations for % change and notes that it is odd that p values for total–C and HDL-C are identical. One study required total cholesterol on entry to be >250 mg/dl (6.47 mmol/L).

The baseline LDL-C was in the very high range (≥ 2.14 mmol/L) according to the NCEP-ATP-III (where the optimal LDL-C is stated to be <1.13 mmol/L or <100 mg/dL). The Apo B level did not rise together with LDL-C, however Apo B was not tested in all trials (tested in 6/8 trials). The following table (Table 14) shows mean percentage changes in Apo A1 and Apo B during the eight Category 1 trials (sponsor's analysis). There was considerable inter-patient variability noted.

Table 14.

Percentage Change	**Apo-A1**		**Apo-B**	
	Omacor 4g	**Placebo**	**Omacor 4g**	**Placebo**
CK85-014	0.84	3.44	5.15	2.75
CK85.017	-	-	-	-
CK85-019	-0.7•	4.6	2.2	-1.3
CK85-022	1.6	1.0	1.4	0.3
CK85-023	0.94	3.15	-2.6*	-4.0
K85-94010	1.4	-	-	-
K85-95009	-1.9	-0.4	0.8	-3.2
K85-013	-1.9	4.36	5.39*	4.62

*p <0.5 versus placebo, Wilcoxon 2-sample test, • p <0.5 versus baseline

The sponsor concluded that the rise in LDL-C was probably the result of a shift from small dense particles implicated in atherogenesis to larger more buoyant LDL particles. The submission contained a number of references investigating the effect of fish oils on LDL particle size distribution.

Category II Trials

Nine controlled trials either employed doses other than 4g daily and/or different study designs ("Omacor" doses ranging from 2 to 8g daily). One of the trials, **CK85-013** had a 4g group considered under Category 1 but 2g and 8g groups were also included (CK85-013b). Three other trials (**K85-95011, K85-95012** and **K85-95014**) carried out in Europe were randomised, DB and placebo-controlled but varied in design.

Study **K85-95011** compared gemfibrozil with Omacor 4g; **K85-95012** compared placebo and 4g Omacor in post-prandial hyperlipidaemia; **K85-95014** employed simvastatin concurrently. In trial **CK85-013**, the comparisons of 2g and 8g with placebo were open (4g versus placebo was DB). Study **K85-95109/95210** which lasted 6 months, compared 2g with 4g daily in an open manner. Three trials compared Omacor 2-3g daily with placebo over 4-12 weeks (Studies **K85-92004a, K85-97018** and **K85-98019).**

In study **CK85-012**, 6g/day produced a significantly larger reduction in median TG compared with corn oil; both absolute and % change from baseline ($p < 0.05$). Only one TG

measurement was taken at baseline and endpoint (after 16 weeks). Two American trials of similar design in patients with very high baseline TG **(K85-97018 and 98019)** demonstrated significant TG reduction compared with placebo based on medians (following a 3g Omacor dose). In these trials, there was a trend for increase in LDL-C compared with placebo but not in the case of Apo B. The patient numbers were small and they were randomised 2:1 (Omacor: corn oil).

In study **K85-92004** (2g Omacor versus placebo), the 2g dose was insufficient over the 4 week period. In the following 4 weeks (3g open dose) the effect on TG was more pronounced (compared with baseline).

Study **K85-95014** enrolled patients with CHD and Type IIb hyperlipoproteinaemia who were taking simvastatin 10 to 40mg daily. This study was a six month comparison of 4g Omacor with corn oil (DB) in 59 patients. The report referred to probability values determined by the Mann-Whitney test on medians; however the summary tables listed the mean % changes as median and referred to analysis of covariance as the statistical test. Using the report as source, there was a significant difference between median % TG change (-28.5% versus +2.1%, respectively; p=0.0019 at 6 months). At 12 months (in 46 patients on Omacor), the median reduction versus baseline was 30%, indicating that the effect was sustained.

With respect to the secondary lipid parameters, the two-sample t-test on means showed significant differences in total cholesterol (-7.2% versus placebo + 3.2%, p= 0.022) but not LDL-C (+2.6% versus +6.4%, p ns much variability) at 6 months. The Mann-Whitney test showed significant differences for HDL-C (medians -3.5% versus + 8.5% for placebo, p= 0.0390). Median reductions in VLDL-C were 47.1% for Omacor and 25.9% for placebo (p=0.0697). The effects of Omacor were still evident after 12 months. There was no significant effect of treatment on Apo B after 6 months (median % changes: -1.6 for Omacor versus 0.6 for placebo; p=0.0699).

Study **K85-95011** compared 4g Omacor per day with gemfibrozil 1200mg per day in 98 patients for 12 weeks. The clinical evaluator could not find the full report, only a protocol and a publication involving a subgroup. The company reported a 48% reduction of TG with gemfibrozil and a 30% reduction with Omacor.

Stalenhoef *et al*. (2000) examined a subgroup of 30 patients (16 given Omacor and 14 given gemfibrozil). The 2 groups exhibited similar reductions in total cholesterol, TG, VLDL-C and similar increases in HDL-C and LDL-C. Both agents reduced cholesterol-enriched VLDL and although LDL-C increased, there was an increase in the more buoyant LDL (equated with "less atherogenicity"). Omacor tended to increase susceptibility of LDL to oxidation *in vitro*, which is considered an unfavourable effect.

Category III Trials

The Category III trials were open extensions of Category I or II trials. They are listed below:

1. CK85-112 (Norway): extension of CK85-012 for 1 year in 35 patients, 27 of whom used lipid lowering drugs. The dose of Omacor was 4g daily and five withdrew (not because of AE).
2. CK85-113 (Sweden): extension of CK85-013 for 1 year in 32 patients, 6 of whom used lipid lowering drugs. The dose of Omacor was 4g daily. Six withdrew, 3 because of AE.
3. CK85-92004 (Norway): 4 weeks only, 3g Omacor per day in 136 (68 per previous group 2g/day and placebo). Four withdrew, 2 because of AE.
4. CK85-94110 (USA): 1 year extension of CK85-94010. All received 4g daily 38 (19 per previous group 4g versus placebo). Seven withdrew, 2 because of AE.

5. K85-95014 (UK): 6 month extension of DB study in 46 patients: all received 4g/day during extension (21 had placebo previously). There were no withdrawals.

The company analysis of efficacy maintenance depended on single TG measurements at various time points.

The patients in study **CK85-112** had established CHD and most of the 35 patients received either lovastatin or fenofibrate. All continued on a low lipid diet. The primary aim was to evaluate safety and change in serum TG every 3 months. This was a continuation of study CK85-012. The daily dose was 2g bd (= 3.3g /day DHA/EPA), preferably with meals. Ten had poor compliance at some stage (< 75% of scheduled intake). There were 24 females and 11 males aged 50.5 years on average. Thirty completed the year; five withdrew including one hospitalised for a serious unrelated arrhythmia. There was a further reduction in serum triglyceride from 3.81 to 2.75 mmol/L (-17% mean p= 0.021) as some originally were on placebo. Other results (total-C and so on) were confounded by concomitant therapy. There was a significant decrease in Apo B (-28.8%, p=0.0001) and an increase HDL (mean 14.8%; p= 0.0001) with treatment. Those previously on corn oil exhibited a 37.9% decrease in serum TG following Omacor treatment.

Study **CK85-113** was a follow-up of the DB trial 013 which compared 2, 4, and 8g with placebo. There was however a delay (1 to 11 months) before the commencement of this trial. CK85-113 was an open trial of 12 months in duration and enrolled 32 patients of whom six did not complete the trial: loss to follow up (n=2), adverse events (n=2), death (n=1– myocardial infarction and diabetes n=1). The dose was 2g bd. Serum TG decreased by 4.1% (ns). The subject variability was considerable.

Study K85-94110 was a 1 year extension of 94010 in 38 patients with Type IV –V HTG, of whom 31 completed the year. Most received concomitant medications (29/38) and 11 were treated for CHD. There were 18 females and 20 males with a mean age of 51.7 years. Half of these had taken placebo in the DB trial. The dose was 4g daily. None received concomitant lipid lowering therapy. Of seven non-completers, one died after surgery. Patients in both previous Omacor and placebo groups exhibited significant reductions in median TG, that is, the effect on TG was maintained over 12 months. There were significant decreases in total cholesterol and increases in HDL-C. One withdrew because of pancreatitis. A few patients exhibited small increases in plasma ALT. Overall 24/38 had a > 30% decrease in serum TG.

Study K85-95014 was carried out in the United Kingdom (UK) and compared 4g Omacor daily with corn oil in patients with Type IIb hyperlipoproteinaemia who had established heart disease. These patients were taking simvastatin. This trial was not classified as pivotal although Omacor and corn oil were compared in a randomised DB manner over 6 months following a 6 week dietary run-in. Patients had the option of open treatment with Omacor for another 6 months. Statistical analysis was carried out on the ITT population with no LOCF. The study recruited 59 randomised patients (30 given Omacor and 29 given placebo) and was classified as Category 2.

At 12 months, the reduction in TG in 46 patients on Omacor was a median 30% in those continuing Omacor and 21.1% in those previously on placebo; overall the median reduction was 28.7% (or highly significant compared with baseline). This was accompanied by a median decrease in VLDL-C (38.4%), which was independent of simvastatin treatment. The latter result was supported in an attached publication.

Study K85-92004 has been described under non-pivotal DB trials (comparing 2g Omacor with corn oil over 4 weeks). In a subsequent 4 week open period (132 from the original trial and 136 patients with moderate HTG), the dose of Omacor was 3g /day. The effect on TG

was relatively modest (ns between Omacor and placebo at Week 4). The 2g dose was considered inadequate and the 3 g dose had a modest effect.

Category IV Trials

1. There were 6 trials not monitored by Pronova and provided as publications.

Study **CK85-009** randomised twenty patients to either 6g/day or corn oil for 5-6 months in DB fashion. They were treated for at least one month before coronary artery bypass graft (CABG), then continued a week after surgery. These patients had hypercholesterolaemia. There was a slight increase in total–C in the Omacor group.

2. Pharmacia 3 (Nordoy *et al*, 1998) enrolled 41 patients (29 males and 12 females) with combined hyperlipidaemia who were randomised to either 4g/day of omega -3 FA ethyl esters or placebo for 5 weeks on a background of simvastatin 20mg/day. There were no withdrawals or AE. Compared with placebo, there was a significant reduction in TG ($p=0.007$) but no significant difference with the respect to cholesterol, Apo B, LDL, or IDL.

3. Pharmacia 5 (Nordoy *et al*, 2001) investigated the comparisons of ω-3 FA and placebo over a five week period on a background of atorvastatin in 42 patients with combined hyperlipidaemia. Omacor, 2g/day was compared with placebo in a DB randomised manner following a dietary run of 12 weeks combined with atorvastatin 10mg daily for at least 10 weeks. The placebo was corn oil.

There were 10 females and 32 males aged 26-81 years. Extensive lipid testing was carried out. Statistical tests were parametric.

No AE were reported. There was a significant fall in SBP compared with baseline (5.5mmHg).

Atorvastatin during run-in significantly reduced TG, total-C, Apo B, Apo E, Apo CI and Apo C II and increased HDL-C ($p<0.001$). Although the 2g dose of ω-3FA did not significantly reduce TG or total-C any further, there was a further increase in HDL-C ($p<0.01$) and a redistribution of LDL subfractions (significant decrease in dense LDL particles). The 2g dose appeared to be inadequate.

4. **Pharmacia 6** (Zieden *et al* 2001) enrolled 20 patients (3 females and 17 males) with severe HTG (TG > 5mmol/L after an 8 week diet). Omacor 4g/day was compared with corn oil over 12 weeks. There was an extensive investigation of lipid metabolism including assessment of LDL oxidation. Statistical tests depended on the skew of the data. Median TG in Omacor group decreased by 48.3% compared with 2.3% in the corn oil group ($p = 0.00\ 4$, using Mann-Whitney test)

In the Omacor group there was a significant decrease in median VLDL-C ($p = 0.01$ versus baseline) and a rise in LDL-C ($p = 0.03$ versus baseline, ns versus placebo). There was no change in Apo B or HDL-C. LDL oxidation susceptibility did not differ between treatments (using +/- test)

5. **Study CK85-018** (Hausen *et al*, 1993) was a pharmacodynamic study comparing Omacor 6g/day with lovastatin 40mg/day alone and the combination in a 3 way crossover DB randomised trial. Those on lovastatin received placebo (olive oil). Each treatment was given for 6 weeks. The baseline TG were not high, nevertheless there was a significant decrease with all treatments. Lovastatin significantly decreased total-C and LDL-C as expected (but not ω-3FA alone). K85 tended to inhibit exercise induced shortening of bleeding time ($p<0.05$ versus lovastatin and placebo oil).

6. Study K85-90001 (Eritsland and Arnesen).

This study was an open randomised trial in which Omacor 4g/day was compared with control (aspirin or warfarin alone = usual care). Those on Omacor also received anticoagulants having undergone CABG previously. The primary aim was to assess whether addition of Omacor to standard treatment reduced the rate of graft occlusion (not a proposed indication). Plasma lipids and safety were also evaluated over a period of 9 months in 207 patients (100 given Omacor and 107 controls). There was 27% reduction in TG following Omacor compared with a 3% reduction in control ($p<0.0001$at 3, 6, and 9 months between treatments). There was slight change in HDL-C ($p<0.05$) following Omacor, but no change in LDL-C or total-C. The occlusion rates were 93/207 shunts (44.9% for Omacor) and 99/237 shunts (41.8% for control). The addition of Omacor did not significantly affect bleeding events (Omacor and aspirin or Omacor and warfarin versus aspirin or warfarin alone: 3, 2, 2, 2, respectively). However, those receiving Omacor experienced more gastro intestinal events of a non-serious nature. The 207 patients were part of a larger trial of 610 patients (317 given Omacor and 293 controls) among who 14 died (8 given Omacor and 6 controls).

The number of bleeding episodes was 34 in the Omacor group and 27 in the control group. The authors concluded that patients undergoing CABG should include omega-3FA supplements in the diet.

Secondary Prevention Indication

Post-Myocardial Infarction

The data package included several **epidemiological studies** reporting a lower risk of CHD in patients whose dietary intake was high in omega-3 fatty acids.

Daviglus *et al* (1997[13]) found a reduction in risk of myocardial infarction (a 30 year risk) following daily consumption of >35g fish (versus no fish) and a reduction in sudden death (RR 0.62) and non-sudden death (RR 0.56) from MI.

The Health Professionals Study (HPS) and the US Physician Health Study (PHS) showed a significant association between the intake of omega-3FA and lower incidence of sudden death.

The DART study[14] investigated fish intake and 2º prevention in 2033 men. Those who ate fatty fish exhibited a 29% reduction in all cause mortality compared with those not receiving dietary advice. Fish was eaten 2-3 times a week. The follow-up period was two years and the omega-3 FA intake was approximately 0.6g daily.

The Lyon Diet Heart study[15] enrolled 605 subjects who had survived a first myocardial infarction. The experimental group followed a Mediterranean style diet while the control group was not given specific dietary advice. The study was stopped prematurely because of significant benefits of a diet high in alpha-linolenic acid (an omega -3 plant derived FA). The diet group exhibited a 30-70% lower risk of recurrent heart disease (composite end points including sudden death).

Clinical Trial not using Omacor

[13] Daviglus *et al* (1992). Fish Consumption and the 30-Year Risk of Fatal Myocardial Infarction. *NEJM* 336:1046-1053.

[14] Burr ML *et al.* (1989). Diet and reinfarction trial (DART): design, recruitment, and compliance. *Eur Heart J*, 10 (6): 558-567 and several other citations.

[15] de Lorgeril *et al. (* 1999). Mediterranean Diet, Traditional Risk Factors, and the Rate of Cardiovascular Complications After Myocardial Infarction. *Circulation* 99:779-785.

Singh *et al* (1997[16]) carried out a RCT trial in three groups of patients with suspected MI: fish oil (EPA 1.08g/day); mustard oil (ALA 2.9g/day) and placebo in 122, 120 and 118 patients, respectively. The trial was double-blind. At one year, total CV events were significantly less in the fish oil and mustard oil groups (24.5% and 28%, respectively, versus placebo 34.7%; $p < 0.01$). Non fatal MI was also significantly less (13% and 15% respectively, versus 25.4%; $p < 0.05$). Total cardiac deaths were significantly less (11.4% versus 22%, respectively; $p < 0.05$). Reductions in TG were modest and not commensurate with the risk reduction. The study suggested that omega-3FA was protective but that a larger study was required to confirm this result.

The effect of fish oil intake on sudden death in these earlier studies suggests a possible anti-arrhythmic effect. This effect has been extensively investigated in other populations, but not the post MI population.

Clinical Trial using Omacor

The submission included two trials employing Omacor at two different doses.

These are listed below:

1. GISSI – Prevenzione an open Italian study, comparing Omacor 1g daily with three other treatments in 11,324 patients following MI. These comparator groups were: Vitamin E 300mg daily; Omacor 1g and Vitamin E 300mg daily; Omacor 1 g + Vitamin E 300mg /day; control or usual treatment (no corn oil). The study was open, randomised, prospective and data were blindly evaluated (PROBE design). The average observation period was 3-5 years.

2. Pharmacia 4 (Nilsen *et al*), a Scandinavian study in 300 patients in whom treatment commenced early after a myocardial infarction. Patients received either Omacor 2g bd or corn oil in a randomised double-blind manner within 4-8 days of a MI. This study was carried out at one site in Norway whereas the larger GISSI-P study was conducted at 172 centres.

GISSI – PREVENZIONE

The definitive publication is in the *Lancet* (1999[17]) authorised by the "Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardio". An internal report was also supplied by the sponsor.

A number of publications emanated from this large trial including Marchioli *et al* (2001[18]) and Dr Marchioli wrote the sponsor's internal report. The main study was carried out between 1993 and 1997. After the results were published, updated information was retrieved through investigations at census offices and hospital records. The follow-up data were right-censored at 42 months. By the end of the study, over 40% were taking cholesterol lowering agents whereas very few were taking them at the beginning. This increase was attributed to the publication of trials supporting the secondary preventative effect of statins (including mortality) in for example, the 4S simvastatin trial.

The protocol planned factorial design with four way analysis to minimise the interaction effects of the four treatments, however two statistical analyses were performed: Omacor versus no Omacor and Vitamin E versus no Vitamin E (2 ways) and the 4-way analysis. The

[16] Singh *et al*. (1997). Randomized, Double-Blind, Placebo-Controlled Trial of Fish Oil and Mustard Oil in Patients with Suspected Actue Myocardial Infarction: The Indian Experiment of Infarct Survival—4. *Cardiovas Drugs Therapy* 11 (3): 485-491.

[17] GISSI-Prevenzione Investigators Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction results of the GISSI-Prevenzione trial. (1999). *Lancet* 354: 447-455 (1999).

[18] Marchioli *et al.* (2001). Prognostic ability of a Mediterranean dietary score in heart failure: Preliminary analysis of the GISSI-Heart failure Trial. *Lipids* 36S: 5119 – 5126.

latter entailed the following comparisons: Omacor 1g daily, Vitamin E 300mg daily and combined Omacor/Vitamin E versus control; combined treatment versus individual interventions.

Table 15. The four and two-way factorial analysis is represented below (from internal report) together with numbers randomised.

n-3 PUFA (Omacor) 2,836 **Control*** 2,828	**n-3 PUFA and Vitamin E** 2,830 Vitamin **E** 2,830	**n-3PUFA** 5,666 **Control*****
Control*** 5,664	Vitamin **E** 5,660	**Total** 11,324
* = standard treatment ** = control for Vitamin E		*** = control for Omacor

Randomisation was carried out within 3 months after the myocardial infarction. By the end of the study 82.5% were taking aspirin. The study was open in design.

Exclusion criteria included: unfavourable short term outlook (for example, overt congestive heart failure – New York Heart Association **(**NYHA**)** III or IV irrespective of treatment, cancer and so on), allergy to polyunsaturated fatty acids (PUFA; Omacor), congenital coagulation defects and any situation that could affect compliance.

Age was not a barrier to entry. Most of the patients were "normolipaemic", that is, a total cholesterol < 5.5mmol/L and TG <1.8mmol/L at baseline; 82.5% regularly consumed olive oil and 87.6% ate fish at least once a week by the end of the study.

The 4 groups were matched at baseline with respect to demographic and disease characteristics. The study included 9659 males (85.3%) and 1665 females (14.7%); 63% of patients were aged 51 to 70, 14.3% 71-80 and 1.9% >80 years. The mean age was 59.4 years. The time from MI to randomisation was less than 1 month in the majority (28.1%≥ 31 days). Secondary diagnoses included hypertension (35.6%), diabetes mellitus (14.8%), a history of angina (40.6%), previous MI to current episode (12%), and claudication (4.4%).

The ejection fraction (EF) was ≤ 30% in 2.6% and 31 to 40% in 11.1% of patients; the rest had an EF of >40%. Nearly 20% of EF patients had a history of ventricular arrhythmias. The mean EF was 52.6% and the body mass index 26.5kg/m². The population was described as broad and "relatively low" risk.

The "Omacor" formulation contained EPA and DHA amounting to 835-863mg/g in 7 batches. The dose was 1g daily. According to both the internal report and Lancet publication, the EPA to DHA ratio was 1:2.

The market formulation is 1.2:1. The dose of Vitamin E (α tocopherol) was 300mg in the Vitamin E and combined groups.

Patients were asked to comply with prescribed preventative treatment including aspirin, beta-blockers and angiotensin converting enzyme inhibitors. Visits were scheduled every 3 months, with clinical assessment at 0, 6, 12, 18, 30 and 42 months. Compliance was evaluated every 3 months and regular dietary questionnaires were carried out at the time of

clinical assessment and blood tests. There was strict adherence to the Intention To Treat (ITT) principle. Randomisation was "done over the phone and by computer network". The trial design included standard care in all.

Primary Endpoints

The primary combined endpoints were:

- The cumulative rate of all cause death, non-fatal MI and non-fatal stroke.
- The cumulative rate of cardiovascular death, non-fatal MI and non-fatal stroke.

A secondary analysis was carried out on individual components of the primary endpoints and in the main causes of death.

Non-fatal MI was defined as at least two of the following: chest pain of typical intensity and duration; ST segment elevation or depression of ≥ 1mm in any ECG limb lead, of ≥ 2mm in any precordial lead, or both; at least a doubling in "necrosis enzymes". Non-fatal and fatal stroke were also defined in the protocol based on symptoms and duration or if needed on hospital research or death certificates.

The group of investigators gained approval from relevant ethics committees and all patients gave informed consent. The trial was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Methods

The estimated cumulative rate of death, non-fatal MI and stroke in the control group over 3.5 years was 20%. At least 3000 patients per group were required to compare the primary endpoint in each of the study groups to that of control and to test the hypothesis that combined treatment with Omacor and Vitamin E would decrease by a further 20% the rate versus n-3 PUFA or Vitamin E alone.

Factorial analysis has been described. The data were analysed by Kaplan-Meier survival curves and the log-rank test. Efficacy was assessed by baseline values of the risk stratification variables fitting Cox's regression models adjusted for confounders, that is, prognostic indicators. A hierarchical approach was adopted, that is, assessing vital status, then if a non-fatal event occurred by study end. No power value was stated. The p-values were 2-sided, that is, $p < 0.08$ was significant.

There was a lower than expected incidence of events according to the authors of the report. Interactions were evaluated by fitting multivariate models (including two experimental treatments and the interaction) to the data. If significant, the latter indicates an effect after treatments are combined.

Patient Disposition (from internal report)

11,324 patients randomised into four groups (= ITT population).

1. n-3 PUFA: n=2836: 3 lost to follow-up, 823 discontinued n-3 PUFA (29%).

2. Vitamin E: n=2830: 4 lost to follow-up, 744 discontinued Vitamin E (26.3%) 11 received n-3 PUFA.

3. Vitamin E and n-3 PUFA: n=2830: 4 lost to follow-up, 906 discontinued n-3 PUFA (32%), 865 discontinued Vitamin E (30.6%).

4. Control: n= 2828: 2 lost to follow-up, 15 received n-3 PUFA, 2 received Vitamin E.

The numbers listed as discontinuations were different in the internal report and the *Lancet* article (which listed 768, 687, 848 Vitamin E/808 n-3 PUFA for each group, respectively, values were not stated for control). The internal report was written by Marchioli and Tognini in November 1999 whilst the publication appeared in the *Lancet* on August 7th 1999.

The average duration of treatment with n-3 PUFA was 31.3 months (± SD 14.9) whereas the average follow-up was 40.5 ± 7.5 months (n-3 PUFA ± Vitamin E).

Side effects were reported as a reason for discontinuing in 3.8% of the n-3PUFA groups and in 2.1% of the Vitamin E groups. On checking the individual discontinuation data in the internal report (discontinuations were not summated), the most common reasons for discontinuation were "organisational problems" and "patient refusal". Some were removed from the study by the physician, the reason not given. In some cases the indication was "other". A surprisingly small number were lost to follow-up.

Results of Efficacy Analysis

The table (Table 16) below shows the outcome of two-way and four-way analysis of primary and secondary end points.

In the 4-way analysis there is a significant reduction in relative risk when n-3 PUFA alone is compared to control: 0.85 (0.74-0.98).

Table 16. Overall efficacy profile of n-3 PUFA at Study Endpoint.

All (n=11324)		Four-way analysis			Two-way analysis		
		n-3 PUFA (n=2836)	**Control** (n=2828)	**Relative risk (95% CI)**	**n-3 PUFA (n=5666)**	**Control (n=5658)**	**Relative risk (95% CI)**
Main endpoints Death, non-fatal MI, and non-fatal stroke	1500 (13.2%)	356 (12.5%)	414 (14.6%)	0.85 (0.74-0.98)	715 (12.6%)	785 (13.9%)	0.90 (0.82-0.99)
Cardiovascular death, non-fatal MI and non-fatal stroke	1155 (10.2%)	262 (9.2%)	322 (11.4%)	0.80 (0.68-0.95)	547 (9.7%)	608 (10.7%)	0.89 (0.80-1.01)
Secondary endpoints All fatal events	1017 (9.0%)	236 (8.3%)	293 (10.4%)	0.80 (0.67-0.94)	472 (8.3%)	545 (9.6%)	0.86 (0.76-0.97)
Cardiovascular deaths	639 (5.6%)	136 (4.8%)	193 (6.8%)	0.70 (0.56-87)	291 (5.1%)	348 (6.1%)	0.83 (0.71-0.97)
Cardiac death	520 (4.6%)	108 (3.8%)	165 (5.8%)	0.65 (0.51-0.84)	228 (4.0%)	292 (5.2%)	0.78 (0.65-0.92)
Coronary death	479 (4.2%)	100 (3.5%)	151 (5.3%)	0.65 (0.51-0.84)	214 (3.8%)	265 (4.7%)	0.80 (0.67-0.96)
Sudden death	286 (2.5%)	55 (1.9%)	99 (3.5%)	0.55 (0.40-0.76)	122 (2.2%)	164 (2.9%)	0.74 (0.58-0.93)
Other deaths	378 (3.3%)	100 (3.5%)	100 (3.5%)	0.99 (0.75-1.30)	181 (3.2%)	197 (3.5%)	0.91 (0.74-1.11)
Non-fatal cardiovascular events	578 (5.1%)	140 (4.9%)	144 (5.1%)	0.96 (0.76-1.21)	287 (5.1%)	291 (5.1%)	0.98 (0.83-1.15)
Other analyses CHD death and non-fatal MI	909 (8.0%)	196 (6.9%)	259 (9.2%)	0.75 (0.62-0.90)	424 (7.5%)	485 (8.6%)	0.87 (0.76-0.99)
Fatal and non-fatal stroke	178 (1.6%)	54 (1.9%)	41 (1.4%)	1.30 (0.87-1.96)	98 (1.7%)	80 (1.4%)	1.21 (0.91-1.63)

MI = myocardial infarction: CHD = coronary heart disease. Patients with two or more events of different types appear more than once in columns but only once in rows.

There was a relative risk (RR) of 0.85 (95% CI 0.74-0.98) following 4-way analysis for the first combined endpoint [death and non fatal MI and non-fatal stroke]; p = 0.023. The RR= 0.80 (95% CI 0.68 – 0.95) for the second endpoint (CV death and non-fatal MI and non-fatal stroke); p = 0.008. The significant difference was due to the mortality component of the combined endpoint. Analysis of the fatal events, CV deaths and so on, revealed significant risk reduction, when n-3PUFA alone was compared with control: 30% reduction for CV deaths, 35% reduction for cardiac and coronary death and 45% reduction for sudden death. Omega-3 PUFA alone did not significantly affect non-fatal CV events or strokes; the risk of stroke was 1.3 (0.87 – 1.96). The positive effect of n-3 on mortality accounted for the benefit on the combined endpoints.

Interaction tests were not significant for combined endpoints but were significant for CV mortality (p = 0.024), CHD deaths (p = 0.0226) and sudden deaths (p = 0.010).

The two way analysis showed a more modest reduction in mortality when n-3PUFA (alone and with Vitamin E) was compared with control. This method does not allow for interaction and confounders. The p-values for the two combined endpoints were 0.048 (death + non fatal MI + non-fatal stroke) and 0.053 (CV death non fatal MI + non-fatal stroke). The following table (Table 17) shows the effect of the combined treatment group n-3PUFA + Vitamin E (n= 2830) versus control (n=2828). The p values were not supplied, however the relative risk values were similar to n-3PUFA alone versus control. The term control here means standard treatment post MI.

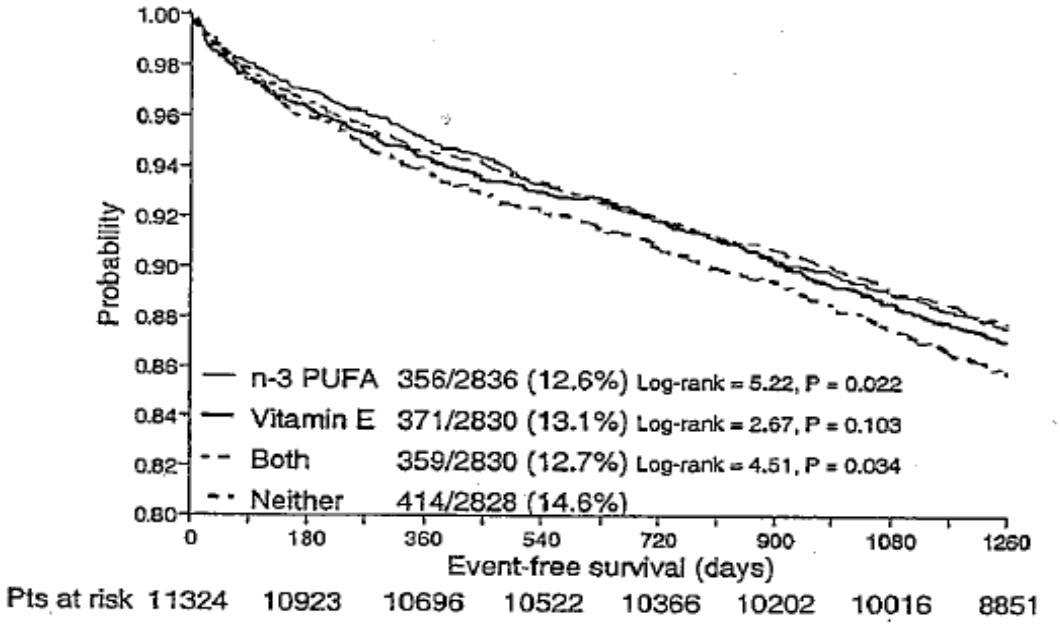
Table 17. Overall efficacy profile of n-3 PUFA plus Vitamin E at Study Endpoint.

	n-3 PUFA plus Vitamin E (n=2830)	**Control (n=2828)**	**Relative risk (95% CI)**
Main endpoints			
Death, non-fatal MI, and non-fatal stroke	359 (12.7%)	414 (14.6%)	0.86 (0.74-0.99)
Cardiovascular death, non-fatal MI and non-fatal stroke	285 (10.1%)	322 (11.4%)	0.88 (0.75-1.03)
Secondary analysis			
All fatal events	236 (8.3%)	293 (10.4%)	0.80 (0.67-0.95)
Cardiovascular deaths	155 (5.5%)	193 (6.8%)	0.80 (0.65-0.99)
Cardiac death	120 (4.2%)	165 (5.8%)	0.72 (0.57-0.91)
Coronary death	114 (4.0%)	151 (5.3%)	0.75 (0.59-0.96)
Sudden death	67 (2.4%)	99 (3.5%)	0.67 (0.49-0.92)
Other deaths	81 (2.9%)	100 (3.5%)	0.80 (0.60-1.08)
Non-fatal cardiovascular events	147 (5.2%)	144 (5.1%)	1.01 (0.80-1.27)
Other analyses			
CHD death and non-fatal MI	228 (8.1%)	259 (9.2%)	0.87 (0.73-1.04)
Fatal and non-fatal stroke	44 (1.6%)	41 (1.4%)	1.06 (0.70-1.63)

One can conclude that Vitamin E addition does not significantly add to the efficacy of n-3 PUFA in reducing mortality risk over the period of follow-up.

Figure 2 shows survival curves and log-rank p values for each group (combined end point and overall survival (mortality) using a 4-way analysis). The difference between n-3 PUFA alone and with Vitamin E versus control was significant. Vitamin E alone had no significant effect on survival. This was supported in a publication by Marchioli *et al* (2001[19]). Revision of the analysis demonstrated no increased benefit of combined treatment with Vitamin E versus n-3 PUFA alone.

Figure 2. Omacor evaluation GISSI – P Study survival curves.



A subsidiary analysis (4-way) of fatal plus non-fatal stroke revealed relative risks (95% CI) of 1.24 (0.82-1.87) – n-3 PUFA; 0.92 (0.59-1.44) – Vitamin E; 1.04 (0.67-1.60) – n-3 PUFA and Vitamin E. None of the p-values were statistically significant. Two way analysis adjusted for interaction gave a similar result overall as for the 4-way analysis.

A second publication by Marchioli *et al* (2002[20]) analysed survival time course in the GISSI – Prevenzione study (3, 6, 9, 12 and 42 months). Overall there were 1031 deaths in 38,417.9 person years of follow-up. The mortality rates at years 1, 2 and 3 were 3.4, 2.0 and 2.3%. There were 57 fatal strokes including 13 ischaemic, 13 haemorrhagic and 31 'other'. The positive effect of n-3 pUFA in reducing mortality was apparent within 3 to 6 months, as described next. The RR is against standard treatment.

The relative risk of sudden death at 3 months was 0.44 (0.19-1.02, p = 0.058) and at 6 months, 0.43 (0.22-0.86; p <0.05). At nine months the RR was 0.37 (0.20-0.67; p <0.01). The risk reduction for all fatal events was significant at each time point in the n-3 PUFA treated patients, calculated by Cox regression analysis adjusted for main confounders. There were similar early reductions in cardiovascular and CHD mortality in comparison with control.

[19] Marchioli R *et al*. (2001). Efficacy of n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardic. *Lipids*, 36S: 119-126.

[20] Marchioli R (2002). Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation*, 105: 1897-1903.

Patients in this trial were asked to increase consumption of fish, trout, raw and cooked vegetables and olive oil.

In 2005, Marchioli *et al* [21] reviewed the results of GISSI-Prevenzione in order to investigate the possible pathophysiological mechanisms underlying the reduction in mortality, in particular the sudden deaths (in the n-3 PUFA group, the risk of sudden death was greater in those with lower ejection fractions;≤ 40%, 4x risk of LVEF >50%). It was proposed that n-3 PUFA stabilises myocardial cell membranes (Leaf *et al.* 2003[22]).

In a review and discussion of clinical trials (including GISSI-P) of Omacor it was concluded that the benefit of Omacor was an addition to other medication and diet in patients with established CHD. It was also pointed out that the American Heart Association (AHA) recommends for such patients to take ≥ 1g/day of EPA/DHA and that those with HTG take 2-4g daily. Those without CHD are advised to eat fish, preferably of the fatty variety at least twice a week and to eat foods rich in α-linolenic acid[23].

Effect on Lipids and Serum Chemistry: GISSI-P study

Blood was collected at baseline and at 6, 12, 18, 30 and 42 months.

There were no differences between treatments (n-3 PUFA, n-3 PUFA and Vitamin E versus control) with respect to total cholesterol and HDL cholesterol which increased in all groups (including Vitamin E alone). Triglyceride concentration decreased by a modest amount following n-3 PUFA as shown below (from internal report). The Vitamin E group was not shown in the internal report table, nor the number of patients tested, in the individual groups.

Table 18.

Triglyceride Concentration			
mg/dL (mean)	**n-3 PUFA**	**n-3 PUFA and Vitamin E**	**Control**
Baseline	162.6	160.3	161.9
6 months	162.6	163.2	167.5
12 months	185.3	158.7	160.8
42 months	150.5	155.5	160.3
Average	155.1	159.2	162.6
Δ - change from baseline(mg/dL)	−7.8	−0.5	0.9
Δ % change	−4.8	−0.3	+0.6

P = 0.0001 (chi^2)

The LDL cholesterol at six months increased in all groups: 9.9% (n-3 PUFA), 7.2% (Vitamin E), and 10.8% (n3-PUFA and Vitamin. E) and 7.4% (control). The fibrinogen level decreased in all groups at 6 months then stabilised (p ns) whilst glucose universally increased (p ns between groups; data from sponsor study).

[21] Marchioli R (2005). GISSI-Prevenzione Investigators. Antiarrhythmic mechanisms of n-3 PUFA and the results of the GISSI-Prevenzione trial. *Journal of Membrane Biology* 206:117-128.

[22] Leaf A. *et al.* 2003. Clinical Prevention of Sudden Cardiac Death by n-3 Polyunsaturated Fatty Acids and Mechanism of Prevention of Arrhythmias by n-3 Fish Oils. *Circulation* 107: 2646-2652.

[23] Dalls T and Bays H. (2006). A Role for Prescription Omega-3 Fatty Acid Therapy: Sidebar: Key Points. *Am J Cardiology* 2006, 98S:71i-76i.

Pharmacia 4 (Nilsen et al 2001)

This study was provided as a publication and produced a negative result. However, it is important that it be included in the discussion of efficacy. The study was carried out in Norway, sponsored by Pharmacia Upjohn and Pronova and published[24]. The study closed at the end of 1997. The results of GISSI-P were published prior to the current article. As the GISSI-P had demonstrated a reduction in the risk of CV death with only 1g daily, the sponsor decided to carry out a single centre trial comparing "pharmacological doses" of n-3 PUFA, that is, 2g twice daily with corn oil placebo not containing n-3 PUFA.

The population included 300 patients recruited four to eight days following an acute myocardial infarction. They were randomised 1:1 to either Omacor-R (Pronova) or corn oil. Each 1g capsule of Omacor contained ethyl esters of EPA and DHA (ratio 1:2), totalling 850-882mg in several batches. The trial was DB in design. Patients were not permitted to receive other fish oil products although their usual diet contained fish. Patients with a life expectancy of < 2 years were not admitted. The diagnosis of MI was based on World Health Organization (WHO) criteria and the ECG showed evidence of recent injury (that is, anterior or inferior Q-wave infarction or any non-Q-wave infarction).

The study received ethical approval and each patient provided informed written consent. Patients underwent clinical examination, blood tests and ECG at 6 weeks, 6 months, 12 months and 18 months and in some after 2 years. All cardiac events were recorded: death, resuscitation, recurrent MI, unstable angina. Revascularisation and death from other causes were also recorded. The median follow-up period was 1.5 years.

Efficacy was evaluated by a univariate time to event analysis (Kaplan-Meier) and the log-rank test was used to examine differences in prognosis. Hazard ratios (HR) and 95% CI were calculated in a Cox proportional hazards regression model. Predefined endpoints were both combined and separate in the primary ITT population. The publication described additional analysis in detail including adjustment for demographic and clinical characteristics (Cox model with first cardiac event as endpoint) and the likelihood ratio test. Relative changes in serum triglycerides, total cholesterol and HDL-C in the first year after MI were analysed in an analysis of covariance (ANCOVA) model with repeated measures after log transformation. Results were adjusted for sex, age at myocardial infarction (MI), body mass index (BMI) and diabetes. Heterogeneity was also investigated. The following table shows the baseline characteristics.

There were no significant differences (chi-square and two-sample tests).

[24]Nilsen DW *et al.* (2001). Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *American Journal of Clinical Nutrition* (2001: 74: 50-6.

Table 19.

Baseline Characteristics	n-3 PUFA (150)	Corn Oil (150)
Male / Females	115 (76.7%) / 35 (23.3%)	123 (82.0%) / 27 (18.0%)
Mean age (range)	64.4 (28.9 – 86.7)	63.6 (29.3 – 87.7)
≥ 65 years	83 (55.7%)	81 (54.0%)
Current Smoker	59 (39.3%)	57 (38.0%)
Mean BMI in Kg/m^2	25.9 (16.9 – 41.8)	26.0 (19.4 – 33.6)
Mean SBP	121.5 (90 – 195)	122.1 (80 – 190)
Fish oil previously	45 (30.2%)	37 (24.7%)
Previous MI	32 (21.3%)	38 (25.3%)
Heart failure	12 (8.0%)	15 (10.0%)
Hypertension	40 (28.6%)	33 (22.8%)
Diabetes	18 (12.0%)	13 (8.7%)

By 1 year, 6 in 10 were taking β blockers and 1 in 10 was taking ACE inhibitors. Aspirin was prescribed in most patients in the first 24 hours and at discharge; at 12 months 87.3% of n-3 patients and 84.6% of placebo patients were taking aspirin whilst 4.8% and 10.0% respectively were on warfarin. At 12 months, 90 patients on n-3 PUFA (71.4%) and 85 on placebo (65.4%) were receiving statins.

Efficacy Results

The incidence of various cardiac events is tabulated below. There were no significant differences in number, type and severity of events. In the calculation of hazard ratios, all 95% CI for n-3 compared with corn oil included one (Cox proportional hazard model, unadjusted).

Table 20.

Number and % Cardiac Events	n-3 PUFA	Corn Oil	P (chi$^{2)}$
0	108 (72.0)	114 (76.0)	0.74
1	27 (18.0)	20 (13.3)	
2	8 (5.3)	9 (6.0)	
≥ 3	7 (4.7)	7 (4.7)	
Type of 1st cardiac event	**N=42**	**N=36**	**0.63**
Cardiac death	4 (9.5)	5 (13.9)	
Resuscitation	0 (0.0)	1 (2.8)	
Recurrent MI	17 (40.5)	12 (33.3)	
Unstable angina	21 (50.0)	18 (50.0)	
Most serious cardiac event	**N=42**	**N=36**	**0.97**
Cardiac death	8 (19.0)	8 (22.2)	
Resuscitation	1 (2.4)	1 (2.8)	
Recurrent MI	15 (35.7)	11 (30.6)	
Unstable angina	18 (42.9)	16 (44.4)	

*chi^2 test for difference in proportions between groups.

Revascularisation (coronary artery bypass graft, CABG, or percutaneous transluminal coronary angioplasty, PTCA) was performed in 43 patients on n-3 PUFA and 49 patients on corn oil (HR 0.92, 0.61 – 1.38).

The total mortality (expressed as cardiac or non cardiac death) occurred in 11 from each group (HR 1.02, 0.44 – 2.36).

The first cardiac event (fatal and non-fatal) in men occurred in 31 patients given n-3 and in 30 patients on corn oil (HR 1.10, 95% CI 0.66 – 1.81); the corresponding figures in women were 11 and 6 (HR 1.62, 0.60 – 4.38).

Even adjusting for various baseline factors did not significantly affect the hazard ratios, nor did the average number of fish meals during follow up (data not shown) affect the combined cardiac events. Overall there was no benefit. Safety results were not presented although a "tendency" to AE was stated. It should be noted that HR compared with corn oil for recurrent MI was 1.43 (0.74, 2.78): in 21 given n-3 and in 15 given placebo. This was an unadjusted HR.

Effect on Serum Lipids

Triglycerides (written as triacylglycerols) levels decreased over a 12 month period by 18.57% (from 1.64 ± 0.82 mmol/L at baseline) following Omacor treatment compared with an increase in the corn oil group by 18.85% (from a baseline of 1.55 ± 0.81 mmol/L; $p < 0.0001$ on comparison of average change, ANCOVA with repeated measures adjusted for age at infarction, sex, BMI, diabetes and deviation from a common follow-up time). In both groups introduction of a statin tended to enhance TG lowering. There was no difference between treatments with respect to total cholesterol (LDL-C not tested). HDL-cholesterol increased by

19.1% at 12 months in the n-3 group and by 7.22% in the corn oil group. ANCOVA revealed a significant difference (p=0.0016).

Comments on Study

1. There was no cardiovascular benefit or any effect on mortality despite a favourable effect on TG and HDL-C following Omacor treatment.
2. The death rate was relatively low which may be related to patient selection for the study. The follow-up period was shorter than in the GISSI study.
3. The patients lived in a coastal region and ate plenty of fish. The earlier DART trial showed the benefit of a diet rich in fish, however the n-3 content was much lower than in the Pharmacia 4 trial.
4. The dosage was much higher than in GISSI-P and therefore had a significant effect on lowering TG. However in GISSI-P, where mortality was significantly decreased, there was no marked effect on TG. The GISSI-P study employed a far greater number of patients, albeit in an open design.
5. The author referred to studies where corn oil was shown to have anti-arrhythmic properties because of the n-6 FA content. One can argue that corn oil is not a true placebo.
6. Aspirin may have confounded the result. Aspirin was given as background treatment in GISSI but not in DART.
7. There may be a threshold where addition of fish oil to a diet rich in fish may not result in an additional effect in 2° prevention.

Singh et al (1997)

This trial (Singh *et al.* 1997[25]) did not use Omacor but 2 fish oil capsules tds (Maxepa; equivalent to1.08g of EPA and 0.72g DHA/day) in patients with a clinical diagnosis of acute MI with onset of symptoms within 24 hours. The trial recruited 404 patients of whom 360 were randomised in DB fashion to fish oil (122), mustard oil (120) or placebo (118). The mustard oil dose included α linolenic acid (2.9g daily). Placebo capsules contained aluminium hydroxide. The treatment period was one year and patients received usual care including trinitrates, aspirin and β blockers, but not universally. Data were analysed according to the ITT principle and the t test was employed. The only side effects were belching (n=6) and nausea (n=8) in patients receiving fish oil.

The total number of deaths were 4 (given fish oil), 6 (given mustard oil) and 6 (given placebo), and the number of non-fatal infarctions were 1, 6 and 6, respectively, in the first 10 days after the original diagnosis. After 28 days the number of total cardiac events were significantly lower in the fish oil (20 – 16.4%) and mustard oil (22 – 18.3%) groups compared with placebo (34 – 28.7%).

Although Omacor was not used in this trial, the results at one year showed a significant reduction of total cardiac deaths in the fish oil group and non-fatal MI and total cardiac events in both fish oil and mustard oil groups compared with placebo as shown below (Table 21).

[25] Singh *et al.* 1997, *Cardiovascular Drugs and Therapy* 11: 485 – 491.

Table 21.

	Fish Oil (122)	Mustard Oil (120)	Placebo (118)
Sudden cardiac death	2 (1.6%)	2 (1.6%)	8 (6.6%)
Total cardiac deaths	14 (11.4%)•	16 (13.3%)•	26 (22.0%)
Non-fatal reinfarction	16 (13.0%)•	18 (15.0%)•	30 (25.4%)
Total cardiac events	30 (24.5%)*	34 (28.2%)*	41 (34.7%)

• $p < 0.01$ versus placebo, * $p < 0.05$ versus placebo

'Total arrhythmias' were less frequent in the treated groups: 13.1% (fish oil), 13.3% (mustard oil) compared with placebo (28.7%; $p < 0.05$). A similar result was noted with respect to 'poor ventricular function' ($p < 0.05$).

The TGA clinical evaluator made the following comment: according to Wang *et al* (2007) there were many limitations including errors of calculation in this study report. The TGA clinical evaluator did not see any original data from the Singh trial to validate this statement.

Omacor for other Indications and Reviews

The evaluator only considered efficacy appropriate to the proposed indications. There were a number of trials in which Omacor was employed for conditions outside the proposed indications. These trials were only evaluated for safety.

Harper *et al* (2005[26]**)** reviewed the efficacy of omega-3FA and the prevention of coronary heart disease in six fish oil studies and six studies with ALA as supplements or in the diet. The GISSI-P trial dominated the analysis of the fish oil trials. Of the latter, three were "designed and powered to analyse hard cardiac endpoints".

The GISSI-P, Nilsen *et al and* Singh *et al* trials have all been described previously. The review authors concluded that there is a role for fish oil or fish in secondary prevention and suggested a dose range of 0.5 to 1.8g daily and noted that mechanistic studies with EPA and DHA suggested an anti-arrhythmic effect; however studies investigating the possible anti-atherogenic effects of n-3FA are inconclusive. The TGA clinical evaluator is in agreement with these conclusions and many publications have also cited the American Heart Association Guidelines in support of the consumption of fish and the taking of fish oil supplements (EPA and DHA) at a dose of 1g daily. Refer to *Conclusions and Recommendations* below.

The outcome of the Singh *et al* study is interesting as the Indian population was basically vegetarian.

Wang *et a*l (2006) carried out a systematic review of the literature on the effects of n-3FA (fish or fish oils rich in EPA and DHA, or sources of ALA) on cardiovascular outcomes and adverse events. The studies were ≥ 1 year in duration. There were six trials of n-3FA supplements including GISSI-P, Pharmacia 4 (Nilsen *et al*) and Singh *et al* which have been considered already. A trial by von Schacky (who wrote the sponsor's clinical expert report for the current Australian submission) investigated the efficacy of fish oil (3.4g/day of EPA/DHA for 3 months, then 1.7g/day for 21 months) in comparison with mixed fatty acid placebo (not n-3). Fewer CV events occurred in the fish oil group but the difference was not statistically significant in 223 patients, half of whom had a history of MI. Two other reviewed trials were considered small.

[26] Harper CR and Jacobson TA. Usefulness of omega-3 fatty acids and the prevention of coronary heart disease. *AMJ Cardiol* 2005; 96: 1521-1529.

The author also reviewed diet or dietary advice trials and trials in patients with implantable cardiovascular defibrillators.

A review of primary prevention studies (not an indication) revealed that in several prospective cohort studies, there was an association between fish oil intake and reductions in all cause-mortality. The Physicians Health Study, a large cohort Chinese study (63,000 men) and a subset of 5103 diabetic women in the Nurses Health Study reported associations between increased fish intake and reduced mortality.

Overall the authors found the evidence suggested that increased consumption of n-3FA (fish or fish oil), but not ALA reduces the rates of all cause–mortality, cardiac and sudden death and possibly stroke and that evidence was stronger in secondary than in primary prevention.

Svensson *et al* (2006)

The author of this paper reported, on behalf of the OPACH Study Group, the results of a secondary prevention trial in 206 patients on haemodialysis (Svensson *et al* 2006[27]). Patients were randomised to either Omacor 2g daily or control (olive oil) for up to 24 months. There were 85 dropouts although all were analysed. The main reasons for discontinuation were AE (9 and 6 respectively), patient refusal (12 and 6, respectively). Omacor had no effect on the composite endpoint (total CV deaths and events), however the secondary parameter, myocardial infarction was significantly lower in the Omacor group (4 versus 13, p=0.036). At 2 years, there were 10 strokes (7 given Omacor and in 3 given placebo) and 7 transient ischaemic attacks (5 and 2 patients, respectively).

There were 64 deaths (34 given Omacor and 30 given placebo) and more AE including serious AE in the Omacor group. Bleeding events included: gastrointestinal (GI) bleeding (8 given Omacor and 5 given placebo), cerebral bleeding (in 2 and 1 patients, respectively) and other (in 5 and 1 patients, respectively; p ns due to relatively small numbers). The increase in bleeding events is a concern.

Safety

Hypertriglyceridaemia Trials

The sponsor provided a good overview of safety pertaining to all studies employing K85 (Omacor) – although % of each main component, DHA and EPA, varied in the formulations used. The summary included 30 efficacy studies (Categories I to IV – hypertriglyceridaemia) and 38 other studies (normal volunteers and patients with various conditions including post-myocardial infarction and hypertension). However integrated analysis was restricted to 22 trials in which case report forms were available (Category I-III studies in patients with HTG). TGA's clinical evaluator presented and discussed these studies as well as any safety findings of note in the secondary prevention and pharmacological trials employing Omacor or Omacor like n-3FA products. A recent review of safety, based on 65 references, has also been published (Bays 2007[28])

[27] Svensson M *et al.* (2006). N-3 Fatty Acids as Secondary Prevention against Cardiovascular Events in Patients Who Undergo Chronic Hemodialysis: A Randomized, Placebo-Controlled Intervention Trial. *Clin J Am Soc Nephrol* 1: 780 – 786.

[28] Bays H E (2007). Safety considerations with omega-3 fatty acid therapy. *A M J Cardiol* 2007; 99S: 35C – 43C.

One specific safety concern is the risk of bleeding and the theoretical interaction with anti-platelet agents and warfarin, which are accepted therapy in patients at risk of cardiovascular events. Other safety concerns expressed in the literature include a possible effect on glucose metabolism and worsening of hyperglycaemia in diabetics. In some trials there were mild elevations of transaminases (ALT and AST). Gastrointestinal complaints were the most frequent adverse events reported and these included burping, fishy taste, dyspepsia, nausea, abdominal upsets and diarrhoea (Table 22).

Table 22. Common Adverse Events (≥ 1%in either group). Summary of treatment – emergent adverse events that were experienced by at least 1% of subjects in either treatment group by body system and preferred term (all subjects from Category 1 studies).

	K85 4g per day (N=226)		**Placebo (N=228)**		
Body System/ Preferred Term	**n**	**(%)**	**n**	**(%)**	**P-value**[b]
Subjects with at least 1 adverse event	80	(35.4)	63	(27.6)	0.0859
Body as a whole	32	(14.2)	26	(11.4)	0.4016
Abdominal pain	2	(0.9)	3	(1.3)	1.0000
Back pain	5	(2.2)	3	(1.3)	0.5025
Flu syndrome	8	(3.5)	3	(1.3)	0.1398
Headache	3	(1.3)	3	(1.3)	1.0000
Infection	10	(4.4)	5	(2.2)	0.2010
Pain	4	(1.8)	3	(1.3)	0.7235
Cardiovascular	9	(4.0)	6	(2.6)	0.4453
Angina Pectoris	3	(1.3)	2	(0.9)	0.6847
Digestive	36	(15.9)	31	(13.6)	0.5103
Diarrhoea	8	(3.5)	8	(3.5)	1.0000
Dyspepsia	7	(3.1)	6	(2.6)	0.7868
Eructation	11	(4.9)	5	(2.2)	0.1351
Flatulence	4	(1.8)	9	(3.9)	0.2599
Nausea	7	(3.1)	7	(3.1)	1.0000
Skin	4	(1.8)	3	(1.3)	0.7235
Rash	4	(1.8)	1	(0.4)	0.2146
Special senses	**7**	(3.1)	1	(0.4)	0.038
Taste perversion	6	(2.7)	0	(0.0)	0.0147

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

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

Overall Exposure

In Category I trials, 226 patients were exposed to Omacor for periods of 0 – 4 weeks to >16 – 20 weeks. Most were treated for 16 weeks or less (n=202). These trials were DB RCT and used corn oil as placebo (in 228 patients). The median and mean durations were around 3 months (range 1 – 19 weeks). Nearly 75% of patients were less than 60 years old and about 95% were Caucasian. In the Omacor group there were 166 males and 60 females (168 + 60 in placebo group). The groups were statistically comparable.

In the 22 trials of the integrated analysis, the K85 exposure was 655 patients. The mean duration was 19.3 weeks (± SD of 20.8). The range was 0 to 100 weeks. Approximately 58% were treated for 8 to 16 weeks. The average age was 51.6 ± 9.95 years (mean ± 5D) and the range 24 to 78 years; 61.5% were less than 60 years old. There were 471 males (71.9%) and 184 females (28.1%). The racial distribution was: Caucasian 74%, 'other' 3.1% and data was not collected from 22.9%.

Adverse Events (AE)

Patients with hypertriglyceridaemia

The following table (Table 23) summarises the overall safety profile in Category I studies (pivotal). The AE are treatment-emergent (TEAE).

Table 23.

	K85 4g/day (226)	Corn Oil (228)
Number of patients with AE	80(35.4%)	63 (27.6%)
Number of events	133	99
Patients with≥ 1 drug-related AE	48 (21.2%)	34 (14.9%)
Number of drug-related events	69	54
Patients with≥ 1 serious AE	7 (3.1%)	6 (2.6%)
Number of serious events	10	7
Discontinuations due to AE	8 (3.5%)	6 (2.6%)
Deaths	1 (0.4%)	1 (0.4%)

The safety profile of all patients (from 22 trials) treated with K85 is summarised below (655 patients).

Patients with at least 1 AE: n=195 (29.8%), 315 events.

Patients with at least 1 drug-related AE: n=162 (24.7%), 248 events.

Patients with at least 1 serious AE: n=16 (2.4%), 23 events.

Patients who died: n=4 (0.6%).

The most common treatment-emergent adverse events (AE) reported in the pivotal HTG trials included eructation (11 or 4.9% K85, 5 or 2.2% placebo), infection (10 or 4.4%, 5 or 2.2%), flu syndrome (8 or 3.5%, 3 or 1.3%), diarrhoea (8 or 3.5%, 8 or 3.5%), dyspepsia (7 or 3.1%, 6 or 2.6%), nausea (7 or 3.1%, 7 or 3.1%) and taste perversion (6 or 2.7%, 0 placebo – p=0.0147, using Fisher's exact test). Table 22 lists TEAE in≥1% in either group. Taste perversion refers to fishy taste and is a "Preferred Term"[29]. The more common TEAE

[29] Adverse events reported by COSTART 'Preferred Term". [Coding Symbols for a Thesaurus of Adverse Reaction **Terms (COSTART) developed by the FDA].**

included: taste perversion n=27 (4.1%), eructation n=29 (4.4%), dyspepsia n=22 (3.4%), diarrhoea n=20 (3.1%), nausea n=16 (2.4%), infection n=15 (1.3%), flatulence n=13 (2.0%), flu syndrome n=11 (1.7%), back pain n=9 (1.4%), pain n=7 (1.1%) and abdominal pain n=7 (1.1%).

Causes of death in the total population were: sudden death (n=1), cardiac arrest (n=1), myocardial infarction (n=1) and suicide (n=1) in those receiving Omacor treatment. Out of 370 placebo patients, one died from a myocardial infarction. These patients are listed:

1. Study CK85-014: 4g. Myocardial ischaemia and sudden death. Case report form (CRF)-assessment of relationship to Omacor missing.

2. Study CK85-014: placebo. Myocardial Infarction, unrelated.

3. Study CK85-012: 6g. Suicide, unlikely related.

4. Study CK85-013: 4g. Apparent myocardial infarction, treatment-relationship was "unclassifiable".

5. Study K85-94110: 4g. Died after CABG, not treatment-related.

Serious Adverse Events Excluding Deaths

The following serious events were reported in Category I studies (K85 4g/day, 228; placebo corn oil, 226). The AE are expressed as COSTART[30] terms.

Total: K85 n=7 (3.1%), Placebo n=6 (2.6%).

Events (n) in K85 group: angina pectoris (2), bypass surgery (1), myocardial infarction (1), myocardial ischaemia (1)*****, syncope (1), cataract not otherwise specified (NOS; 1), cervix disorder (1), endometrial carcinoma (1).

Events (n) in placebo group: angina pectoris (3), coronary artery disorder (2), myocardial infarction (1), lung surgery (1).

***** This patient died (sudden death).

Among the total K85 population evaluated (655 patients), there was at least one serious event in 16 (2.4%) patients. Apart from deaths, these included (n) flu syndrome (1), angina pectoris (2), arrhythmia (1), bypass surgery (1), heart arrest (1), myocardial infarction (2), myocardial ischaemia (1), peripheral vascular disorder (1), syncope (1), tachycardia (1), extensive colitis (1), pancreatitis (2), central nervous system (CNS) neoplasia (1), dyspnoea (1), pneumonia (1), cataract NOS, cervix disorder (1) and endometrial carcinoma (1). There is overlap with Category I. Narratives about individual cases were provided.

Possibly related SAE included: extensive colitis (ischaemic colitis) while taking 2g/day (K85-95109). The event resolved on discontinuation. Hyperglycaemia was reported in two patients in study K85-98019 given 3g K85/day but there were no cases in the placebo group.

Treatment-emergent Adverse Events leading to Withdrawal

In the Category I trials, eight subjects on Omacor (3.5%) and six on placebo (2.6%) discontinued treatment because of one or more AE. The most common reasons for withdrawal were (n in K85/Omacor and placebo groups, respectively) nausea (3 and 2), dyspepsia (2 and 1) and flatulence (0 and 2). Two discontinued because of MI (1 per group). Other AE leading to withdrawal included: abdominal pain (1 and 0), back pain (1 and 0), rheumatoid arthritis (1 and 0), angina pectoris (1 and 0), diarrhoea (1 and 0), eructation (1

[30] The Coding Symbols for a Thesaurus of Adverse Reaction **Terms (COSTART) developed by the FDA.**

and 1), oesophagitis (0 and 1), flatulence (0 and 2), problem swallowing pills (0 and 1), hyperlipaemia (0 and 1), lung surgery (0 and 1) and pneumonia (1 and 0).

In the larger population (Category I to III studies), 24 patients (3.7%) discontinued K85; the most common AE (n) leading to withdrawal included abdominal pain (3), dyspepsia (3), nausea (3), myocardial infarction (2), eructation (2), pancreatitis (2) and pneumonia (2). One discontinued because of rash. The total number of events was 30 in 655 patients.

Clinical Laboratory Test Evaluation

The sponsor analysed shifts from baseline to end of study in patients enrolled in Category I & II trials (DB, parallel, randomised, placebo-controlled, 3-4g K85/day and graded the toxicity based on the National Cancer Institute–Common Toxicity Criteria (NCI CTC) version 2 and normal ranges. No subject had shifts greater than toxicity Grade 2 (on a scale of 0 to 4). There were sporadic reductions in haemoglobin and white cell count that were not clinically significant. The platelet count decreased to Grade 1 status in 3 patients on K85 and 2 patients on placebo (lowest value 128 x 10^9/L – 4g dose). The AST rose to Grade 1 in 15 patients on K85 and 9 patients on placebo, the highest value being 61 IU/L following placebo.

The ALT at endpoint was Grade 1-2 in 40 patients receiving 3-4g K85 daily compared with 19 patients on placebo. Grade 2 toxicity occurred in 5 patients given K85 and in 2 placebo patients, respectively (levels of 99-119 IU/L). There were sporadic cases of TEAE pertaining to transaminase increases. The sponsor analysis revealed a significant difference between treatments with respect to shift in toxicity grade: 40 (K85) versus 8 (placebo) $p<0.0001$, using Fisher's exact test. There was no significant difference for the other parameters tested: haemoglobin, white cell count, platelet count, AST, creatinine. The highest ALT level was 119 IU/L (baseline 78) in Category I-II studies. The rise in transaminases, albeit relatively small, was a consistent feature in other studies in patients with HTG (Category III & IV).

Bleeding and Coagulation Parameters

Bleeding time and coagulation time have been discussed in the *Pharmacodynamics* section above. Clinical trials reported sporadic episodes of minor and major bleeding in patients taking aspirin, warfarin and other anticoagulants. Some of these patients had undergone CABG. Average bleeding time was increased in some trials within the normal range. There is a potential for interaction when larger doses of Omacor are combined with anticoagulants and anti-platelet agents based on increased bleeding time in some trials and evidence from nonclinical mechanistic studies.

SAFETY EVALUATION IN POST MYOCARDIAL INFARCTION PATIENTS

Most of the safety information comes from the GISSI-P study. An internal report of the GISSI-P study was provided (although not comprehensive) in addition to the publication. The Nilsen study was provided as a publication. The sponsor provided an updated (to 2008) literature search (supplementary information) following a TGA request for more recent literature. Any information of relevance from the latter will be presented as dot points.

GISSI-Prevenzione Study

This multicentre (172) Italian trial enrolled 11,324 patients suffering a recent (≤ 3 months) myocardial infarction. They were randomised in an open manner into four groups (n): n-3PUFA 1g daily (2836), Vitamin E 300mg daily (2830), both (2830) and control or no treatment (2828) for a projected 42 months follow-up period. Patients continued to take standard medication for secondary prevention (aspirin, β blockers, angiotensin converting enzyme inhibitors and later on statins following results of large trials). Forms were provided for serious unexpected AE. Safety evaluation included reasons for hospitalisation, causes of

death other than CV disease, minor AE not leading to discontinuation, non-fatal clinical events such as cancer diagnoses as well as fatal events. Laboratory testing included lipid profile (total-C, HDL-C, TG), fibrinogen, C reactive protein, full blood count, glucose, hepatic enzymes, creatinine and uric acid. The study also employed an external efficacy and safety monitoring committee.

The reasons for discontinuation were tabulated in the study report (see Table 24 below).

Table 24. Reasons for discontinuation.

Group/n	n-3PUFA	n-3 + Vitamin E	Total n-3 PUFA
Side Effects	97 (3.4%)	117 (4.1%)	214 (3.8%)
Physician decision	46 (1.6%)	59 (2.1%)	105 (1.9%)
Hospital dropout	214 (7.5%)	214 (7.6%)	428 (7.6%)
Patient refusal	462 (16.3%)	513 (18.1%)	975 (17.2%)
Other	4 (0.1%)	3 (0.1%)	7 (0.1%)
Total	823 (29%)	*****906 (32%)	1729 (30.5%)

***** refers to n-3, 865 ceased Vitamin E in combined group. NB: Vitamin E alone group: 744 discontinued (26.3%)

From the publication, 28.5% receiving n-3 PUFA and 26.2% receiving Vitamin E had permanently discontinued treatment. In the n-3 PUFA "groups" 3.8% discontinued because of side effects and 2.1% in the Vitamin E "groups" discontinued.

From the internal report, fibrinogen means decreased by 13.8% (n-3), 15.7% (n-3 + Vitamin E) and 13.8% (control; p=0.0785; chi^2). There was no difference between treatments with respect to glucose, creatinine and uric acid level. C-reactive protein decreased in all groups as did mean AST and ALT. The latter decreased by 30.9% (n-3), 33.2% (n-3 + Vitamin E) and 31.9% (control) across all the three groups. As expected the white cell count decreased as the myocardial tissue healed. The changes in biochemical values reflected the healing process.

Malignancy was diagnosed in 281 during follow-up (2.5%), most commonly involving the lung, gastrointestinal tract and bladder. The incidence of cancer is summarised below (Table 25 from report).

Table 25. Cancer incidence.

Group:	n-3	Vitamin E	Combination	Control
Non-Fatal	42 (1.5%)	35 (1.3%)	27 (1.0%)	33 (1.2%)
Fatal	38 (1.3%)	38 (1.3%)	39 (1.4%)	29 (1.0%)
Total	80 (2.5%)	73 (2.6%)	66 (2.3%)	62 (2.3%)

Adverse Events

There was little information in the publication. In the internal report, control patients were counted as having no "side effects". Table 26 shows the incidence of side effects attributed to n-3PUFA and Vitamin E (two separate lists in the internal report). Following n-3 the most common events causing discontinuation included dyspepsia, nausea, gastroenteritis, abdominal colic, gastrointestinal (GI) disturbances, allergy and gastritis. The total was 348 in 214 (3.8%) patients taking n-3PUFA ± Vitamin E.

Table 26. Adverse Events leading to discontinuation (COSTART terms).

Events attributed to Omacor and Vitamin E respectively. Number (%)

	Combined Omacor	**Combined Vitamin E**
Dyspepsia	151 (2.7)	79 (1.4)
Nausea	58 (1.0)	16 (0.3)
Abdominal colic	19 (0.3)	14 (0.2)
Allergy	17 (0.3)	16 (0.3)
Gastritis	12 (0.2)	16 (0.2)
GI disturbances	17 (0.3)	16 (0.2)
Gastroenteritis	26 (0.5)	7 (0.1)
Pyrosis (heartburn)	12 (0.2)	5 (0.09)
Bowel disease	5 (0.09)	5 (0.09)
Gastric ulcer	4 (0.07)	2 (<0.05)
Liver disease	4 (0.07)	2 (<0.05)
Dizziness	4 (0.07)	1
Headache	4 (0.07)	0
Gingivitis	1	3 (0.05)
Leukopenia	1	1
Neurological disease	0	3 (0.5)

The list continues with single occurrences in each group. NB Adverse events were updated in the Annex to the Periodic Safety Update Report (PSUR 5-6). The spectrum of events was the same. GI=gastrointestinal.

Following Vitamin E (± n-3), the most common events included dyspepsia, nausea, abdominal colic, and allergy. The total number of events was 185 in 109 (1.9%) patients. There were no clinical episodes of bleeding attributable to treatment, although serious bleeding episodes occurred and resulted in hospitalisation in all groups.

The spectrum of AE not resulting in discontinuation was similar to that resulting in premature cessation of therapy. A total of 376 patients (6.6%) experienced 452 AE attributed to n-3PUFA, mostly dyspepsia (3.2%) and nausea (1.4%). Some 234 AE in 207 patients (3.7%) were attributed to Vitamin E, most commonly dyspepsia (1.8%), nausea (0.3%) and abdominal colic (0.3%).

There was one case of epistaxis in a patient on n-3+Vitamin E.

The report described "AE" leading to hospitalisation, and included procedures such as angioplasty, coronary artery bypass graft and coronary angiography (even across groups). Arrhythmias resulted in 194 patient hospitalisations (1.7%)-the lowest percentage was in the n-3 alone group (1.4%). Nine patients required defibrillation (6 in patients on Vitamin E only). There were 16 cases of gastrointestinal (GI) haemorrhage requiring hospitalisation (n-3: 2, Vitamin E: 4, combination: 3 and control: 7) and 5 cases of epistaxis (1, 0, 3 and 1 respectively.) One in each group was also admitted following haematemesis and six were admitted with melaena (n-3:3, Vitamin E: 1, combination: 1, control: 1) whereas four presented with haematuria (0, 2, 1 & 1 respectively).

Thirty two patients were admitted with unbalanced diabetes (n-3: 10, Vitamin E: 8, combination: 4, control: 10) while six were diagnosed with diabetes (3, 0, 2, 1 respectively). Two patients were admitted with diabetic coma (n-3: 1, control: 1). Thirteen patients experienced pancreatitis (n-3: 1, Vitamin E: 4, combination: 3, control: 5). Five patients were admitted with hepatopathy (n-3: 3, combination: 1, control: 1).

The current Australian submission included a Periodic Safety Update Report (PSUR; dated 2 September 2002-July 2004) with some further information on GISSI-P. The spectrum of events was unchanged although the numbers were increased for example, there were 180 cases of dyspepsia attributed to Omacor (3.2%), 85 in the n-3 group and 95 in the combined group. There were 78 cases of nausea (43 in the n-3 group and 35 in the combined group). The total number of patients with AE were 186 (6.6%) on Omacor alone and 190 (6.7%) on combined treatment. In the Vitamin E groups, the incidence of dyspepsia was 1.8% and nausea 0.3%, that is, both less common than with Omacor treatment. The total incidence of AE was 3.7%.

Nilsen Study (Pharmacia 4)

This study was described in detail under *Efficacy* above. This publication contained no safety data. The trial enrolled 300 Norwegian post-MI patients who were randomised equally to either n-3PUFA 4g daily or corn oil. Treatment proceeded for 12-24 months in a DB manner. Clinical follow-up was carried out at 6 weeks, 6 months, 1 year, 18 months and in some patients also after 2 years. Cardiac outcomes and mortality have been considered. The publication did not contain any safety data. There was no clinical benefit with respect to efficacy variables however there was an improvement in lipid profile, namely reduced triglycerides and increase in HDL-cholesterol (confounded by the use of statins).

Review by Wang et al *(2006)*

The authors of this review (Wang *et al* 2006[31]) reported on the benefits of fish or fish oil supplements in primary and secondary prevention studies. The paper also reviewed prospective trials for adverse events and drug interactions (and both prospective and retrospective studies for potential interactions). Of 395 articles, 247 provided no information on AE among 148 studies, 71 reported ≥1 AE and most of these studies enrolled small numbers for < 6 months. Only one study defined clinical bleeding yet 9 studies involving 2,612 patients addressed the risk of clinically significant bleeding episodes. No consistent association was found and moreover some patients took concomitant aspirin or warfarin (5 studies).

There were a considerable number of publications on fish oils in this submission but relatively limited data on safety – mainly confined to adverse events or bleeding investigations.

Studies using Omacor for other Indications

- Study **CK85-008** enrolled 79 patients with rheumatoid arthritis who were treated for 16 weeks with either placebo (corn oil) + naproxen 750mg/day or naproxen + K85 7g/day or naproxen reduced dose + K85 7g/day. Four withdrew due to bleeding time increase (> 11 minutes) – 3 on K85, 1 on placebo. There were no instances of clinical bleeding.

[31] Wang C *et al* (2006). Fatty acids from fish or fish-oil supplements, but not α-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr* 84:5-17

- Study **CK85-010** enrolled 204 patients with Crohn's disease, 70 (K85 6g daily), 65 (corn oil) and 69 (low carbohydrate diet) in each group. The follow-up was one year. Those in the K85 group experienced more eructation and heartburn, consistent with other trials.
- Study **CK85-011** randomised 64 patients with ulcerative colitis to K85 (31) or maize oil (33). The study period was 2 years. There were 17 withdrawals (8 given K85 and 9 given placebo). K85 was well tolerated. There was a reduction in TxA_2 in the omega-3 group.
- Study **K85-015a** enrolled 145 patients with plaque psoriasis, randomised to K85, 6g/day or placebo corn oil. There were 62 completers in each group. Adverse events were not mentioned in the 4 month trial. There was a similar trial in 145 patients with atopic dermatitis, 120 of who completed the trial. There was said to be no change in laboratory safety parameters.
- Study **CK85-016** enrolled 8 patients with chronic glomerular disease treated with either MaxEPA (33% EPA/DHA) or K85 (9g/day). In the K85 group bleeding time increased from 5.8±0.4 to 7.7±0.4 minutes (NB. still within the normal range with a large n-3 dose).
- Study **K85-91002** in Norway compared Omacor 6g/day with corn oil in 388 evaluable patients undergoing coronary angioplasty (529 stenoses). About two thirds took aspirin and 17%, warfarin. There were four deaths (2 MI, 2 sudden). There were no laboratory test results pertaining to safety.
- Study **K85-95015** enrolled 73 patients with IgA nephropathy, randomised openly to Omacor 4 or 8 capsules daily for 2 years. Safety was a secondary endpoint. The effect on BP was inconsistent. Nine experienced AE and of these, two withdrew. No AE were directly related to Omacor treatment. One had rectal bleeding due to haemorrhoids and another had "cryptogenic" GI bleeding before, during and after study participation.
- Study **K85-98020** was carried out in 45 patients who were hypertensive following heart transplant. They received either 4g Omacor daily or corn oil for one year. Three died from conditions unrelated to treatment. None withdrew because of side effects. All received cyclosporine, prednisolone and azathioprine and most were taking antihypertensives. There were no serious AE.
- **Pharmacia** 7 was a multicentre study in 339 patients receiving cyclosporine following renal transplant. Patients received either K85 or corn oil. There were 13 deaths (2 patients given K85 and 11 given placebo) and 131 serious AE (59 events in 38 patients on K85 and 72 events in 46 patients on placebo). The AE were confounded by various other medications. Very little data were available from this study.
- Study **CK85-003** enrolled 156 patients with hypertension who were randomised to either 6g/day of K85 or corn oil for 10 weeks. Mean SBP and DBP fell significantly in the K85 group. AE were mild to moderate. There was no significant change in bleeding times, platelet count or plasma fibrinogen. However in a study by Smith in 1989, 40 patients received 4g of K85 daily for 4 weeks of which 22 were taking anticoagulants post MI. The Ivy bleeding time increased from a median of 240 to 270 seconds. Fibrinogen levels also increased. Clotting time shortened significantly. One patient on warfarin experienced minor nasal bleeding.
- Study **K85-90001** (Eritsland *et al,* 1995[32]). This study evaluated patients before and 9 months after CABG. Out of 610 patients, 511 evaluable patients were randomised to

[32] Eritsland J *et al* (1995). Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and

Omacor 4g daily (25%) and control (standard treatment; n=260). Patients received either aspirin 300mg/day or warfarin (INR[33] 2.5-4.2). They were randomised on the second post-operative day. The primary aim was to evaluate graft patency. Bleeding episodes are tabulated below. There was no significant treatment difference. Most were described as minor except for 1 episode of intrathoracic bleeding post-operatively.

Table 27.

Treatment (n)	**Nasal**	**Haematuria**	**GI**	**Other**	**Total**
Aspirin (106)	7	1	0	0	8
Aspirin + Omacor (119)	7	1	1	1	10
Warfarin (154)	7	3	2	2	14
Warfarin + Omacor (132)	10	5	1	1	17

Out of 610 patients enrolled, 12 died in the 9 months post-operatively and 66 deviated from randomised treatment; 9 because of bleeding (5 given Omacor and 4 placebo) and 34 because of gastrointestinal complaints. Others were excluded for various reasons leaving 511 evaluable. Bleeding time increased by similar amounts in both groups (p ns between treatments) and fibrinogen levels increased slightly in both groups (that is, Omacor versus control). One patient (from the group receiving warfarin alone) died from multi organ failure and gastric bleeding early post operatively. A related publication by Eritsland *et al 1996*[34] reported additional bleeding episodes following aspirin (n=23), warfarin (n=38), fish oil (n=34), control (n=27). Most of the INR measurements were either in the target range or lower.

Other Safety Information

The submission contained numerous publications. One paper **(**Busnach *et al*[35]) reported on an interaction study in kidney transplant recipients receiving cyclosporine. Forty-two patients were equally randomised to either n-3PUFA (K85) or placebo (olive oil). The patients were on a quadruple immunosuppressive regimen. The dose of "Esapent"[36] was initially (from Day 1 post-operatively) 6g daily but was reduced to 3g on Day 30 (study duration was 12 months). At 6 months, the plasma creatinine was significantly lower in the n-3PUFA group (1.22 ± 0.06 (standard error) mg/dL versus 1.6 ± 0.1 mg/dL; $p<0.05$). A similar difference was seen at 12 months.

Numerically the cyclosporine C_{max} was higher in the n-3PUFA group but the difference was significant only at 1 month (1831 ± 940 versus 1524 ± 607 ng/mL; $p = 0.04$). The levels were very similar at 6 and 12 months.

bleeding episodes in patients with coronary artery disease. *Blood Coagulation and fibrinolysis* 6, 17-22.

[33] INR (International Normalised Ratio) is the ratio between the coagulation time of a sample of blood and the normal coagulation time, when coagulation takes place in certain standardised conditions.

[34] Eritsland J *et al* (1996). Effect of dietary supplementation with n–3 fatty acids on coronary artery bypass graft patency. *Am J Cardiol* 77:31-36.

[35] Busnach G *et al*. (1998). Effect of n-3 polyunsaturated fatty acids on cyclosporine pharmacokinetics in kidney graft recipients. A randomised placebo-controlled study. *J Nephrology* 11 (2):87-93

[36] Fish oil supplement (Pharmacia & Upjohn) containing 85% of eicosapentaenoic and docosahexaenoic acids in the ratio of ≈0.9% to 1.5% to ≈84%, respectively.

Periodic Safety Update Reports

The submission included a Periodic Safety Update Report (PSUR), for period 2 September 2002 to July 2004, which was presented to the European Union. No individual case reports were sent to Pronova, the EU sponsor and none from Pronova to regulatory authorities. One ongoing study (K85-02024) was described in the efficacy section as a publication (Svensson *et al*). There were a number of instances of clinical bleeding, however the population commonly took warfarin or aspirin and were undergoing chronic dialysis. Another ongoing study (OCEAN – K85-02025) in patients awaiting carotid endarterectomy was a multicentre DB randomised trial with an estimated enrolment of 121 patients allocated to either Omacor 2g daily or placebo. The aim was to determine if Omacor was effective in stabilising atherosclerotic plaques. Results were not provided in the current Australian submission although the PSUR revealed some serious AE including myocardial infarction, lacunar infarction, cerebral stroke, crescendo transient ischaemic attack and death from intracerebral bleeding. None were attributed to Omacor treatment.

A subsequent **PSUR 7** (to 22/7/2005) and its addendum (to July 2006) provided significantly more post-marketing data. The exposure to July 2006 was 207,409 patient years and 34,500 in nine ongoing clinical trials. In PSUR 7 there were three serious reports (and some SAE in blinded studies). These included ventricular bigeminy, ventricular ectopic beats and vasculitis. There was a non-serious report of raised glucose. In the PSUR 7 addendum, there were 17 case reports to Pronova including pancreatitis, post-operative pharyngeal bleeding, hypersensitivity, chest pain and dizziness, elevated ALT and AST, rhabdomyolyses, erythema multiform, epidural haematoma and intracerebral haemorrhage.

Miscellaneous Studies

● An open randomised, 2-way crossover, single dose and steady state trial studying the possible effect of Omacor on simvastatin kinetics was submitted (**McKenney *et al.*, *2006***[37]). The two groups were given 4g/day Omacor + 80mg simvastatin or simvastatin alone. The rationale for the trial was based on a report of increased hepatic concentration of CYP450 enzymes in rodents.

The human study enrolled 24 subjects including 20 Hispanics. There was a numerical increase in AUC and C_{max} when Omacor was added, however the difference from simvastatin alone was not significant. The apparent clearance was higher in patients given simvastatin alone (p=0.0522) on Day 1 (single dose). On Day 14, there was no significant difference in the PK parameters between the two groups.

Effect on Insulin and Glucose

Patel et al (2007) carried out a small study in 35 evaluable post-MI patients (16 were given Omacor 1g daily for 3 months and 19 patients continued their usual treatment). In the Omacor group, median insulin increased from 31.6 to 48.8 mU/mL (p ns), however, the mean change was 3.39 mU/mL (p ns). In contrast, the median and mean insulin decreased in the control group. A trial by the same group (Lee *et al*, 2006) reported no significant treatment differences with respect to indices of thrombogenesis in 77 patients post-MI. Omacor was of no value in improving coagulation status or inflammatory status.

A randomised, DB trial of 8 weeks duration was carried out in 256 patients with hypertriglyceridaemia (123 patients were given Omacor 4g + simvastatin 40mg, 133 patients

[37] McKenney JM *et al*, (2006). Study of the Pharmacokinetic Interaction Between Simvastatin and Prescription Omega-3-Acid Ethyl Esters. *Journal of Clinical Pharmacology* 46: 785-791.

were given simvastatin + placebo) (Davidson *et al.*, 2004[38]). There were 243 patients who completed the study (n=116 Omacor + simvastatin and n=127 simvastatin + placebo). AEs accounted for discontinuation in 3 from each group. The addition of Omacor significantly reduced TG and VLDL-C levels compared with simvastatin treatment alone. Combined treatment also caused a modest rise in HDL-C and LDL-C levels. In this study mean ALT increased by 5.7 U/L in the Omacor group and decreased by -0.7U/L in the placebo group ($p<0.032$). The safety profile was otherwise similar in the two groups. The study was ongoing and planned to run for 24 months.

Biscione F *et al*

A review of the cardiovascular effects of n-3 fatty acids was also submitted (Biscione F *et al* 2007[39]). One conclusion was that the effect of omega-3 fatty acids on blood coagulation was marginal. The authors also discussed metabolic mechanisms to explain for example the antiarrhythmic effect of n-3 PUFA. Many of the publications submitted by the sponsor showed inconsistent effects on coagulation parameters including inhibition of platelet aggregation and alterations in bleeding times (some trials showed mean increases within the normal range) and levels of fibrinogen (both increases and decreases reported).

Von Schacky 2006

A review of the use of omega-3 ethyl esters for CV prevention and treatment of hypertriglyceridaemia was submitted (Von Schacky 2006[40]). This paper cited studies demonstrating that DHA and EPA inhibited platelet aggregation.

Literature References 2007-2008

- A meta-analysis by Jenkins *et al 2008*[41] was carried out on randomised controlled trials examining the effect of fish oil supplementation on ventricular fibrillation and ventricular tachycardia in patients with implantable cardioverter defibrillators (ICDs). Three trials showed disparate results (the second largest trial showed a benefit of treatment whereas the smallest trial detected an adverse tendency with respect to ICD discharge). An anti-arrhythmic effect has not been clearly demonstrated in clinical trials. Doses of fish oil in the 3 cited trials ranged from 0.9 to 2.6g/day.
- McClaskey *et al 2007*[42] reported subdural haematoma in an elderly patient taking 6g/day of n-3FA+aspirin and warfarin. In 2000, the FDA concluded that EPA and DHA were safe as dietary supplements provided intake not exceed 3g daily. Various studies reported reduction in platelet AA and TxA_2 as well as reduction in Vitamin K dependent coagulation factors but clinically significant bleeding was not demonstrated. The author concluded that prescribing information should describe a potential interaction with anticoagulants and therefore recommend periodic monitoring.

[38] Davidson MH *et al* (2004). Efficacy and tolerability of adding prescription Omega-3 fatty acids 4 g/d to Simvastatin 40 mg/d in hypertriglyceridemic patients: An 8-week, randomized, double-blind, placebo-controlled study. *Clin Ther* 29(7): 1354-1367.

[39] Biscione F *et al*. (2007). Cardiovascular effects of omega-3 free fatty acids [Review]. *Current Vascular Pharmacology* 2007; 5 (2): 163-172.

[40] von Schacky C (2006). A review of Omega-**3** ethyl esters for cardiovascular prevention and treatment of increased blood triglyceride levels. *Vasc Health Risk Management* 2 (3): 251-262.

[41] Jenkins DJ *et al* (2008). Fish-oil supplementation in patients with implantable cardioverter defibrillators: a meta-analysis. *CMAJ* 78(2): 157-164 2008

[42] McClaskey EM and Michalets EL. (2007). Subdural hematoma after a fall in an elderly patient taking high-dose omega-3 fatty acids with warfarin and aspirin: Case report and review of the literature. *Pharmacotherapy* 27(1): 152-160

- There were several reviews discussing mechanisms that might explain the cardio-protective effects of fish oils: anti-arrhythmic (ion channel alteration, increased heart rate variability); inhibition of platelet aggregation; reduction in vascular cell adhesion molecules such as e-selectin, vascular cell adhesion molecule (VCAM) and inflammatory mediators; down regulation of lipid synthesis or up regulation of lipid oxidation.
- Lavie *et al 2009*[43] reviewed n-3PUFA and cardiovascular disease in a "State of-the-Art" paper. This review focused on secondary prevention following myocardial infarction especially retrospective epidemiological studies (as background) and large RCTs showing benefits of fish oils in 1^o and 2^o prevention. The AHA endorsed the use of n-3PUFA, 1g/day (EPA + DHA) in the form of fatty fish or fish oil supplements (capsules or liquid) in patients with documented CHD. The large trials reviewed included DART, GISSI-P and JELIS (Japan EPA Lipid Intervention Study). The latter enrolled 18,645 subjects (14,981 as 1^o prevention and 3,664 in 2^o prevention). Patients were randomised to statin alone or statin and highly purified EPA (1.8g daily). In the 5 years of the trial, there was a 19% reduction in major CV events in the EPA group, however there was no reduction in sudden cardiac deaths (there were very few sudden deaths reported).
- The results of the OMEGA trial were presented to the American College of Cardiology 58th Annual Scientific sessions in March 2009. This trial was not submitted with the current Australian submission. The patients (n=3,851; all 3-14 days post MI) were randomised to 1g fish oil/day (460mg EPA, 380mg DHA) for 1 year or to placebo at 104 centres in Germany. The patients received aspirin (85 – 95% of patients), clopidogrel, statins, β blockers and ACE inhibitors. This trial showed no benefit of EPA/DHA for any of the 1^o or 2^o endpoints. The trial was described as underpowered and the patients received intensive conventional treatment in hospital and on discharge.

- Lavie *et al* (2009) also reviewed evidence of benefit of n-3PUFA in patients with arrhythmias. There appeared to be a reduction in sudden cardiac deaths post MI and in CHD patients with LV dysfunction. However, 3 trials in patients with ICDs showed mixed results (reviewed in Jenkins *et al.*,2008). The GISSI-HF study did not show any benefits with sudden cardiac death (1g/day), however there was a reduction in total mortality. The authors considered that n-3PUFA was potentially beneficial in 1^o prevention, CHD and post MI, sudden cardiac death, heart failure, atherosclerosis and atrial fibrillation.
- Besides the American Heart Association (which recommends 1g daily (EPA/DHA) in patients with established CHD and 2 oily fish meals a week for those without CHD), the National Cholesterol Education Programme Adult Treatment Panel III, the WHO, European Society of Cardiology, the UK Scientific Advisory Committee on Nutrition and the American Diabetes Association have all provided guidelines advocating increasing the consumption of fish. "Studies are needed to determine the optimal mixture of DHA relative to EPA in various populations."

Clinical Summary and Conclusions

Before making recommendations the clinical evaluator made conclusions in the form of a risk benefit analysis.

Benefits:

- Fish oil is considered by some as a panacea for a number of illnesses ranging from arthritis and other inflammatory diseases to the prevention of cardiovascular disease.

[43] Lavie CJ *et al* (2009). Omega-3 polyunsaturated fatty acids and cardiovascular diseases. .*J Am Coll Cardiol*, 54: 585-594

The current submission is intended to support the indications of hypertriglyceridaemia and secondary prevention as defined in the proposed product information. The active ingredient, omega-3 fatty acid ethyl esters, is proposed for general marketing. It contains at least 90% of n-3FA with the largest contributions by EPA (46%) and DHA (38%)

- The ingredients are highly concentrated which reduces the number of capsules (1g) required per day which may increase patient compliance. The proposed dose for HTG is 2 to 4g daily (2-4 capsules). Some patients are intolerant of the larger number of capsules required with less concentrated n-3 formulations.
- The manufacturing process removes most of the other constituents of fish oil including Vitamins A and D_2 cholesterol and contaminants such as mercury and dioxins. A small amount of α-tocopherol is added as an antioxidant.
- Omacor was first registered in Norway in 1994, a country known for a rich fish diet. The formulation was approved in the UK in 1996 and Netherlands in 2003 and the submissions were said to be "identical" – at least the core part of the submission. Omacor (called Lovaza in US) was approved for severe hypertriglyceridaemia in the USA in 2004. It is however not registered for post MI patients in the USA although the American Heart Association Guideline recommends fish and fish oils in cardiovascular disease prevention.
- There is a wealth of literature on the subject of fish and fish oils and the treatment of patients with cardiovascular disease and hyperlipidaemia. The current submission contained hundreds of publication as well as internal reports on trials conducted by Pronova; the application can be considered a hybrid submission. The publications included large epidemiological studies as well as double-blind trials. The amount of research published on fish oils is overwhelming.
- Elevated TG levels have been described as an independent risk factor for CHD disease and severe hypertriglyceridaemia may be complicated by pancreatitis. The 8 pivotal trials on HTG, all DB randomised in design, demonstrated a significant reduction in TG levels in comparison with placebo [mean reduction across studies ranged from 20.4% to 49.6% following 4g daily whereas the change on placebo (corn oil) ranged from −4.3% to +20.8%]. The greatest reduction in TG levels occurred in two US trials where the patients presented with very high baseline TG levels.
- Reductions in TG levels were accompanied by reductions in VLDL-C levels, small reductions in total cholesterol and small rises in HDL-C levels, however there were rises in LDL-C ranging from means of 7.22 to 16.7% in 5 studies and a rise of 52.8% in the sixth study (out of 8 studies tested). The latter included patients with very high baseline TG levels. Apo B did not change significantly.
- The HTG package included reports of 30 trials divided into 4 categories. Some 655 patients received Omacor or an Omacor-like formulation.
- The positive effect of Omacor on HTG applied to patients with Type IIb (mixed hyperlipidaemia) and patients with Type IV/V hyperlipidaemia. However, the reduction was relatively greater in patients with severe HTG enrolled in two American trials.
- There was no significant pharmacokinetic interaction between Omacor and statins in trials using simvastatin, lovastatin and atorvastatin. Addition of Omacor led to a greater reduction in TG compared with statin alone.
- In extension trials the reduction in TG levels was maintained.

- The proposed dose of TG is 4g daily in spite of higher doses producing greater reductions in TG levels (Study CK85-013; 2, 4 and 8g daily doses tested). The 2g/day dose appeared to be inadequate in that trial.
- PD studies and several publications suggest a number of actions of n-3 PUFA in addition to its effects on serum lipid profile. These were based on both *in vivo* and *in vitro* studies and included: dampening of the inflammatory response through incorporation into eicosanoid pathway; antithrombotic action by inhibiting platelet aggregation and reducing TxA_2 (and therefore an increase in bleeding time); reduction in BP (inconsistent results); anti-arrhythmic action based on *in vitro* cardiomyocyte cultures, whole animal experiments and studies in post-myocardial infarction patients (as in the GISSI – Prevenzione study and the trial by Singh *et al*). One study showed that Omacor did not interfere with Apo-B disposition.
- The large secondary prevention trial (GISSI-P) was open in design, however evaluation was blinded. This trial was carried out in 1993-1997 and followed on the positive results of the DART trial in which all cause mortality was reduced in the group who ate fatty fish. Patients in GISSI-P received either Omacor 1g daily or placebo for up to 3.5 years. There was a significant reduction in CV mortality and sudden death, however no significant difference from placebo with respect to cardiovascular non-fatal events. There was a significant reduction in the co-primary combined endpoints which included all cause mortality (refer to section on *Efficacy* for a full explanation). Addition of Vitamin E to Omacor did not significantly increase the survival over the period of follow-up. A post hoc analysis by Marchioli revealed a greater reduction in the risk of sudden death in those with low ejection fractions at baseline. Patients in this trial were asked to consume more fish, fruit, vegetables and olive oil. Despite the positive results, subgroup analysis lacked statistical power.
- The study by Nilsen *et al* (Pharmacia 4) did not demonstrate any difference from placebo in RCT. The lack of effect on mortality was attributed to a low mortality overall and a high fish diet.
- Singh *et al* reported significant effects of fish oil and mustard oil on sudden and total cardiac deaths as well as non-fatal re-infarctions and total cardiac events. Total arrhythmias were also less frequent in treated patients.
- Omacor bore an acceptable safety profile in doses of 1 to 4g daily covering the range recommended in the proposed Australian PI. The main adverse reactions involved the GI tract: fishy eructation, dyspepsia, nausea and flatulence. There were no episodes of significant bleeding attributed to Omacor, although bleeding was reported in Omacor trials in which patients received concomitant aspirin or anticoagulants. The proposed Australian PI covers a potential interaction under the *Precautions* section. No deaths were attributed to Omacor treatment. A relatively small number of patients discontinued therapy because of adverse events.
- In the Category I and II hypertriglyceridaemia trials, at end point, the ALT was Grade 1-2 (CTC criteria) in 40 patients on 3-4g daily compared with 19 patients on placebo. The corresponding figures for AST were 15 and 9 patients, respectively. There was a significant difference with respect to shift in toxicity grade of ALT but not the other laboratory parameters tested (AST, placebo count, white cell count, creatinine, haemoglobin). During Category III and IV studies, the ALT rise was consistent but modest. The same applies to pharmacological trials.
- In the large GISSI-P trial an external efficacy and safety committee was employed. In this study "mean SGOT and SGPT"[44] decreased, no doubt attributable to healing of

[44] SGOT=AST and SGPT=ALT.

the myocardial damage in this patient group. This was accompanied by a decrease in white cell count and C-reactive protein. There was no difference among groups in the incidence of malignancy during follow-up. The most common AE involved the GI tract. There were sporadic cases of allergy in all active groups. There were no clinical episodes of bleeding attributable to treatment. Dyspepsia and nausea were more frequent with Omacor (±Vitamin E) compared with Vitamin E (± Omacor).

- Wang *et al* found no consistent associations between fish or fish oil intake and clinical bleeding in a review of 148 studies with safety data.
- Sporadic cases of bleeding were reported in Periodic Safety Update Reports, mostly attributed to concomitant antiplatelet agents and anticoagulants.
- The American Heart Association endorsed the use of n-3 PUFA, 1g daily containing EPA and DHA in the form of fatty fish or fish oil supplements, in patients with documented coronary heart disease.
- A more recent trial, JELIS, carried out in over 14,000 (1º prevention) and 3,644 (2º presentation) compared statin alone or statin plus EPA 1.8g daily. There were very few sudden deaths, however there was a significant reduction in major CV events in the combined group.

Risks/Deficiencies

- The current submission, compiled in early 2008 was a hybrid of internal reports and literature references. It was laid out in Common Technical Document (CTD) format with respect to the original Pronova sponsored trials which were supplemented with literature references. A sponsor's expert report (by a clinician who carried out a RCT of dietary omega-3FA in the 1990's employing patients with coronary atherosclerosis) was included. The additional references covered the period to 2007. An evaluation of the literature based submission search methods by TGA library staff found several deficiencies and the sponsor provided updated literature references to December 2008, which included safety in the search terms.
- In summary, it was difficult to formulate a cohesive view of Omacor especially with respect to the pharmacological effects of Omacor and fish oils in general as well as the efficacy. There is no doubt that Omacor (and related fish oil preparations) is effective in lowering serum TG levels mainly through its action on VLDL. However, this action is more pronounced in patients with very high baseline TG levels. Nevertheless Omacor is still effective for lesser degrees of HTG.
- In some trials, Omacor was associated with increases in LDL-C (but not apolipoprotein B) levels. The rises in LDL – C levels were small to moderate but statistically significant. In those with combined hyperlipidaemia with elevated LDL-C, combination with a statin will offset this secondary effect. The sponsor argued (from a limited number of experimental studies) that the increase in LDL-C concerned larger more buoyant particles rather than smaller dense LDL particles associated with atherosclerosis. In the USA, Omacor is approved only in patients with more severe forms of HTG, however the Clinical Trials section of the US prescribing information refers to clinical trials in patients with lower baseline TG levels (<500mg/dL). The clinical evaluator has no objection to the proposed indication for hypertriglyceridaemia despite the rises in LDL-C levels. Patients prescribed Omacor should undergo routine monitoring of their lipid profile, not just triglyceride.
- Some of the formulations in the early trials, although referred to as Omacor or K85, contained proportions of EPA and DHA that were different from that of the proposed for marketing formulation. The significance of this is uncertain.

- The data to support the secondary prevention indication in post-myocardial infarction patients is based mainly on the GISSI- Prevenzione study which enrolled over 11,000 patients. The design was open although evaluation of data was blinded. This could be classified as Level II evidence according to the National Health & Medical Research Council (NH&MRC).
- The submission included a number of systematic reviews on the use of omega- 3 fatty acids (DHA and EPA) in 2º prevention. Hooper (Cochrane review[45]) concluded there was no clear benefit when the DART 2 study was included among RCTs and cohort studies, however there was a significant reduction in mortality when DART 2 was excluded (DART 2 did not use Omacor but was, rather, dietary advice).
- The Nilsen study which compared Omacor 4g/day (as opposed to 1g/day in GISSI-P) and placebo corn oil did not show any beneficial effect on mortality and CV outcomes. GISSI-P did not show a beneficial effect on CV disease (non-fatal).The Nilsen study was a double blinded RCT. There was no beneficial effect, despite a significant reduction in serum TG levels with Omacor treatment. The sponsor attributed this failure to a high background fish intake in a Norwegian population.
- The sponsor's clinical expert described several ongoing trials for which data were not submitted. These included:
  - ORIGIN: effects of glucose lowering with insulin glargine ± 0.85g/day EPA/DHA on risk of CV events (final results expected in 2009-2010; n=10,000).
  - ASCEND: 100mg aspirin, 1 Omacor capsule or none-effect on CV events in diabetics (recruiting in 2008; n=10,000).
  - OMEGA: effects of n-3FA on reduction of sudden cardiac death after MI. One capsule of Omacor versus standard treatment alone. A publication this year indicated a negative trial result.
  - GISSI-heart failure: This has been discussed, Omacor ± rosuvastatin or no treatment.
  - AFORRD: patients with Type 2 diabetes on 20mg atorvastatin ± EPA and DHA or none.
  - A trial in patients with a history of symptomatic atrial fibrillation. (NCT 00402363)
  - FAVOURED: an Australian trial in 1200 haemodialysis patients given 4g EPA and DHA ± aspirin 100mg/day in prevention of early thrombosis of arteriovenous fistulae.
- The sponsor's clinical expert supported Omacor in 2º prevention in post MI patients. It is uncertain whether the expert has financial interests in the sponsor.
- Potential safety concerns include:
  - Increased bleeding tendency: increase in bleeding time reported in some trials, especially with doses exceeding 4g daily. Reasons for the potential risk have been described (antithrombotic action, inhibition of platelet aggregation, reduction in TxA_2, reduction in prothrombin activity).
  - GI intolerance, fishy eructation.
  - Potential for interaction with antiplatelet agents and anticoagulants.
  - Elevation of LDL-C in some but not all trials.

[45] Hoper L *et al* (2006). Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *BMJ* 332 : 752.

- There appears to be no significant effect on blood glucose levels but one study by Patel in 2007 reported a rise in serum insulin.
- Relatively small, but consistent rises in ALT.

Recommendations

The evaluator recommended approval for registration for the altered indication:

Endogenous hypertriglyceridaema as a supplement to diet when dietary measures alone are insufficient to produce an adequate response. This includes more severe forms of hypertriglyceridaemia (Type IV) as monotherapy, and Type IIb/III in combination with statins when control of triglycerides is insufficient. Patients with higher baseline levels of TG are more likely to exhibit a better response to Omacor.

Omacor is not indicated in exogenous hypertriglyceridaemia (Type I hyperchylomicronaemia). There are insufficient data to support use in patients with secondary hypertriglyceridaemia including patients with diabetes mellitus.

The clinical evaluator also recommends approval for the secondary prevention indication as specified in the proposed PI, Post Myocardial Infarction:

Adjuvant treatment in secondary prevention after myocardial infarction, in addition to standard therapy (for example, statins, antiplatelet medicinal products, beta-blocker, ACE inhibitors).

Although this submission has several deficiencies, the clinical evaluator considered the evidence enough to support the use of Omacor as adjuvant therapy in patients with a history of recent myocardial infarction. Omacor should not be promoted for secondary prevention but as an addition to standard or best therapy.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

i) The drug substance is a mixture of omega-3 fatty acids all derived as their ethyl esters, the two main components being EPA and DHA. There were a total of 7 bioavailability/bioequivalence studies which were evaluated by the quality evaluator. From these studies it was not possible to determine whether the levels of EPA and DHA in the body after dosing with the proposed product are greater than with the other products tested. The latter included lower strength products containing omega-3-acid ethyl esters and products containing omega-3-marine triglycerides. There were a number of reasons for the uncertainty:
   - Ø the assay methods used were not validated to the standard expected
   - Ø EPA and DHA are endogenous and are distributed, stored and metabolised as a source of energy as part of the body lipid pool
   - Ø the responses had high intra- and inter-subject variabilities due in part to the intake of dietary fish not having been controlled during the studies
   - Ø all studies were of parallel group design rather than cross-over design.

However, the quality evaluator was able to conclude that the levels of EPA and DHA in the body do increase on ingestion of Omacor, although in less than a dose-proportional manner.

Also, it was not possible to determine if there is a food effect. This is partly due to the reasons stated above and partly due to the fact that olive oil was chosen as the food and this is not considered an appropriate meal. These conclusions were supported by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its 129th meeting in November 2009.

In summary the quality evaluator recommended approval of the company's application with respect to chemistry and quality control. In relation to bioavailability, the evaluator was more circumspect, stating that:

- Ø levels of EPA and DHA increase after ingestion of Omacor
- Ø it is not known if the increase is greater (or lesser) than with other products
- Ø It is not known if there is a food effect
- Ø The proposed Australian PI reflects these conclusions apart from the statement in relation to food.

Because of the uncertainty in relation to the food effect, the quality evaluator has, for consistency, recommended that Omacor should be taken with food.

Nonclinical

ii) There were no non-clinical objections to the registration of Omacor for the proposed indication. Below are the conclusions and recommendations of the non-clinical evaluator:

Issues addressable from the non-clinical data

The non-clinical evaluation has not raised any significant safety issues relating to the proposed use of Omacor. The submitted toxicity studies were considered adequate for this product and included repeat dose toxicity studies in rats and dogs of up to 52 weeks, genotoxicity studies, carcinogenicity studies in mice and rats and a full package of reproductive toxicity studies. The main toxicity findings were skin lesions that appeared to be due to deficiency of omega-6 fatty acids. There were also some minor changes in a variety of organs, mainly relating to the fatty nature of the product. There was some evidence of an effect on blood clotting from non-clinical studies, but only at high doses.

Issues likely to be addressable from the clinical data

Assessment of efficacy for both indications will need to rely on clinical data. Non-clinical studies provided evidence for the cardioprotective, anti-arrhythmic activity of omega-3 fatty acids, although doses employed in the animal studies were higher than the proposed clinical dose. Similarly, while there was consistent evidence in non-clinical studies that the omega-3 fatty acids lower the levels of blood triglycerides, significant reductions were generally only achieved at doses in excess of that proposed clinically for this indication (approximately 20-40 fold higher).

As no data on drug interactions were submitted, it will be necessary to rely on clinical data to determine the safety of use of Omacor with other drugs.

Ø There are no objections on non-clinical grounds to the registration of Omacor for the proposed indications.

The sponsor responded to the non-clinical evaluation report, stating that it did not have any comments on that report.

Clinical

iii) The clinical data in the submission were comprehensively summarised by the clinical evaluator:

- six bioequivalence/bioavailability studies in healthy subjects
- one PK dose-finding study in healthy subjects (there was another, K85-98023, which was not available)
- a pooled analysis of dose proportionality across hypertriglyceridaemia (data from 10 efficacy and safety trials in patients with hypertriglyceridaemia)
- data about pharmacokinetics and triglyceride/fatty acid levels from 11 efficacy and safety trials in patients with hypertriglyceridaemia (9 of these 11 were also included in the pooled analysis of 10 studies mentioned under the previous dot point)
- 11 pharmacodynamic studies in various patient populations
- 28 efficacy and safety studies in patients with hypertriglyceridaemia, divided into 4 categories beginning with 8 double-blind, parallel, placebo-controlled studies in patients with hypertriglyceridaemia; these were the pivotal studies; the remaining 20 studies were divided into 3 groups with progressively lower level evidence
- 2 efficacy and safety studies for secondary prevention after myocardial infarction
- A number of other studies in a variety of other patient populations, for example, rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, IgA nephropathy, chronic glomerular disease, chronic hepatitis and other diseases.
- Literature-based part of the submission – 35 papers, divided according to the NH&MRC classification of evidence (up to Dec '07)
- Literature Review from Dec '07 to Dec'08 – another 5 significant papers.

iv) The clinical evaluator has recommended approval for the secondary prevention indication as specified in the proposed PI, that is, for post-myocardial infarction. With regard to its proposed use in the treatment of hypertriglyceridaemia, the clinical evaluator has recommended approval for the following altered indication:

"*Endogenous hypertriglyceridaemia as a supplement to diet when dietary measures alone are insufficient to produce an adequate response. This includes the more severe forms of hypertriglyceridaemia (Type IV) as monotherapy and Type IIb/III in combination with statins when control of triglycerides is 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 I hyperchylomicronaemia). There are insufficient data to support use in patients with secondary hypertriglyceridaemia including patients with diabetes mellitus."

Pharmacodynamics

v) There were 11 pharmacodynamic (PD) studies:

- **CK85-003**: 156 patients randomised double-blind to either omega-3-acid ethyl esters or corn oil as placebo. The differences between groups were significant: -6.4 mm Hg for SBP, p = 0.0025 and -2.8 mm Hg for DBP, p = 0.029. No significant changes in bleeding time, fibrinogen or platelet count. Serum TG decreased from 1.48 to 1.18 mmol/L, p = 0.0007.
- **K85-92005**: A sub-group of 78 patients selected from previous trial. Omega-3-acid ethyl esters at a dose of 4 g daily compared with placebo caused significant falls in SBP of 4.1 mm Hg, p = 0.004, DBP of 3.3 mm Hg, p = 0.0008 and mean arterial pressure of

3.6 mm Hg, p = 0.0003. Significant reductions in TG and VLDL-C but not in total and LDL-C nor in Apo B nor Apo A1. No significant effects on glucose or insulin.

- **CK85-004**: some significant increases in bleeding time in a study of 22 men with stable coronary artery disease on omega-3-acid ethyl esters alone and when combined with aspirin but no significant increase on combination compared with aspirin alone; significant reduction in platelet count when omega-3-acid ethyl esters added to aspirin
- **CK85-005**: in a study in 40 post–MI patients, significant increases in bleeding time (240 to 270 seconds, $p < 0.001$), fibrinogen levels (2.5 to 2.8 g/L, $p < 0.001$) and a significant decrease in the thrombotest (114% to 905, $p = 0.014$). No changes in platelet count, plasminogen activator inhibitor (PAI), factor VII or factor VII phospholipid complex levels. The aim of the study was to determine whether warfarin could be taken concomitantly but patients on warfarin were not analysed separately.
- **CK85-025**: conducted in 16 females who received omega-3-acid ethyl esters 6 g or corn oil capsules; significant increase in EPA within erythrocyte membranes coincided with fall in osmotic fragility which by study end had increased back towards baseline. No significant change in patients on placebo.
- **CK85-020**: to assess effect on leukotrienes and inflammation; conducted in 14 healthy males half of whom received 7 g/day of omega-3-acid ethyl esters and the other half received no specific treatment. Ingestion of omega-3-acid ethyl esters resulted in depletion of LT5 and reduction in pro-inflammatory LT4 (unaltered in control).
- **CK85-015d**: investigation of human T lymphocyte function in 41 patients with inflammatory skin diseases; active group received omega-3-acid ethyl esters 6 g/day; some evidence of immunosuppression in the active group in stimulated isolated T-cells (production of interleukin 2 & 6, TNFα, T-cell proliferation and CD25 expression).
- **CK85-97026**: 30 patients with hypercholesterolaemia treated with either omega-3-acid ethyl esters 4 g/day or corn oil (placebo) for 4 months; there was no difference between groups with respect to brachial artery peak flow; a significant decrease in flow-mediated dilation was noted but no correlation between the latter and TG reduction was detected.
- **K85-92007**: to test efficacy of omega-3-acid ethyl esters in prevention of cyclosporine-associated hypertension in 30 heart transplant patients; at 6 months, SBP decreased by 2 ± 4 mm Hg in omega-3-acid ethyl esters group and increased by 17 ± 4 mm Hg in placebo group ($p < 0.01$ between treatments); DBP increased by 10 ± 3 and 21 ± 2 mm Hg, respectively ($p < 0.01$ between treatments).
- **CK85-015c**: to test effects on LDL in 23 patients with psoriasis or atopic dermatitis on either omega-3-acid ethyl esters 6 g/day or placebo; significant rise in phospholipid enhancement on omega-3-acid ethyl esters after 4 months' treatment and significant reduction in n-6FA (both $p < 0.01$). No measurable differences in LDL metabolism, LDL size or susceptibility to lipid peroxidation.
- **97027**: study in 48 men with insulin resistance randomised to one of four groups - omega-3-acid ethyl esters 4 g/day, atorvastatin 40 mg daily, omega-3-acid ethyl esters + atorvastatin and corn oil/ placebo for 6 weeks; study conclusion was that omega-3-acid ethyl esters did not significantly affect Apo B disposition nor did they interact with atorvastatin.

Pharmacokinetics

vi) The digestion and absorption of omega-3 fatty acids involves 3 different steps: hydrolysis from the alcohol to which they are bound, absorption and subsequent uptake and incorporation into membranes of various cell types. The hydrolysis of omega-3 ethyl esters by esterases in the intestine is complete and rapid. After hydrolysis, the free fatty acids are absorbed by the enterocytes where they are rapidly

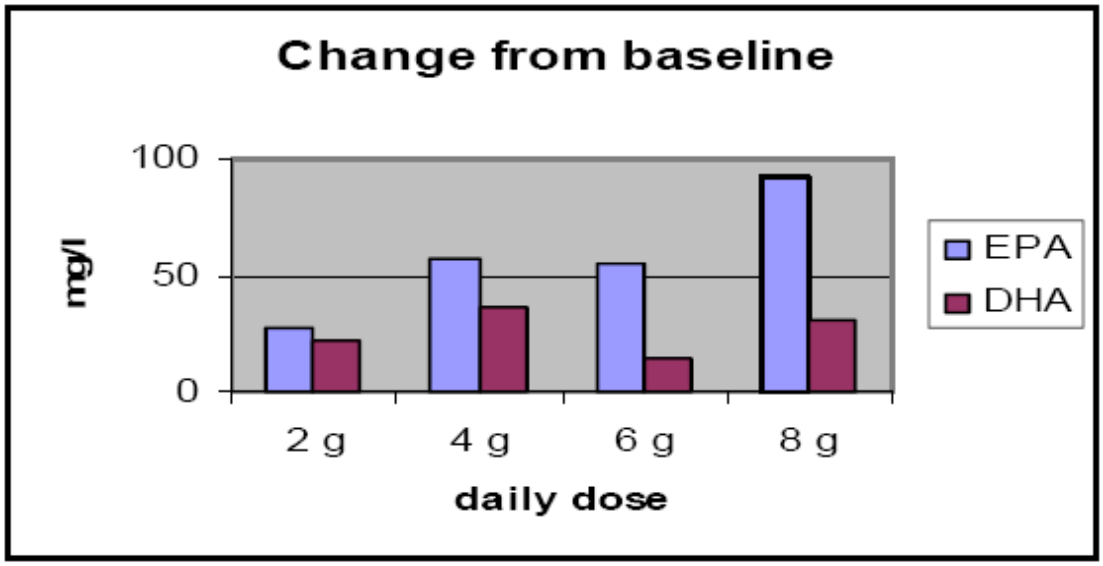
re-esterifed and from which they enter the circulation as chylomicrons. Following passage through the thoracic duct, the chylomicrons enter the plasma. The normal half-life of chylomicrons in the circulation is approximately 10 minutes. The enzyme lipoprotein lipase, which is present on the endothelial surfaces of capillary beds in all tissues, hydrolyses the triglyceride core of the chylomicron, setting free the fatty acids for tissue uptake. Because of this process, it is not possible to perform standard bioavailability studies with meaningful estimates of C_{max}, time of maximum plasma concentration (T_{max}) or AUC for either the parent drug or its metabolites.

vii) The fatty acid composition of the plasma phospholipids correlates with levels incorporated into the membranes. Omega-3 fatty acid composition of erythrocyte and thrombocyte membranes, in turn, correlates with whole body content of these compounds. Therefore, analysis of blood phospholipids is used to assess the performance of products intended to increase total body stores of omega-3 fatty acids. Thus, when investigating the absorption of Omacor, the increase of EPA and DHA in plasma or serum phospholipids was measured.

viii) The principal study (CK85-002) of fatty acid incorporation in healthy volunteers was an open-label, randomized, parallel group study in 24 subjects with doses of Omacor of 4, 8 or 14 g daily. Omacor induced a dose-dependent increase in serum EPA content. Intake of 14 g provided only slightly higher EPA values than 8 g, suggesting that the degree of incorporation of EPA into serum phopholipids was saturated at dose levels greater than 8 g daily. The DHA increase was less marked and not dose-dependent. To varying degrees, these results were supported by the other studies summarised.

ix) In addition to individual studies, a pooled analysis for dose proportionality results was performed using data from a number of studies. Changes from baseline in EPA uptake were dose proportional for 2, 4 and 8g daily. The change from baseline for 6 g daily was slightly less than that for 4 g daily but the sponsor states that the data for 6 g daily were likely to have been skewed by outliers, including one subject who had high baseline values. For DHA the change from baseline in uptake was highest at 4 g daily. Subjects receiving 8 g daily showed similar DHA levels to those receiving 4 g daily. Figure 3 below shows graphically the changes from baseline as a function of the dose. In summary, incorporation of EPA into serum lipids is dose-dependent, with higher doses resulting in increased levels of incorporation of EPA into serum phospholipids. Incorporation of DHA does not appear to be dose-dependent and appears to be roughly maximal at 4 g daily.

Figure 3. Changes from baseline in EPA & DHA uptake from pooled analysis



x) The pharmacokinetics were also analysed in patients with hypertriglyceridaemia, patients with IgA nephropathy and patients with hypertension. In these special patient groups tested, incorporation of EPA and DHA into serum phospholipids was comparable to that observed in healthy volunteers.

Efficacy

xi) The studies documenting the clinical efficacy of Omacor in patients with hypertriglyceridaemia were divided into four categories:

- Ø Category I – 8 double-blind, parallel group, placebo-controlled studies in patients with hypertriglyceridaemia, using Omacor 4 g daily.
- Ø Category II – 9 other controlled studies in patients with hypertriglyceridaemia where doses other than Omacor 4 g daily and/or different study designs were used.
- Ø Category III – 5 uncontrolled extensions studies or uncontrolled parts of studies in patients with hypertriglyceridaemia.
- Ø Category IV – 8 other studies (6 according to the clinical evaluator) measured triglyceride levels. Studies were investigator-initiated studies.

Except for those studies listed under Category IV, all studies were performed according to GCP and CRFs were available.

xii) ***Category I Studies***:

Changes from baseline in triglyceride levels for the Category I studies are summarised in Table 10 above.

The sponsor claims that the above results demonstrate that Omacor 4 g daily consistently produced statistically significant reductions in triglyceride levels compared with placebo. However, according to the footnotes to Table 10, only 4 out the 8 studies produced reductions which were statistically significant, although it is clear that there were substantial reductions in all studies.

Other lipid levels

Changes from baseline in TC, HDL-C, LDL-C and VLDL-C levels for the Category I studies were evaluated. In all Category I studies, median changes from baseline in TC levels were small and generally not significantly different between the Omacor 4 g and placebo treatment

groups. Generally, LDL-C levels increased in the Omacor 4 g treatment group. Median changes from baseline in HDL-C levels were not significantly different between the Omacor 4 g and placebo treatment groups, except for two studies (K85-94010 and K85-95009) in which a statistically significant increase was seen. Both studies enrolled patients with Type IV hypertriglyceridaemia. Compared with those patients on placebo, patients taking Omacor 4 g daily had greater reductions in VLDL-C levels (in 3 out of 5 studies, statistically significantly so).

Additional lipoprotein measurements

xiii) Omacor 4 g daily had no effect on levels of Apo-A1, the major lipoprotein in HDL particles. While Omacor 4 g daily was associated with increases in LDL-C levels, it had no effect on Apo-B levels.

Integrated analysis of Category I studies:

Since the eight Category I pivotal studies had very similar designs but small sample sizes, data from these studies were integrated to allow further analysis. In all studies a daily dose of Omacor 4 g was used and averaged values for baseline and endpoint triglyceride measurements were used. Also all studies were randomized, double-blind and placebo-controlled. All studies were short-term, ranging from 6 weeks to 16 weeks in duration with five of the eight studies being of 12 weeks' duration.

The primary efficacy endpoint was the change from baseline to the end of study in serum triglyceride levels. Secondary efficacy endpoints included changes from baseline to the end of study in the levels of TC, HDL-C, LDL-C and VLDL-C. The efficacy results were also analysed with regard to gender, age and baseline triglyceride level. All integrated analyses used the PP population.

Consistent with the overall population, subjects in each baseline triglyceride level category in the Omacor 4 g daily treatment group had significantly larger mean absolute and relative changes in triglyceride levels compared with those in the placebo treatment group. For the subjects who received Omacor 4 g per day, those with higher baseline triglyceride levels (5.65-8.46 mmol/L and $\geq$ 8.47 mmol/L) had greater reductions in triglyceride levels.

These results are shown in Table 28 below.

Table 28. Mean change from baseline in TG levels at endpoint, overall and by baseline TG level, Integrated analysis of eight 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	0.13	0.0001
Relative change (%)	–39.4		2.8		<0.0001

[a] P-values were computed using ANOVA

Reductions in triglyceride levels were comparable for both males and females and for those aged less than and greater than or equal to 60 years.

The absolute and relative changes in the secondary lipid parameters were also evaluated. Decrease in triglyceride levels appear to be at the expense of significantly larger mean absolute and relative increases in LDL-C levels compared with those in the placebo group. As noted by the sponsor, although LDL-C levels increased for subjects who received Omacor, mean baseline and endpoint LDL-C levels remained within the same NCEP ATP III category or were within the next successive category. The mean LDL-C changed from a baseline value of 4.31 mmol/L to one at endpoint of 4.68 mmol/L, which is still less than 5 mmol/L. However, one must remember that these are mean values and inevitably there will be individuals who would have had increases above this level. This will have to be acknowledged in the Australian PI. Also it should be remembered that the target LDL-C is to be less than 2.5 mmol/L (less than 2.0 mmol/L for high-risk patients with existing cardiovascular disease)[46]. The high risk group of great concern with respect to elevated triglyceride levels is that of people with Type 2 diabetes mellitus in particular. There is a distinct lack of data in this group. Given the targets mentioned above, it may be that a large proportion of patients meriting treatment for hypertriglyceridaemia would also merit treatment for

[46] Taken from page 60 of version 5 (2008) of Therapeutic Guidelines – Cardiovascular; these target levels are adapted from the Heart Foundation/Cardiac Society of Australia and New Zealand Position Statement on lipid management, 2005. Note that intervention studies have not been designed to determine lipid targets.

their elevated LDL-C levels. There is a lack of robust data of the use of Omacor in combination with agents to reduce LDL-C levels, for example, statins. Finally, while it is of some reassurance that the movement in HDL-C was in the right direction, that is, upwards, only the relative change was statistically significant. The absolute change in HDL-C was not statistically significant.

xiv) ***Category II trials***

Nine controlled trials either employed doses other than 4 g daily and/or different study designs. The two most important in this group were K85-95014 and K85-95011. Study K85-95014 studied the effects of Omacor 4 g per day in patients with established CHD and with Type IIb hyperlipoproteinaemia who received treatment with simvastatin (10-40 mg per day). After a run-in of 6 weeks, patients were randomized to Omacor 4 g per day + simvastatin or placebo + simvastatin for 6 months. The 6 months' duration is notable. Table 29 below shows the changes from baseline in the various lipid parameters after 6 months' treatment.

Table 29. Summary of median relative changes from baseline in TG levels and other lipid levels for K85-95014 (double-blind part).

	Omacor 4 g/Simvastatin	Placebo/Simvastatin
	Relative change (%)	Relative change (%)
TG levels	(n=30)	(n=29)
	-19.3	3.4
TC levels		
	-7.2	3.2
HDL-C levels		
	4.3	26.7
LDL-C levels		
	2.6	6.4
VLDL-C levels		
	-30.2	-9.5
Apo-A1 levels		
	-5.8	1.9
Apo-B levels		
	-4.0	1.6

One can observe from this table that there was a significant reduction in TG levels. However, one can also observe that there were small increases in LDL-C in both groups and the rise in HDL-C was much greater in the group receiving placebo + simvastatin.

In Study K85-95011, a double-blind randomized trial, the effect of Omacor 4 g per day versus gemfibrozil 1200 mg per day was evaluated. The absolute changes in TG levels were -4.1 mmol/L in the Omacor group and -5.1 mmol/L in the gemfibrozil group. The corresponding relative changes were -30% in the Omacor group versus -48% in the gemfibrozil group. All changes, both absolute and relative were statistically significant. There was no significant change in LDL-C levels in either group.

In the Category II trials, there were only 3 studies which evaluated a dose of Omacor 2 g daily. These were Study K85-92004a (a double-blind, parallel, placebo-controlled trial in 136 subjects over 4 weeks), Study CK85-013b (an open-label, parallel study in 52 subjects over 8 weeks comparing Omacor 2 g versus 8 g daily) and Study K85-95109/K85-95210 (an open-label, parallel study in 65 subjects over 6 months comparing Omacor 2 g vs. 4 g daily). In Study K85-92004a, a 4 week study, there was a 2.9% reduction in triglycerides on Omacor 2 g daily versus a 4.2% reduction on

placebo (there were 68 subjects in each group). The 2.9% reduction in triglycerides on Omacor 2 g daily was claimed to be statistically significant with p = 0.034 while that of 4.2% on placebo was reported as not statistically significant with p = 0.130. In Study CK85-013b, the relative changes in triglyceride levels were reductions of 22.0% in the Omacor 2 g daily group, 38.0% in the Omacor 8 g daily group and 17.0% in the placebo group. All of these reductions were statistically significant. In Study K85-95109/K85-95210, triglyceride levels actually increased in both arms, by 24.0% in the Omacor 2 g daily group and by 8.0% in the Omacor 4 g daily group.

xv) ***Category III trials***

These uncontrolled extension studies for hypertriglyceridaemia were open-label extension studies of double-blind placebo-controlled studies. Changes from baseline in triglyceride levels for the Category III studies are summarised in Table 30 below:

Table 30. Summary of mean relative changes from baseline in triglyceride levels for Category III studies

	Study Duration	n	Relative Change (%)	n	Relative Change (%)
		Omacor 4 g/Omacor 4 g		Placebo/Omacor 4 g	
CK85-112	1 year	16	–0.1	16	–37.9
K85-94110	1 year	19	–18.0	19	–37.5
K85-95014	6 months	25	-14.3	21	–25.6
			Omacor 4 g		
K85-113*	1 year	32	-16.3		
		Omacor 2 g/Omacor 3 g		Placebo/Omacor 3 g	
K85-92004	4 weeks	66	–6.3	66	–5.6

* Primarily a safety trial, see below

The above data does support the view that the triglyceride-lowering effect of Omacor 4 g per day is at least maintained for up to 12 months of continuous use. However, the sponsor should clarify the 0.1% reduction in TG levels at 1 year compared with baseline in the Omacor 4 g/Omacor 4 g group in Study CK85-112. Is this figure the comparison with baseline, that is, the beginning of the study or with the end of the double-blind period? The result stands in stark contrast with the two results immediately below it.

There were no studies in this group which evaluated the efficacy of Omacor 2 g daily. Study K85-92004 has been discussed in the previous section on Category II trials. It was a double-blind comparison of Omacor 2 g daily and placebo in patients with moderate hyperlipidaemia. After the double-blind phase, all patients received Omacor 3 g daily for another 4 weeks. In the second treatment period, in which all patients received Omacor 3 g daily, there was a significant decrease in serum triglycerides. Patients previously receiving Omacor 2 g daily had a further and significant decrease in triglycerides. Changes from baseline in LDL-C levels for the Category III studies are shown in Table 31 below:

Table 31. Summary of mean relative changes from baseline in LDL levels for Category III studies*.

	Study Duration	n	Relative Change (%)	n	Relative Change (%)
		Omacor 4 g/Omacor 4 g		Placebo/Omacor 4 g	
CK85-112	1 year	14	16.8	14	16.8
K85-94110	1 year	16	–9.2	15	3.4
		Omacor 2 g/Omacor 3 g		Placebo/Omacor 3 g	
K85-92004	4 weeks	60	3.0	63	5.6
		Omacor 4 g		---	
CK85-113	1 year	28	6.2	---	---

*Data from subjects who used simvastatin as concomitant therapy in Study K85-95014 were not included in this table. NB. a reduction of LDL-C levels was actually seen in study CK85-112- that is, there should be a minus sign before the 16.8% relative change Omacor 4g/Omacor 4g (corrected in sponsor's pre-ACPM response).

While generally the Delegate would agree with the sponsor that no additional increases in LDL-C levels were observed in the uncontrolled extension studies, the Delegate does query the assertion by the sponsor that in Study CK85-112 a mean reduction of 16.8% in LDL-C was recorded in subjects who continued to receive Omacor 4 g daily. The figures in the above table strongly suggest the reverse, that is, a 16.8% increase compared with baseline (there is no minus sign in front of the 16.8% in the table).

xvi) ***Category IV trials***

xvii) ***Deficiencies in the submission so far – no analysis by dyslipidaemic classification; only fragmentary low level evidence with regard to the concomitant treatment with statins & only limited evidence of the efficacy of a dose of 2 g of Omacor daily***

From the point of view of the Delegate, one of the most puzzling features of this submission is that, even though an indication for hypertriglyceridaemia is sought according to dyslipidaemic type (Fredrickson classification) and furthermore is sought in part for use as concomitant treatment with statins, there is almost no breakdown of the data from these perspectives. There was no sub-group analysis by dyslipidaemic type provided in the original submission and the data concerning concomitant treatment with statins does not come from the pivotal Category I studies but rather is scattered amongst the lower level evidence.

Analysis by dyslipidaemic classification

The Delegate first became aware of the existence of an analysis of the data by dyslipidaemic classification while checking the web-site of the US FDA for all documents associated with the approval of Lovaza in the US in 2004. Under s31 of the Therapeutic Goods Act, the Delegate requested the sponsor to provide full details of any sub-group analyses by dyslipidaemic classification, that is, I, IIa, IIb III, IV & V which have been performed in the integrated analysis of the data from the eight pivotal Category 1 studies. In reply, the sponsor provided a comprehensive series of tables which displayed the changes from baseline in a number of separate parameters at endpoint, overall and by hyperlipidaemia Type (IIb, IV, V & IV/V combined). These parameters were TG, VLDL, LDL-C, HDL-C, non-HDL-C, TC. The Delegate has summarised all of these tables into the one table below (Table 32) which shows the median % changes from baseline for the various lipid parameters overall and according to dyslipidaemic classification (IIb, IV, V & IV/V).

Table 32. Summary of median percent, that is, relative[#] changes from baseline for lipid parameters overall and by dyslipidaemic classification in the eight Category I studies which were all double-blind, placebo-controlled studies for hypertriglyceridaemia which used Omacor (K85) 4 g daily, per-protocol (PP) population

Fred.	TG		TC		HDL		LDL		VLDL		Non-HDL	
Classific.	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo
Overall	-28.0*	+2.5	-2.9[$]	-0.5	+8.9[J]	+3.5	+16.8*	+0.7	-25.2*	+8.0	-3.9[$]	-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
Types IV/V	-29.4*	+4.0	-3.1[$]	0.9	+13.1*	+0.6	+36.2*	+7.8	-33.3*	+4.8	-4.2[$]	+0.9

#the absolute changes have not been summarised in the above table; p-values in all cases were computed using analysis of variance (ANOVA) and were versus placebo; *these relative change (%) values were statistically significant and so too were the corresponding absolute changes; [†]neither the relative change (%) nor the corresponding absolute change was statistically significant [J]while the relative change (%) was statistically significant, the corresponding absolute change was not statistically significant; [$]while the relative change (%) was not statistically significant, the corresponding absolute change was statistically significant.

From the above table one can clearly see that Omacor significantly reduces median plasma triglycerides by between 25.5 and 39.4% over the various sub-groups with the largest reductions being seen in patient groups with higher baseline triglycerides. Likewise VLDL-cholesterol is significantly reduced by between 10.9 and 34.3% over the sub-groups. The changes in both HDL and non-HDL, while not all statistically significant, were at least in the right direction. There were modest increases in HDL and modest decreases in non-HDL, the one exception being Type IV dyslipidaemia where there was a very slight increase in non-HDL. By and large, total cholesterol remains stable, except for a statistically significant decrease in Type V dyslipidaemia. The picture becomes much less clear when one considers LDL-C. The pooled analysis demonstrates an overall increase in LDL-C of 16.8%, this result clearly being driven by the results for Type IV dyslipidaemia where there was a 33.8% increase in LDL-C (the results for both the relative and absolute changes were highly significant, $p < 0.0001$) and to a lesser extent by those for Type V dyslipidaemia where there was a 42.8% increase in LDL-C (but against a 19.9% increase in the placebo group, the comparisons with placebo for neither relative nor absolute change being statistically significant).

In the table below (Table 33), supplied by the sponsor at the Delegate's request, the mean changes from baseline in LDL-C levels by dyslipidaemic sub-group are displayed.

Table 33. Mean change from baseline in **LDL-C levels** at endpoint, overall and by dyslipidaemic classification in the eight Category I studies which were all double-blind, placebo-controlled studies for hypertriglyceridaemia which used Omacor (K85) 4 g daily, per-protocol population

	K85 4 g		Placebo		*P*-value[a]
	n	Mean Value	n	Mean Value	
Overall					
Baseline value (mg/dL)	199	166.7	199	172.3	
Endpoint value (mg/dL)	206	180.9	202	169.0	
Absolute change (mg/dL)	197	14.5	191	-4.7	<0.0001
Relative change (%)	197	16.8	191	0.7	<0.0001
Type IIb Hyperlipidemia					
Baseline value (mg/dL)	111	207.5	118	204.1	
Endpoint value (mg/dL)	111	209.4	118	196.1	
Absolute change (mg/dL)	110	1.9	114	-8.6	0.0136
Relative change (%)	110	1.4	114	-3.9	0.0099
Type IV/V Hyperlipidemia					
Baseline value (mg/dL)	88	115.3	77	120.5	
Endpoint value (mg/dL)	90	145.6	76	121.5	
Absolute change (mg/dL)	87	30.3	73	1.3	<0.0001
Relative change (%)	87	36.2	73	7.8	0.0020
Type IV Hyperlipidemia					
Baseline value (mg/dL)	65	125.1	54	127.1	
Endpoint value (mg/dL)	65	159.1	53	128.5	
Absolute change (mg/dL)	64	34.2	50	1.6	<0.0001
Relative change (%)	64	33.8	50	2.2	<0.0001
Type V Hyperlipidemia					
Baseline value (mg/dL)	23	87.6	23	104.7	
Endpoint value (mg/dL)	25	110.4	23	105.3	
Absolute change (mg/dL)	23	19.6	23	0.6	0.2099
Relative change (%)	23	42.8	23	19.9	0.3840

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

One can see from this table that the largest LDL-C level increases are seen in patients with the lowest baseline values of LDL-C, that is, Types IV & V. The sponsor have enlarged upon this issue by having a closer look at the publications for two studies describing a marked increase in LDL-C following Omacor administration. They were both Category I studies (K85-95009 & K85-94010). In both studies, because of the very low baseline LDL-C levels (2.05 mmol/L & 1.1 mmol/L, respectively), even modest increases in LDL-C of the order of 0.64 mmol/L & 0.3 mmol/L, respectively,

resulted in substantial relative increases which may not be clinically significant. This argument of the sponsor has merit. However, these were only two out of the eight Category I studies and they were both at the lower end of the spectrum in terms of subject numbers. Furthermore, there is no information as to the make-up (by dyslipidaemic type) of the subjects in these two studies.

Another mitigating factor raised by the sponsor in the submission was that the increases in LDL-C are secondary to a shift from smaller, more atherogenic LDL particles to larger, less atherogenic ones. The Delegate asked for further clarification of this. The sponsor acknowledged that although LDL particle size was not measured in the Category I studies, one Category II study (K85-95011) and one Category IV study (K85-95013) did measure LDL particle size. For example Study K85-95011 was a double-blind study comparing the effect of Omacor 4 g daily with the effects of 1200 mg gemfibrozil. A total of 98 patients with Types IIb, IV and V dyslipidaemia were treated for 12 weeks after a dietary run-in period of 6 weeks. A sub-study evaluated LDL-particle size in 28 out of the 98 patients and it showed that for both treatments, the main LDL sub-fractions at baseline were the small and dense ones represented by LDL3 and LDL4. After treatment with either Omacor or gemfibrozil, an increase in the more buoyant LDL1 and LDL2 particles was seen. The sponsor also assembled a wide range of literature-based evidence to support the claim that LDL particles get lighter, more buoyant and thereby less atherogenic with the use of Omacor.

The Delegate also asked the sponsor for justification of the use of Omacor in Type III dyslipidaemic patients. The sponsor replied that the company did not specifically design double-blind, placebo-controlled studies to investigate the effect of Omacor in Type III dyslipidaemic patients. However, the sponsor was seeking a specific indication in such patients. As pointed out by the sponsor, Type III patients are homozygotes for Apo E and genotyping of patients was only carried out in one of the studies, namely K85-95011. Thus, as correctly pointed out by the sponsor, there may well be more Type III patients, unidentified, in the clinical documentation. The problem is of course that one doesn't know how many. Of the 98 patients in K85-95011, there were 4 patients with Type III dyslipidaemia and of these 4, 2 received Omacor and 2 received gemfibrozil. The reduction of TG was -65% and -41% in the 2 patients receiving Omacor and -72% and -46% in the 2 patients receiving gemfibrozil. The sponsor states that there is no reason to believe that Type III dyslipidaemic patients do not respond to Omacor treatment. The sponsor is probably right but the problem is that there is no robust clinical trial evidence to support the claim.

In its concluding statement concerning Omacor efficacy, the US FDA review stated the following:

"*In conclusion, while K85 is an effective Tg-lowering agent, subgroup analyses by dyslipidaemic classification demonstrated more favourable lipid-altering in the Type V dyslipidaemic population whose primary lipid derangement was Tg elevation. These patients received significantly greater reductions in Tg, TC, VLDL-C and non-HDL-C and significantly greater increases in HDL-C levels. Although percent LDL-C increase was higher in this sub-group, the increase was not statistically different from that associated with placebo. In contrast, patients with Types IIb and IV dyslipidaemia had less of a reduction in Tg and VLDL-C and achieved no statistical difference in TC, HCL-C and non-HDL-C relative to placebo*".

As a result of the US FDA medical review, the application was split into two, the first (NDA 21-654) for dyslipidaemia Fredrickson's Type V, TG > 500 mg/dL and the second (NDA 21-853) for dyslipidaemia Fredrickson's Type IIb and IV, TG < 500 mg/dL. The first, NDA 21-654 was approved for the following indication: "*Omacor is indicated as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride (TG) levels in adult patients*".

Concomitant use with statins

In the clinical evaluator's risk-benefit discussion, it is stated that there was no significant interaction between Omacor and statins in trials using simvastatin, lovastatin and atorvastatin and that addition of Omacor led to a greater reduction in triglycerides compared with statins alone. The evidence to support concomitant use with statins is fragmentary. However, what evidence there is in the submission on this topic is at least consistent.

Firstly, there were no Category I clinical trials which studied the concomitant use of Omacor with statins. There was a Category II trial, K85-95014, which was a 6-month study in 59 patients with CHD & Type IIb hyperlipoproteinaemia of Omacor 4 g daily versus placebo (n=30 in the Omacor group and n=29 in the placebo group). Both groups received concurrent simvastatin (mostly 20-40 mg daily). The Omacor group had significantly greater reductions in TG levels. Changes in TC and HDL were statistically significant and in the right direction while the change in VLDL was not significant but in the right direction. There was no significant change in Apo B for either group. The change in LDL-C is not reported in the clinical evaluation report but it is in the submission. There was a median relative change of +2.6% in the Omacor + simvastatin group compared with +6.4% in the placebo + simvastatin group. The Category III trials were open-label extensions of Category I or II trials and so K85-95014 has already been captured in the discussion. In the Category IV studies, there were 3 studies which examined concomitant use with statins. Pharmacia 3 compared Omacor 4 g daily to placebo on a background of simvastatin 20 mg/day. There was a significant reduction in triglycerides in the Omacor group but no significant difference with respect to TC, Apo B or LDL. Pharmacia 5 compared Omacor 2 g daily versus placebo on a background of atorvastatin. While the 2g dose of Omacor did not significantly reduce TG or TC any further there was a further significant increase in HDL-C and a redistribution of LDL subfractions with a reduction in the more dense LDL particles. Study CK85-018 compared Omacor 6 g/day alone with lovastatin 40 mg/day alone and also with the combination in a 3-way crossover trial with each treatment given for 6 weeks. There was a significant decrease in TG with all 3 treatments. Lovastatin significantly decreased TC and LDL-C as expected which was not achieved by Omacor alone. Unfortunately the CER does not report the results for the combination. This is a pity because this appears to be the only study in the submission rigorously comparing the add-on effect of Omacor to a statin and as such the results may have been helpful.

The sponsor has cited more recent studies of concomitant use with statins which have demonstrated that Omacor did not significantly increase LDL-C levels. One of these studies was included in the submission; a randomised, double-blind trial of 8 weeks' duration (reported by Davidson *et al*), completed by 243 subjects, 116 on Omacor 4 g + simvastatin 40 mg and 127 on placebo + simvastatin 40 mg. The addition of Omacor significantly reduced triglycerides and VLDL-C compared with simvastatin. Combined treatment also caused modest rises in HDL-C and LDL-C. The clinical

evaluator also notes that in this study, mean ALT increased by 5.7 U/L in the Omacor group and decreased by 0.7 U/L in the placebo group ($p < 0.032$). The sponsor also noted that while TG levels decreased and LDL-C levels increased in some studies, Omacor treatment has not been shown to increase Apo B levels. The sponsor further argued that plasma Apo B is a better index of coronary artery disease than total LDL-C. This argument does have merit.

Efficacy of a dose of Omacor 2 g daily

In the Dosage and Administration section of the proposed PI, the sponsor proposes for the treatment of hypertriglyceridaemia an initial treatment regimen of 2 g daily (two capsules daily), with an increase to 4 g daily (four capsules daily) if an adequate response is not obtained. Given that none of the pivotal Category I studies evaluated a dosage regimen of 2 g daily, the Delegate requested the sponsor to provide a justification for the recommendation in the proposed PI. The sponsor provided a table with the integrated analysis of the efficacy of Omacor 2 g daily in comparison with other dosage levels. The overall mean absolute change in TG levels on Omacor 2 g daily was -24.5 mg/dL (-0.28 mmol/L) while the corresponding mean relative change was -4.2% (median relative change -12.2%). For a dosage regimen of Omacor 4 g daily, the corresponding values were as follows: mean absolute change -137.1 mg/dL (-1.55 mmol/L) and mean relative change -28.0% (median relative change -31.2%). The sponsor submitted these data to show the efficacy of Omacor 2 g daily in patients with hypertriglyceridaemia. On the basis of the above comparisons, the Delegate was not so persuaded. The relative changes in TG levels were considerably less on Omacor 2 g daily than they were on Omacor 4 g daily. The Delegate sought the advice of the ACPM on this issue.

xviii) ***Secondary prevention after myocardial infarction***

Two secondary prevention studies in patients who had experienced a myocardial infarction have been performed, the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico from the Associazione Nazionale Medici Cardiologi Ospedalieri, Instituto di Ricerche Farmacologiche) – Prevenzione study and the Pharmacia 4 study. Each is briefly summarised in Table 34 below:

Table 34. Summary of types of studies in secondary prevention after MI

Study Ref. No.	Study Objective	Study Design	Treatments Dose	Subjects, No. Type
GISSI-Prevenzione	Efficacy post-MI	PROBE design	Omacor 1 g	11,324 Post-MI
Pharmacia 4	Efficacy post-MI	Double-blind, randomized, placebo-controlled	Omacor 4 g	300 Post-MI

PROBE = Prospective, Randomized, Open, Blinded Evaluation

xix) ***GISSI-Prevenzione***

This was a multicentre study using the PROBE design. From October 1993 to September 1995, 11,324 patients surviving recent (≤ 3 months) myocardial infarction were randomly assigned to 4 groups:

1. Omacor (n-3 PUFA , n-3 polyunsaturated fatty acids), one capsule of 1 g per day, n = 2,836
2. Vitamin E, 300 mg per day, n = 2,830

3. Omacor, one capsule of 1 g per day + Vitamin E 300 mg per day, that is both, n = 2,830
4. control group; neither Omacor nor Vitamin E, n = 2828.

Drugs for secondary prevention such as antiplatelet drugs, beta-blockers and ACE inhibitors were recommended according to prevailing standard practice. Patients were also encouraged to adhere to recommended preventive measures, including a Mediterranean-style diet with a high content of fruit and fish and a relatively low content of saturated fats.

Baseline demographic and clinical characteristics were well balanced across the four groups. The mean duration of treatment was 3.5 years and follow-up visits were performed after 6, 12, 18, 30 and 42 months of treatment. At the end of the study, 28.5% of patients receiving Omacor and 26.2% of those receiving Vitamin E had discontinued treatment.

The primary combined endpoints were:

1. the cumulative rate of all-cause death, non-fatal MI and non-fatal stroke
2. the cumulative rate of cardiovascular death, non-fatal MI and non-fatal stroke.

Analysis was done by intention to treat and according to the two strategies defined in the protocol. The first involved a factorial design with two-way analysis of efficacy of n-3 PUFA supplements (Omacor) compared with no n-3 PUFA and efficacy of Vitamin E supplements compared with no Vitamin E. For n-3 PUFA, this involved the comparison of the two groups who took Omacor, that is, Omacor alone or Group 1 and Omacor + Vitamin E or Group 3 versus the two groups who did not take Omacor, that is, Vitamin E alone or Group 2 and neither OMACOR nor Vitamin E or Group 4. Thus the two-way analysis involved comparison of the following numbers of subjects: 2,836 (Group 1) + 2,830 (Group 3) versus 2,830 (Group 2) + 2,828 (Group 4), in other words 5,666 versus 5,658. The second strategy involved a four-way analysis of efficacy of n-3 PUFA supplements alone (Group 1), Vitamin E supplements alone (Group 2) and the combined treatment (Group 3), each compared with control (Group 4), as well as the efficacy of the combined treatment compared with individual interventions.

The overall efficacy profile of n-3 PUFA is shown in the Table 16 above. In the two-way factorial analysis, the 10% relative decrease in risk for the combined primary endpoint of death, non-fatal myocardial infarction and non-fatal stroke was significant (relative risk = 0.90, 95% CI [0.82-0.99], p = 0.048). However, the decrease in risk for the other combined endpoint of cardiovascular death, non-fatal MI and non-fatal stroke was not significant (relative risk = 0.89, 95% CI [0.80, 1.01], p = 0.053).

The four-way analysis provides a clearer picture of the effects of n-3PUFA, with a relative decrease in the risk for the combined endpoint of 15% (relative risk = 0.85, 95% CI [0.74, 0.98], p = 0.023) and for cardiovascular death, non-fatal MI and non-fatal stroke of 20% (relative risk = 0.80, 95% CI [0.68, 0.95], p = 0.008).

Analyses of the individual components of the main endpoint showed that the decrease in mortality (20% for total deaths, 30% for CV deaths and 45% for sudden death in the four-way analysis) which was obtained with n-3 PUFA accounted for all the benefit seen in the combined endpoint. There was no difference seen across the treatment groups for non-fatal cardiovascular events. As noted in the original article

in The Lancet in August 1999[47], the results of the tests for interaction were not significant when the two combined endpoints and the overall mortality were analysed. The significance values reached when a similar analysis was applied to the individual components of the endpoints ($p = 0.0242$ for cardiovascular mortality; $p = 0.0226$ for coronary mortality; $p = 0.024$ for fatal plus non-fatal coronary events and $p = 0.010$ for sudden death) better approximate the true unconfounded effect of n-3 PUFA and show that the results of the four-way analysis are not influenced by an effect modification due to the combination of the treatments.

Although the two-way analysis showed more modest reductions in mortality when Omacor alone and with Vitamin E was compared with control, it does not allow for interaction and confounders. It was also shown that the addition of Vitamin E does not significantly add to the efficacy of Omacor in reducing mortality risk over the period of follow-up.

The results for the combined treatment (n-3 PUFA + Vitamin E) compared with controls (neither n-3 PUFA nor Vitamin E) were evaluated. The effects seen on the primary combined endpoint and on total mortality were consistent with those obtained with n-3 PUFA alone. Thus, Vitamin E addition did not significantly increase the efficacy of n-3 PUFA in reducing mortality risk over the period of follow-up.

The effect on lipids was also evaluated in this study. There were no differences between treatments with respect to total cholesterol and HDL-C which increased in all groups. Triglyceride concentration decreased by a modest amount following Omacor treatment. The LDL-C at six months increased in all groups. However, overall no clinically significant changes from baseline in any of these parameters were seen.

[47] GISSI-Prevenzione Investigators, Dietary supplementation with n-3 polyunsaturated fatty acids and Vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial, *The Lancet*, 1999; 354: 447-455 (August 7)

xx) ***Pharmacia 4***

This was a much smaller study, a double-blind, placebo-controlled study over 12-24 months, in 300 patients with an acute MI recruited at one hospital centre in Norway. All patients were randomized either to Omacor 2 g twice daily or 2g corn oil placebo twice daily. No significant group differences in baseline demographic or clinical characteristics were seen. There were no significant differences in the number, type or severity of events. There were favourable effects on triglyceride and HDL-C levels following Omacor compared with the placebo. There was no difference between treatments with respect to total cholesterol. LDL-C was not tested. There was no discussion in the CER about the power provisions of this study. Given that only 300 patients in total were recruited for this study, it was not adequately powered to demonstrate its primary endpoint.

xxi) ***Singh R B et al (1997)***

This trial did not use Omacor but patients with a clinical diagnosis of acute MI used fish oil capsules, 2 capsules three times a day. The trial recruited 404 patients of whom 360 were randomized in double-blind fashion to fish oil (n=122), mustard oil (n=120) or placebo (n=118). The analysis in the CER demonstrates that there were significant reductions at the end of one year in total cardiac deaths, non-fatal re-infarction and total cardiac events in each of the fish oil and mustard oil groups compared with placebo. However, once again, it is clear that such a small study was not powered to detect a clinical outcome effect. Furthermore, as noted by the sponsor in a response to a question asked by the Delegate under s31 of the Act, it would be well nigh impossible to compare the results of this study and the much larger GISSI-Prevenzione trial because of the differences in design, drugs, study length and inclusion criteria to name but a few.

Safety

xxii) ***Patients with hypertriglyceridaemia***

The sponsor's Summary of Clinical Safety includes safety data from all studies that used K85 (Omacor). In addition to the thirty studies in the Summary of Clinical Efficacy (Categories I, II, III and IV), thirty-eight other studies (in healthy volunteers or for other indications) have been included. Thus, a total of sixty-eight studies have been conducted to examine K85 for treatment of a variety of indications, including hypertriglyceridaemia, post myocardial infarction and hypertension. For the integrated analysis of safety, only the twenty-two studies or parts of studies for hypertriglyceridaemia which had case report forms (CRFs) available were used. These studies came from the Category I, II & III studies. None of the Category IV studies was used in the integrated analysis of safety.

In the 8 Category I trials, 226 patients were exposed to Omacor for up to 20 weeks. Most (202/226) were treated for 16 weeks or less. In the 22 trials of the integrated analysis, the Omacor exposure was 655 (patients) with a mean duration of 19.3 weeks (± 20.8).

The most common treatment-emergent adverse events reported in the pivotal hypertriglyceridaemia trials included eructation (Omacor 4.9% versus placebo 2.2%), infection (Omacor 4.4% versus placebo 2.2%), flu syndrome (Omacor 3.5% versus placebo 1.3%), diarrhoea (Omacor 3.5% versus placebo 3.5%), dyspepsia (Omacor 3.1% versus placebo 2.6%), nausea (Omacor 3.1% versus placebo 3.1%) and taste perversion (Omacor 2.7% versus placebo 0.0%). Similar rates were observed in the integrated analysis.

Serious Adverse Events (SAE) occurred at rates of 3.1% Omacor versus 2.6% placebo in the Category I studies. Similar rates occurred in the integrated analysis. One possible related SAE was a case of extensive colitis (ischaemic colitis) in a patient taking Omacor 2 g daily. Four subjects (0.4%) died.

In the Category I trials, eight subjects on Omacor (3.5%) and six on placebo (2.6%) discontinued treatment because of one or more AE; the most common being nausea (Omacor 3, placebo 2), dyspepsia (2 versus 1, respectively) and flatulence (0 versus 2, respectively). In the larger population of twenty-two Category I to III studies, 24 patients (3.7%) discontinued Omacor with a similar spread of events.

The only potentially drug-related laboratory abnormality was mild elevation in ALT levels without concurrent elevation in AST levels. The Delegate drew attention to the fact that the clinical evaluator noted that in the study reported by Davidson *et al*, mean ALT increased by 5.7 U/L in the Omacor group and decreased by 0.7 U/L in the placebo group ($p < 0.032$). The clinical evaluator also noted that this study was ongoing and planned to run for 24 months.

There is a potential for drug interactions when larger doses of Omacor are combined with anticoagulants and anti-platelet agents based on increased bleeding times in some trials and nonclinical mechanistic studies.

xxiii) ***Post Myocardial Infarction Patients***

Only limited data are available on the safety in post-myocardial infarction patients. According to the GISSI-Prevenzione investigators, 97 patients in the Omacor group dropped out of the study due to adverse events.

The spectrum of adverse events not resulting in discontinuation was similar to that resulting in premature cessation of therapy. A total of 376 patients (6.6%) experienced 452 adverse events attributed to Omacor, mostly dyspepsia (3.2%) and nausea (1.4%).

There would appear to be no evaluable safety data submitted for the small Pharmacia 4 study.

No consistent association with regard to the risk of clinically significant bleeding episodes was found in the review by Wang *et al* of primary and secondary prevention studies even though some patients took concomitant aspirin or warfarin.

The clinical evaluator reviewed the use of Omacor for other indications. There was no specific robust safety signal. The impression gained on reading the summary was of a possible increased bleeding risk with Omacor.

xxiv) ***PSURs***

As noted by the clinical evaluator, a subsequent PSUR (no. 7; to 22/07/2005) and its addendum (to July 2006) provided significantly more post-marketing data. The exposure to July 2006 was 207,409 patient-years and 34,500 in 9 ongoing clinical trials. In PSUR no. 7, there were 3 serious reports: ventricular bigeminy, ventricular ectopic beats (VEBs) and vasculitis. In the PSUR addendum, there were 17 reports including pancreatitis, post-operative pharyngeal bleeding, hypersensitivity, chest pain and dizziness, elevated ALT & AST, rhabdomyolysis, erythema multiforme, epidural haematoma and intracerebral haemorrhage. PSUR no. 8 and addendum I were also submitted as part of the sponsor's Pre-ACPM response.

Risk-Benefit Analysis

xxv) **Effects on lipids:**

- In the integrated analysis of efficacy for the 8 Category I studies, subjects in each baseline triglyceride level category in the Omacor 4 g daily treatment group had significantly larger mean absolute and relative changes in triglyceride levels compared with those in the placebo group; consistent results were also obtained for the overall population. In Table 33, one can see evidence of significant reductions in TG for dyslipidaemia types IIb, IV & V.
- The Delegate found the proposed exclusion of Type V from the indications somewhat odd; Type V, although rare, is a pure endogenous hypertriglyceridaemia and appeared to display the most significant reductions in triglyceride levels of all the types.
- The above results were comparable for male and female subjects and for groups stratified by age (less than 60 years and greater than or equal to 60 years).
- There is very little robust evidence to support a dose of Omacor 2 g daily in the treatment of hypertriglyceridaemia (only 3 trials in the Category II group with contradictory results). According to an analysis supplied by the sponsor at the Delegate's request, the overall mean relative change in TG levels on Omacor 2 g daily was -4.2% (median relative change -12.2%) while for a dosage regimen of Omacor 4 g daily, the mean relative change was -28.0% (median relative change -31.2%).
- The significant reductions in triglyceride levels are at the expense of general increases in LDL-C; the pooled analysis requested by the Delegate demonstrates that the increase in LDL-C was driven by the results for Type IV dyslipidaemia where there was a 33.8% increase in LDL-C (the results for both the relative and absolute changes were highly significant, $p < 0.0001$). However, in the latter group one is starting from quite low baseline values of LDL-C and even the small to modest increases in the parameter can be statistically significant while their clinical significance is open to question. Another mitigating factor, raised by the sponsor in the submission, is that the increases in LDL-C are secondary to a shift from smaller, more atherogenic LDL particles to larger, less atherogenic ones.
- There appear to have been only 4 patients with Type III dyslipidaemia studied, 2 on the study drug and 2 on a comparator, gemfibrozil. However, the TG-lowering effects were confirmed. Whether such low level evidence can be used to support an indication in this type is highly questionable.
- The sponsor argues that in those patients with combined hyperlipidaemia with elevated LDL-C, combination with a statin will offset the secondary effect of modest LDL-C elevation. As noted already by the Delegate the evidence supporting concomitant use with statins, while fragmentary, is consistent. The sponsor also argued that while TG levels decreased and LDL-C levels increased in some studies, Omacor has not been shown to increase Apo B levels, the latter being a better index of risk of coronary artery disease than total LDL-C. This argument does have some merit. The sponsor has been requested to supply the outcomes of the study CK85-018 in tabular form – this was the study of the add-on effect of Omacor to lovastatin
- The Delegate is of the view that the approach taken by the US FDA, while based strictly on the evidence, may be somewhat too prescriptive, that is, the approach to limit the patient population to adult patients with severe ($\geq$500 mg/dL or 5.7 mmol/L) hypertriglyceridaemia. However, because it is quite clear from the evidence that patients with higher baseline levels of triglyceride are more likely to exhibit a better response to Omacor, the Delegate is of the view that, in order for the submission to be approvable, then the proposed indication must somehow reflect this fact. In this regard the Delegate intended to frame an indication which, in the Delegate's opinion, more

accurately reflected the clinical trial evidence. The Delegate sought specific advice from the ACPM regarding this issue.[48]

Post-MI indication

- In the large GISSI-Prevenzione trial, treatment with Omacor (n-3 PUFA) but not Vitamin E, significantly lowered the risk of the combined primary endpoint of death, non-fatal myocardial infarction and non-fatal stroke by 10% in the two-way analysis and by 15% in the four-way analysis
- Also in this trial, there was a co-primary endpoint, also combined, of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; by two-way analysis. The risk reduction of 11% was not significant. However, by four-way analysis the risk reduction was estimated to be 20% which was significant.
- The benefit was attributable to a decrease in the risk of death (all-cause) – 14% two-way and 20% four-way and in the risk of cardiovascular death – 17% two-way and 30% four-way.
- The study results showed an absolute risk difference for the combined endpoint of 2% ($p = 0.022$) when the n-3PUFA group was compared with control and an absolute survival difference of 2.1% ($p = 0.009$) between the same groups. This gives numbers needed to treat (NNT) of 50 and 47.6, respectively, over 3.5 years. The sponsor asserts that these results are comparable to those for other secondary preventative interventions among people with cardiovascular disease with statins typically having 5-year NNT values between 20 and 50. The sponsor was asked to show, in its pre-ACPM response, the full details of the calculations of these NNT values (see response below under xxix) 5.).
- Although the GISSI-Prevenzione trial was not double-blinded, it was run according to the PROBE design[49] which has been well validated. There were also remarkably few patients lost to follow-up
- The Delegate did not consider the evidence from any of the other much smaller trials to be of sufficient robustness for any reasonable conclusions to be drawn from them
- The Delegate supported the recommendation of the clinical evaluator to approve the indication sought by the sponsor in secondary prevention

xxvi) ***Potential safety concerns***:

- increased bleeding tendency with increase in bleeding time reported in some trials, especially with doses exceeding 4 g daily and potential for interaction with anti-platelet agents and anti-coagulants,
- elevation of LDL-C in some but not all trials,
- relatively small but consistent rises in ALT,
- GI intolerance, fishy eructation,
- no significant effect on blood glucose levels but a rise in serum insulin reported in one study (Patel, 2007).

The sponsor provided (in its pre-ACPM response; see xxx) 9 below) a brief comment on each of these issues.

Overall, the medication appears to be well-tolerated

xxvii) The sponsor is requested to provide the most up-to-date version of the company Risk Management Plan and to detail any post-registration commitments that it has entered

[48] Does the ACPM agree that the indications for hypertriglyceridaemia should in some way convey that the efficacy is greater in the more severe forms of hypertriglyceridaemia? and
Following on from the previous question & given the range of efficacy results and the effects on LDL-C, should the indication for hypertriglyceridaemia be framed

[49] Prospective Randomized Open, Blinded End-point trial.

into with the European Medicines Agency (EMA). The sponsor is also requested to provide comment on the progress of NDA 21-853, the application in the USA for dyslipidaemia Fredrickson's types IIb and IV, TG < 500 mg/dL.

Recommendation:

xxviii) The Delegate proposed to **approve** the submission by Abbott Products (formerly Solvay) to register the new chemical entity, Omacor, omega-3-acid ethyl esters 90 for the following indication as amended by the clinical evaluator and slightly modified by the Delegate:

- ***Post Myocardial Infarction:*** *Adjuvant treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (for example, 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:*
- *Types 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 I hyperchylomicronaemia). There are insufficient data to support the use in patients with secondary endogenous hypertriglyceridaemia including patients with diabetes mellitus.

ACPM's advice was requested on the following issues:

a) Does the ACPM agree that there is sufficient evidence to support an indication for Omacor as adjuvant treatment in secondary prevention after MI?
b) Does the ACPM agree that there should be in the PI a much more comprehensive and clearer discussion of both pre-defined analyses in the reporting of the GISSI-Prevenzione trial?
c) Does the ACPM agree that the indications for hypertriglyceridaemia should in some way convey that the efficacy is greater in the more severe forms of hypertriglyceridaemia?
d) Following on from the previous question and given the range of efficacy results and the effects on LDL-C, should the indication for hypertriglyceridaemia be framed according to dyslipidaemic type, that is, the Fredrickson classification or should it be framed according to the degree of hypertriglyceridaemia as in the USA?
e) Does the ACPM agree that there is no robust evidence to support the use of a dose of 2 g daily (TWO capsules daily) in hypertriglyceridaemia?

xxix) The sponsor should address the following issues in their Pre-ACPM response:

- **The actual extent to which Omacor 4 g daily consistently produced statistically significant reductions in TG levels compared with placebo** (see Delegate's regarding Table 10 above at xii) Category I Studies).

Sponsor's response:

There is an error in Table 10: Mean changes from baseline in TG levels for each of the 8 Category I studies. Significant reductions in triglyceride levels compared to placebo were shown in 7 of the 8 concerned studies. For CK85-013 study, the Kruskal-Wallis test was used to evaluate the treatment effect between the Omacor 2g, 4g, 8g and placebo treatment groups. Since no significant differences were found no pair-wise comparisons were made. For the rest of the studies pair-wise comparisons were made and the p-values for the differences between the Omacor and placebo groups are summarised in the following table and Table 10 above.

Table 35.

Compared to placebo	Study number
p<0.05	CK85-019, CK85-022, CK85-023, K85-94010
p<0.0001	CK85-014, CK85-017, K85-95009

2. Give clarification of the proportions of patients treated with Omacor 4 g daily who experienced rises in LDL-C and the range of rises experienced (with also IQR).

Sponsor's response:

The information provided in previous answers to TGA is based on integrated analyses where patients from several studies have been pooled according to their dyslipidaemia class. These analyses had been performed by Pronova's US partner at that time (Ross). It is therefore not possible for the company to identify individual patients from these analyses. However we can provide some data from one of the pivotal clinical trials in patients with Type IV and V dyslipidaemia (K85-95009 study) which demonstrated the highest LDL-C increases: 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 dyslipidemia mean LDL-C was 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.

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.

3. Provide the outcomes, in tabular form, of Study CK85-018 (the study of the add-on effect of Omacor to lovastatin).

Sponsor's response:

The following table (Table 38) compares both the absolute and relative (%) changes of the usual lipid parameters from baseline to endpoint for each of the three treatments in the CK85-018 study.

Table 38.

Lipid parameters	Baseline	Omacor		Lovastatin		Omacor + Lovastatin	
	mmol/L	Absolute change (mmol/L)	Relative[1] change (%)	Absolute change (mmol/L)	Relative[1] change (%)	Absolute change (mmol/L)	Relative[1] change (%)
Total-C	10.13	-0.37	-3.7	-2.76	-27.2	-3.18	-31.4
HDL-C	1.70	0.12	6.9	0.24	14.4	0.10	5.6
LDL-C	7.69	0.67	-8.7	-2.81	-36.5	-3.01	-39.1
TG	1.66	-0.40	-24.2	-0.30	-17.8	-0.67	-40.4

[1]Values from the CK85-018 study report. The publication corresponding to this CK85-018 study was provided with the current Australian submission; reference: Hansen *et al.* 1993 *Arteriosclerosis and Thrombosis* 13(1): 98-104)

4. Provide the final 24 -month results from the study reported by Davidson et al.
Sponsor's response:

The requested information relates to a 24-month extension study of the *Combination of Prescription Omega-3-acid ethyl esters Plus Simvastatin* (COMBOS) trial. The findings of this trial were recently published[50].

A brief summary of the COMBOS trial is given in the following:

The COMBOS trial studied the effect on non-HDL cholesterol and other variables of adding Omacor to stable statin therapy in patients with persistent hypertriglyceridaemia. 254 patients were randomized to receive Omacor (4 g/day) + simvastatin (40 mg/day) or placebo + simvastatin (40 mg/day) for 8 weeks following an at least 8 weeks period of stable statin therapy.

Results: Non-HDL-cholesterol was significantly reduced in the Omacor group compared to the group receiving placebo + simvastatin. Triglycerides (TG), VLDL-C and the Total Cholesterol/HDL-C ratio were also significantly reduced in the Omacor group, and HDL-C was significantly increased compared to simvastatin + placebo ($p<0.001$ for all groups). LDL-C changed by a median of +0.7% in the Omacor group compared to a median change of -2.8% in the simvastatin + placebo group (not significant, $p=0.052$). Completers of the COMBOS study were eligible to participate in a 24-month extension study. Patients who were in the simvastatin + placebo group were switched to Omacor + simvastatin ("Switchers"), and patients who received Omacor + simvastatin continued the same regimen (open-label) in the extension phase ("Non-switchers"). The primary endpoint of this study was the difference between Non-switchers and Switchers in median percent change in non-HDL-C from the COMBOS end of treatment to Month 4 of the extension phase. At month 4 from end of COMBOS treatment, non-HDL-C was reduced by a median of 9.4 % in Switchers and increased by 0.9% in Non-switchers ($p<0.001$). For the total population (Non-switchers + Switchers) the median percent change from COMBOS baseline to Months 4, 12 and 24 was -8.3%, -7.3% and -8.9% respectively (all $p<0.001$). Regarding the other lipid parameters: median percent reductions from COMBOS baseline in TG, TC and VLDL-C in the total population were maintained at Months 4, 12 and 24. Omacor produced small median

[50]Bays *et al.* 2010. Long-term up to 24-month efficacy and safety of concomitant prescription omega-3-acid ethyl esters and simvastatin in hypertriglyceridemic patients. *Current Medical Research & Opinion*, 26(4); 907-915.

percent increases from baseline LDL-C levels at Months 4, 12, and 24. An additional post-hoc LDL-C tertile analysis was performed in this extension study, which demonstrated that increases in LDL-C in these hypertriglyceridemic patients were greater in those with lower baseline LDL-C compared to those with higher LDL-C levels as was observed in the base COMBOS study. But as with the COMBOS results, the increases in LDL-C levels in this open-label extension were offset by reduction in cholesterol carried by non-HDL particles (such as larger decreases in VLDL-C concentration), which resulted in a reduction in non-HDL-C concentration in all baseline LDL-C tertiles.

5. Give full details of the calculations of the NNT values in the GISSI-Prevenzione trial.
Sponsor's response:
The number 'needed to treat' (NNT) is the number of patients who need to be treated in order to prevent one additional bad outcome. It is defined as the inverse of the absolute risk reduction. Therefore, with a risk difference of 2.0% the NNT is given by 1/0.02 = 50. If we assume the same risk ratio over time and extrapolate the risk difference of 2.0% to a 5-year result we get a risk difference of about 2.9% and the corresponding number needed to treat is 1/0.029 = 34.5. For survival differences the number needed to treat is calculated as the inverse of the survival difference. Therefore, with a survival difference of 2.1% the NNT is equal to 1/0.021 = 47.6. If we again extrapolate these data to a 5-year result we have to assume a survival difference of 3.0% and a corresponding number needed to treat of 1/0.03 = 33.3.

6. Provide the most up-to-date version of the company Risk Management Plan and the details of any post-registration commitments entered into with the EMA and the US FDA.
Sponsor's response:
An initial Risk Management Plan (RMP) for Omacor is under preparation and will be submitted in the first quarter of 2011, together with the next Periodic Safety Update Report (PSUR 9 covering the period from 23 July 2009 to January 2011). The company asserts that this application was submitted before the current requirement for provision of an RMP for review in parallel with the evaluation of an NCE. No post-registration commitments have been agreed with EMA, and as the company Abbott (formerly Solvay) is not the sponsor for Omacor in US, we are not in a position to detail any possible post-registration commitments agreed with the US FDA. To our knowledge, no post-registrations commitments have been posted on the FDA website.

7. Provide comment on the progress of NDA 21-853, the application in the USA for dyslipidaemia Fredrickson's types IIb and IV, TG < 500 mg/dL.
Sponsor's response:
As the company Abbott (formerly Solvay) is not the sponsor for Omacor (Lovaza) in the US, we are not in a position to comment in detail on the progress of NDA 21-853 (the application for dyslipidaemia Fredrickson's types IIb and IV, TG < 500 mg/dL), which was subject to confidential discussions between the FDA and Reliant/GSK (Pronova's US partners).

From the FDA website, we can only provide the following comments:

i.) A supplemental New Drug Application (s-NDA) has been submitted to the FDA by Reliant on June 12th 2007, providing information on the use of Omacor (since renamed as Lovaza) as an add-on therapy to HMG-CoA reductase inhibitors in patients with persistent high triglycerides (200-499 mg/dL) despite HMG-CoA reductase inhibitor therapy. FDA implemented this supplemental application in June 2007 as a Labelling revision. The indication remained unchanged.

NB: the study submitted with the s-NDA concerned the effects of Lovaza 4 g per day as add-on therapy to treatment with simvastatin evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 254 adult patients (122 on Lovaza and 132 on placebo) with persistent high triglycerides (200-499 mg/dL) despite simvastatin therapy.

ii.) Given the current indication of Lovaza in the latest approved US labelling dated 16.09.2009, we conclude that the indication "treatment of dyslipidaemia Fredrickson's types IIb and IV, TG < 500 mg/dL" was not approved by the FDA, although FDA issued initially an approvable letter for NDA 21-853.

Lovaza (omega-3-acid ethyl esters) Capsules - Initial U.S. Approval: 2004. Indications and usage:
"EPA and DHA, indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridaemia. "

8. Comment on potential safety concerns (identified at point xxvi in the overview above) regarding increased bleeding tendency[51], elevation of LDL-C in some trials, rises in ALT, GI intolerance & fishy eructation and rise in serum insulin.
Sponsor's response:
a) Increased bleeding tendency with increase in bleeding time have been reported in some clinical studies, possibly due to the ability of omega-3 fatty acids to inhibit platelet aggregation. These properties of omega-3 fatty acids are known for more than 30 years. However, clinical trial evidence has not supported increased clinically relevant bleeding with omega-3 fatty acids intake, even when combined with other agents that are known to increase bleeding such as aspirin and warfarin (References: *Bays HE, Am J Cardiol 99:35C-43C, 2007; Harris WS, Am J Cardiol 99:S44-S46 2007*). The issues of increased bleeding have been addressed in the Company Core Safety Information (CCSI dated 16 April 2010), section "Special warnings and special precautions for use" and section "Interaction with other medicinal products and other forms of interaction". The interaction between Omacor and aspirin has been recently updated in a signal report dated 4 September 2009.

b). As explained in the answer to Question 2, the LDL-C-elevation seems to be partly dependent on the LDL-C baseline value: the lower the LDL-C baseline value, the higher the increase. Also, there seems to be a dependent positive relationship between high baseline TG and VLDL-C values and LDL-C increase during omega-3-fatty acids treatment. The mechanism for this increase was explained in detail in a previous response to TGA.

c). Increased AST and ALT is adequately covered in the CCSI dated 16 April 2010. There are no data indicating an increased risk for patients with hepatic impairment, but regular monitoring of transaminases (AST and ALT) is required in patients with any signs of hepatitis in particular with the high dose, that is, 4 capsules.

d). Gastrointestinal disorders are the most frequently reported adverse events with Omacor treatment, including eructation. This is also adequately covered in the CCSI. Due to the fact that the Omacor capsules contain eicosapentaenoic acid and docosahexaenoic acid from fish oil, the eructations may lead to a "fishy taste".

e). The trial reported by Patel *et al* (2007) consists of a small number of 35 post-MI patients, 19 patients on usual care and 16 patients on usual care plus Omacor (Omacor group). In the usual care group two patients were on oral hypoglycaemics (unkown, whether sulfonylurea or

[51] *Increased bleeding tendency with increase in bleeding time reported in some trials, especially with doses exceeding 4 g daily and potential for interaction with anti-platelet agents and anticoagulants.*

biguanide or other) and one patient on insulin. In the Omacor group, one patient was on oral hypoglycaemics and two patients on insulin. This imbalance of concomitant medication may have an influence on the insulin finding, especially as the oral hypoglycaemics are not further specified. Furthermore, insulin values are known to vary widely and a patient number of 35 may not be adequate for a clinically relevant message. Nevertheless, the observation of a rise in serum insulin will be subject to a signal evaluation, the results of which will be reported in the next PSUR.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

1. The ACPM recommended approval of the submission from Abbott Products Pty Ltd to register a new chemical entity of for omega-3-acid ethyl esters 90 (Omacor) soft capsule 1000 mg for the indication:

> *Post Myocardial Infarction: Adjuvant treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (for example, 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:*
> *Types 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 I hyperchylomicronaemia). There are insufficient data to support the use in patients with secondary endogenous hypertriglyceridaemia including patients with diabetes mellitus.*

In making this recommendation, the ACPM agreed that while the mechanism of action is unclear, the efficacy data supported the indication for post myocardial infarction. However the evidence provided was insufficient to support a broad indication for all types of hypertriglyceridaemia and therefore the ACPM agreed with the Delegate in support of the revised indication clearly specifying the different types of hypertriglyceridaemia indications. ACPM advised that the 2g dose was not supported by clinical data for use in hypertriglyceridaemia.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Omacor (1000 mg Omega-3-acid ethyl esters 90 capsule) for oral administration, indicated for:

Post Myocardial Infarction: Adjuvant treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (for example, 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:
-Types 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 I

hyperchylomicronaemia). There are insufficient data to support the use in patients with secondary endogenous hypertriglyceridaemia including patients with diabetes mellitus.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Appendix 1. Nonclinical references

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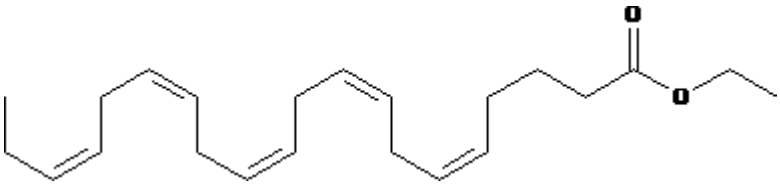
PRODUCT INFORMATION

OMACOR® (Omega-3-acid ethyl esters 90) 1,000 mg Soft capsules

IDENTIFICATION OF THE PRODUCT

Omega-3-acid ethyl esters 90 (Omacor®).

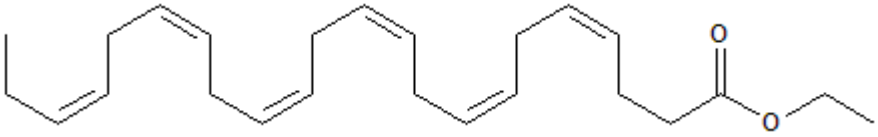
Eicosapentaenoic acid (EPA) ethyl ester.
Structural formula:



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

CAS: 86227-47-6

Docosahexaenoic acid (DHA) ethyl ester.
Structural formula:



Molecular formula: $C_{24}H_{36}O_2$
Molecular Weight: 356.55
CAS: 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 C_{max}, T_{max}, 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

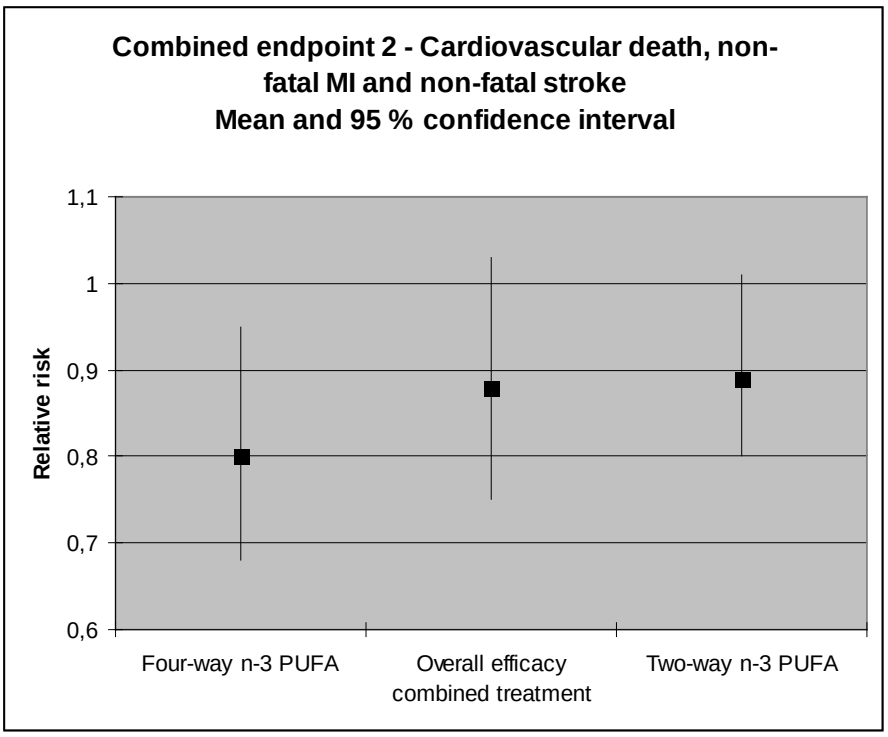
Four-way analysis					
	All (n=11324)	**Omacor® (n=2836)**	**Log rank**	**Control (n=2828)**	**Relative risk (95% CI)**
Main endpoints					
Death + nonfatal MI + nonfatal stroke	1500 (13.3%)	356 (12.3%)	P=0.023	414 (14.6%)	0.85 (0.74-0.98)
Cardiovascular death + nonfatal MI + nonfatal stroke	1155 (10.2%)	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**		
	Mean Value		**Mean Value**		***P*-value[a]**
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.

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 section INTERACTIONS WITH OTHER DRUGS.

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 section 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.

Hepatic Impairment:

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

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

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).

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).

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.

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.

Immune system disorders:

Uncommon: hypersensitivity

Metabolism and nutrition disorders:

Rare: hyperglycaemia

Nervous System disorders:

Uncommon: dizziness, dysgeusia

Rare: headache

Vascular disorders:

Very rare: hypotension

Respiratory, thoracic and mediastinal disorders

Very rare: nasal dryness

Gastrointestinal disorders:

Common: dyspepsia, nausea
Uncommon: abdominal pain, gastrointestinal disorders (such as gastro-oesophageal reflux disease, eructation, vomiting, abdominal distension, diarrhoea or constipation)
Very rare: lower gastrointestinal haemorrhage

Hepatobiliary disorders:

Rare: liver disorders

Skin and subcutaneous tissue disorders:

Rare: acne, rash pruritic

Very rare: urticaria

Investigations:

Very rare: White blood cell count increased, blood lactate dehydrogenase increased, transaminases increased (ALT: alanine aminotransferase increased, AST: aspartate aminotransferase 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

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.

AUST R 155717

STORAGE:

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

POISON SCHEDULE

Schedule 4.

NAME AND ADDRESS OF THE SPONSOR

Abbott Products Pty Ltd
Level 1, Bldg 2, 20 Bridge Street,
Pymble, NSW 2073
Australia

DATE OF TGA APPROVAL: 28 JULY 2010

Therapeutic Goods Administration

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