Taiwan Food and Drug Administration

Assessment Report

Trade Name： 脂妙清軟膠囊**1000**毫克**/ Omacor Soft Capsule 1000mg**

Active Ingredient：Omega-3-Acid Ethyl Esters 90

License Number：衛部藥製字第 059019 號

Applicant：科進製藥科技股份有限公司

Approval Date：2016/2/4

Indication：Hypertriglyceridaemia

Background Information

Trade Name	脂妙清軟膠囊 1000 毫克/ Omacor Soft Capsule 1000mg
Active Ingredient(s)	Omega-3-Acid Ethyl Esters 90
Applicant	科進製藥科技股份有限公司
Dosage Form & Strengths	Soft capsules/1000mg
Indication	Hypertriglyceridaemia
Posology	The daily dose of Omacoris 2 capsules per day taken as a single 1000 mgdose (1capsule).
Pharmacological Category **ATC Code**	C10AX06

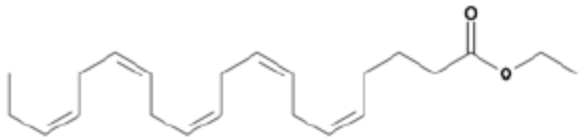
2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

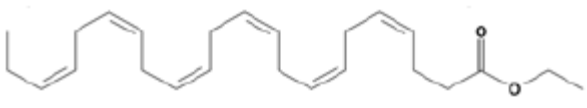
Omega-3-acid ethyl esters, practically insoluble in water, are ethyl esters of *alpha*-linolenic acid (C18:3 n-3), moroctic acid (C18:4 n-3), eicosatetraenoic acid (C20:4 n-3), timnodonic (eicosapentaenoic) acid (C20:5 n-3; EPA), heneicosapentaenoic acid (C21:5 n-3), clupanodonic acid (C22:5 n-3) and cervonic (docosahexaenoic) acid (C22:6 n-3; DHA). The content of omega-3-acid ethyl esters in omega-3-acid ethyl esters 90 is minimum 90% as defined in Ph. Eur. with minimum 40% of EPA ethyl esters and minimum 34% of DHA ethyl esters.

EPA ethyl ester has following structure:



EPA ethyl ester is a pale yellow liquid. The molecular formula and the molecular weight are $C_{22}H_{34}O_2$ and 330.51, respectively. It is very soluble in methanol, ethanol, acetone, heptane, practically insoluble in water.

DHA ethyl ester has following structure:



DHA ethyl ester is a pale yellow liquid. The molecular formula and the molecular weight are $C_{24}H_{36}O_2$ and 356.55, respectively. It is very soluble in ethanol, acetone, heptane, freely soluble in methanol, practically insoluble in water.

The analytical techniques utilized to elucidate the structure include ^{1}H-NMR and ^{13}C-NMR spectroscopy.

The specification includes tests for appearance, identification, acid value, peroxide value, anisidine value, oligomers, absorbance, α-tocopherol, heavy metals, EPA ethyl esters, DHA ethyl esters EPA+DHA ethyl esters, sum of omega-3-acid ethyl esters, other n-3 FAEE, other identified FAEE, unidentified FAEE, and microbial limits. The specification is set according to Ph. Eur.

2.1.2 Drug product

Each Omacor Soft Capsule 1000 mg contains 1000 mg of omega-3-acid ethyl esters 90. The present product is manufactured by filling the drug substance into capsule. The manufacturing process is confirmed by three consecutive batches of process validation.

The specification has been presented for Omacor Soft Capsule 1000 mg and the test items include description, filled weight, friability, hardness, identification, content uniformity, acid value, peroxide value, anisidine value, oligomers, absorbance, α-tocopherol, EPA ethyl esters, DHA ethyl esters EPA+DHA ethyl esters, other n-3 FAEE, sum of n-3 FAEE, other identified FAEE, unidentified FAEE, and microbial limits. Analytical methods are described well and validated.

Stability studies under long term (25°C/60% RH and 30°C/65% RH) and accelerated (40°C/75% RH) conditions have been carried out with three full scale production batches according to the protocol. The parameters evaluated during the stability study are appearance, disintegration time, identification, EPA ethyl esters, DHA ethyl esters, other n-3 FAEE, other identified FAEE, unidentified FAEE, acid value, α-tocopherol, peroxide value, anisidine value, oligomer, absorbance, hardness, uniformity of mass, average fill weight, microbial contamination. Stability data up to 18 months are available. The shelf-life is under the condition of 30°C. The container closure system is type III amber glass bottle.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Omacor (ethyl ester K85, K85, or omega-3 concentrate) is oil which consists of ethyl esters of EPA and DHA. Literature data and in vivo pharmacological studies have shown that K85 can lower the plasma triglyceride level. However, the mechanism is not completely understood. No safety pharmacological studies were performed with Omacor. The CNS, respiratory function, and cardiovascular function had been evaluated in chronic toxicity studies. Stand-alone pharmacological studies could be omitted.

2.2.2 Toxicological Studies

In rats, oral administration of K85 at dose levels up to 2000 mg/kg/day for 52 weeks did not cause significant toxic effects. The decreases in plasma cholesterol, total lipid, phospholipid and triglyceride concentrations with associated minor morphological changes in the liver were considered consistent with the pharmacological activity of K85. In dogs, oral administration of K85 at dose levels up to 1000 mg/kg/day for 52 weeks elicited minor toxic effects (increased intensity of adrenal vacuolation and splenic pigmentation) in females. No toxic effects were observed in males. K85 had no mutagenic potential and did not cause significant effects on reproductive function and fatal development. K85 had no carcinogenic potential in mice and rats.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Each capsule of Omacor® contains 1000 mg omega-3-acid ethyl esters, which is predominantly a combination of EPA and DHA ethyl esters. Following oral administration, EPA and DHA ethyl esters was completely hydrolyzed into free acid in the gut before absorption. The free acid of EPA and DHA cannot be detected directly; therefore the uptake of EPA and DHA in serum phospholipids is used as marker.

Following administration of different doses of omega-3-acid ethyl esters, the increase in serum phospholipid EPA content was following dose-dependent behavier whereas the increase of DHA content was less marked and not dose-dependent. No food effect was conducted since Omacor were received with a meal in Phase III studies for avoiding GI disturbance.

The metabolism of omega-3-acid ethyl esters was expected as other natural long-chain fatty.

2.3.2 Interaction Studies

Based on the result of an in vitro inhibition study with human liver microsome, it is considered unlikely to inhibit cytochrome P450, including CYP1A2, 2A6, 2C9, 2C19, 2D6, 3A4 and 2E1, at therapeutic dose level of EPA and DHA.

Three human drug-drug interaction studies were conducted to investigate the multiple-dose effect of Omacor® on the PK characteristics of simavastatin, atorvastatin and rosuvastatin. No significant influence was observed on the statin drugs and their metabolites. Therefore, no dose adjustment was needed.

2.3.3 Special Populations

According to the pooled data from different clinical trials, age doesn’t have significant impact on the uptake of EPA and DHA into serum phospholipids.

Nevertheless, the uptake of EPA was higher in female than in male subjects. No dedicated study or analysis was conducted in renal and hepatic impaired population..

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The main evidence of Omacor (omega-3-Acid Ethyl Esters 90) soft capsule for the treatment of hypertriglyceridemia were based on three randomized, multicenter, double-blind, placebo-controlled studies, including two US studies (K85-94010 and K85-95009) and one Taiwanese study (OM3-99001).

A total of 43 and 41 subjects were randomized for Study K85-94010 (Omacor 4g/day N=22; placebo N=21) and Study K85-95009 (Omacor 4g/day N=20; placebo N=21), respectively. A total 253 subjects were randomized in Study OM3-99001 (Omacor 4g/day N=84; 2g/day N=82; vs. placebo N=87).

In both US studies, the efficacy of Omacor 4g/day was assessed in patients with very high triglyceride (TG) levels at baseline (500-2000 mg/dl). In the Taiwanese study, the efficacy of Omacor 2g/day and 4g/day was assessed in subjects with TG level of 200-1000 mg/dL. The primary endpoint of the three studies was the percent change from baseline of serum TG concentration at the end-of-treatment (6 weeks for Study K85-94010; 16 weeks for sudy K85-95009; 8 weeks for Study OM3-99001).

The results are summarized as below.

Study [K85-94010] and [K85-95009]

The changes of lipid profiles in study K85-94010 and K-85-95009 were shown in Table 1.

Table 1 Change of lipid profiles in study K85-94010 and K-85-95009

Lipid profile	Omacor 4g/day (n=42)		Placebo (n=42)		Difference (%)
	Baseline (mg/dL)	Change from baseline (%)	Baseline (mg/dL)	Change from baseline (%)	
TG	816	-44.9	788	+6.7	-51.6
Non-HDL-C	271	-13.8	292	-3.6	-10.2
TC	296	-9.7	314	-1.7	-8.0
VLDL-C	175	-41.7	175	-0.9	-40.8
HDL-C	22	+9.1	24	0.0	+9.1
LDL-C	89	+44.5	108	-4.8	+49.3

Results from the two US studies indicated that Omacor 4g/day was efficacious in reducing total TG concentration compared with placebo (Study K85-95009: -45.3% vs. 16.4%, $p<0.0001$; Study K85-94010: -31.4% vs. -3.9%, $p=0.0009$). However, LDL-C was also significantly increased in the Omacor 4g/day group compared with placebo in both studies (Study K85-95009: 42.6% vs.-3.2%, $p=0.0003$; Study

K85-94010: 27.2% vs. 4.0%, p=0.0127).

Although the increase in LDL-C was noted in Omacor group compared to placebo, the baseline LCL-C were low in both studies (K85-94010: 44±16 mg/dl in Omacor group; K85-95009: 79±36 mg/dl in Omacor group). In study K85-95009, LDL at endpoint was 104±38 mg/dL indicating that the majority of subjects had LCL-C less than 160 mg/dl {104 plus one standard deviation (38) = 142mg/dl, less than 160mg/dl}.The increase in LDL-C associated with Omacor treatment was still within acceptable range. Besides, subjects in these two studies had higher baseline TG who were at high risk for pancreatitis. Treatment with Omacor lead to greater reduction in TG for these high baseline TG subjects while LDL-C remained in the acceptable range.

Study [OM3-99001]

Study OM3-99001 was a bridging study to evaluate efficacy and safety of Omacor 2g and 4g in Taiwan population.

Results of the Taiwanese study (Study OM3-99001) showed a statistically significant decrease in the percent change of TG level (Table 2) for both Omacor groups (4g/day: -32.1%, p<0.0001, 2g/day: -29.7%, p<0.0001) compared with the placebo group (-5.4%). Similar to the US studies, compared with the placebo group (-3.5%), LDL-C was also significantly increased in the Omacor 4g/day (7.2%, p=0.0136) and 2g/day (9.9%, p=0.001) groups.

A subgroup analysis of primary efficacy endpoint based on statin usage or TG levels on ITT population showed consistent efficacy results (Table 3).

Overall, both 4g and 2g Omacor per day were concluded to be superior to the placebo for lowering TG level, whether in subjects with stain use or not, and also in subjects with moderate (TG <500 mg/dL) or severe (TG ≥500 mg/dL) hypertriglyceridemia.

Table 2 Change of lipid profile in study OM3-99001

Lipid profile	Omacor 4g/day (n=84)		Omacor 2g/day (n=82)		Placebo (n=87)	
	Baseline	% change	Baseline	% change	Baseline	% change
TG	351.2	-32.1	338.6	-29.7	336.9	-5.4
non-HDL-C	146.1	-4.8	146.6	-4.2	147.4	-0.1
TC	184.0	-3.1	186.9	-3.0	185.7	0.6
VLDL-C	59.5	-21.9	57.7	-24.5	56.7	-6.2
HDL-C	37.1	2.4	39.3	1.6	37.4	3.2
LDL-C	80.4	7.2	80.8	9.9	83.4	-3.5

Table 3 Subgroup analysis with stain usage or TG level in study OM3-99001

Subgroups		Treatment group	N	Baseline TG level	% change from baseline (Intra p-value)	Omacor vs Placebo (Group difference)
Statin Usage	Stable statin	Omacor 4g	28	339.8	-28.7 (<0.0001)	-29.7%
		Omacor 2g	29	309.1	-27.5 (<0.0001)	-31.3%
		Placebo	31	325.0	4.3 (0.6775)	-
	No lipid altering agent	Omacor 4g	54	357.3	-33.8 (<0.0001)	-25.0%
		Omacor 2g	53	356.0	-30.8 (<0.0001)	-22.0%
		Placebo	56	343.7	-10.4 (0.0721)	-
Baseline TG level	200-499 mg/dL	Omacor 4g	68	311.3	-28.4 (<0.0001)	-25.3%
		Omacor 2g	70	302.3	-25.2 (<0.0001)	-22.7%
		Placebo	73	301.3	-3.0 (0.5877)	-
	≧500 mg/dL	Omacor 4g	14	631.4	-47.7 (0.0012)	-35.6%
		Omacor 2g	12	656.4	-50.7 (0.0003)	-38.3%
		Placebo	14	603.0	-16.8 (0.2309)	-

2.4.2 Safety Results

Adverse reactions reported in at least 3% and at a greater rate than placebo for subjects treated with Omacor based on pooled data across 23 clinical trials were shown in Table 3. Additional adverse reactions observed from clinical trials include constipation, gastrointestinal disorder, vomiting, increased ALT, increased AST, pruritus and rash.

Table 3 Adverse Reactions Occurring at Incidence ≧3% and Greater than Placebo in Clinical Trials of Omacor

Adverse Reactions*	Omacor (N=655)		Placebo (N=370)	
	n	%	n	%
Eructation	29	4	5	1
Dyspepsia	22	3	6	2
Taste perversion	27	4	1	<1

* Trials included subjects with HTG and severe HTG

Safety data were also collected from Taiwan study OM3-99001. Please see Table 4.

Table 4 Safety data from Taiwan study OM3-99001

	Omacor 4g/day n (%)	Omacor 2g/day n (%)	Placebo n (%)
AEs	19 (22.6%)	23(28.0%)	21(24.1%)
Drug related AEs	1(1.2%)	4(4.9%)	0(0.0%)

The most frequently reported adverse events in Omacor 4g/day group were upper respiratory tract infection (2.4%, n=2), liver function (AST/ALT) elevation (2.4%, n=2) and hyperuricaemia (2.4%, n=2). In Omacor 2g/day group, liver function elevation was 3.7% (n=3) and in placebo group, upper respiratory tract infection was reported 4.6% (n=4). For those cases with liver function elevation, *none of them had elevation of ALT ≧3 ULN , all of them had liver function elevation <3 ULN* and resolved or recovery during follow up.

The major safety concerns with Omacor use were LDL-C increase and AST/ALT elevation. Periodically monitoring LDL-C concentration and AST/ALT (especially in patients with hepatic impairment) during Omacor treatment are recommended.

Omacor is contraindicated in patients with known hypersensitivity to Omacor or any of its components. Because Omacor contains ethyl esters of omega-3 fatty acids (EPA and DHA) from several fish sources, patients with known hypersensitivity to fish and/or shellfish should use Omacor with caution.

In a double-blind, placebo-controlled trial of 663 subjects with symptomatic paroxysmal AF (n = 542) or persistent AF (n = 121), recurrent AF or flutter was observed in subjects randomized to Omacor who received 8 g/day for 7 days and 4 g/day thereafter for 23 weeks at a higher rate relative to placebo. Subjects in this trial had median baseline triglycerides of 127 mg/dL, had no substantial structural heart disease, were taking no anti-arrhythmic therapy (rate control permitted), and were in normal sinus rhythm at baseline.

At 24 weeks, in the paroxysmal AF stratum, there were 129 (47%) first recurrent symptomatic AF or flutter events on placebo and 141 (53%) on Omacor [primary endpoint, HR 1.19;95%CI:0.93, 1.35]. In the persistent AF stratum, there were 19 (35%) events on placebo and 34 (52%) events on Omacor [HR 1.63; 95% CI: 0.91, 2.18]. For both strata 61 combined, the HR was 1.25; 95% CI: 1.00, 1.40. Although the clinical significance of these results is uncertain, there is a possible association between Omacor and more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation. (Omacor is not indicated for the treatment of AF or flutter.)

In addition to adverse reactions reported from clinical trials, the events described below have been identified during post-approval use of Omacor. Because

these events are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or to always establish a causal relationship to drug exposure.

The following events have been reported: anaphylactic reaction, hemorrhagic diathesis.

2.5 Bridging Study Evaluation

Sponsor has submitted a phase I PK study conducted in Japanese healthy volunteers. The deposition of EPA and DHA in human was expected as other natural fatty acid. No food effect study was investigated to estimate the food impact on Omacor®. Considering the food habit is different and the contribution of Japanese PK data in ethnic sensitivity was limited, domestic clinical trial to investigate the Omacor® effect on lipid profile in Taiwanese population was necessary.

Study OM3-99001 was a bridging study conducted in Taiwan. For efficacy and safety assessment, please refer to paragraph **2.4 Clinical Efficacy and Safety Evaluation**.

2.6 Conclusion

Submitted dossier for CMC, PT, PK were assessed and thought to be acceptable.

The efficacy results from US studies K85-94010 and K85-95009 showed statistically significant reduction in TG in subjects with severe hypertriglyceridemia (TG≧500 mg/dl and <2000 mg/dl) treated with Omacor 4g/day. In Taiwan study OM3-99001, subjects with moderate (TG≧200 mg/dl and <500 mg/dl) or severe (TG ≧500 mg/dl) hypertriglyceridemia revealed statistically significant reduction in serum TG with Omacor 2g/day or 4g/day treatment. As a result, the efficacy of Omacor 2g/day and 4g/day in the treatment of patient with moderate and severe hypertriglyceridemia was acceptable.

Possible side effects with Omacor use are elevated liver function and increase LDL-C levels. In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with Omacor. Besides, lipid profile such as TG, LDL should be monitored periodically during therapy with Omacor.

The benefit-risk ratio is regarded positive and approval of Omacor is recommended while the following indication and dosage:

Indication:

Treatment of hypertriglyceridemia

Omacor is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients who has endogenous hypertriglyceridemia and lipid lowering diet alone cannot reach appropriate response. Patients should continue this diet during Omacor treatment.

Base on the submitted data, there were still some limitations needed to be declared:
The effect of Omacor on the risk for pancreatitis has not been determined.
The effect of Omacor on cardiovascular mortality and morbidity has not been determined.

Dosage:

The initial daily dose of Omacor is 2g per day. It can be taken by 1 capsule /per time, twice daily (after meal).If appropriate response is not achieved by the initial dose, the dose may increase to 4g per day and taken by 2 capsules/per time, twice daily (after meal)

3. Post-Marketing Requirements

No post-marketing requirement is recommended.