HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion

2 October 2013

OMACOR, capsule, soft

B/28 (CIP: 34009 357 025 8 6)

Applicant: PIERRE FABRE MEDICAMENT

INN	Omega-3-ethyl esters
ATC code	C10AX06 (cholesterol and triglyceride reducers)
Reason for the review	**Re-assessment of Actual Benefit at the request of the Directorate-General for Health, pursuant to Article R.163-19 of the Social Security Code.**
List concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"Adjunctive treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (including statins, platelet aggregation inhibitors, beta-blockers and angiotensin converting enzyme inhibitors)"**

Actual benefit	**Insufficient Actual Benefit**
Improvement in Actual Benefit	**Not applicable**
Therapeutic use	**Not applicable**
Recommendations	**Not applicable**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (mutual recognition): 02/10/1995 Rapporteur Member State: United Kingdom
Prescribing and dispensing conditions / special status	Not applicable
ATC Classification	2012 C Cardiovascular system C10 Lipid modifying agents C10A Lipid modifying agents, plain C10AX Lipid modifying agents, plain C10AX06 omega 3

02 BACKGROUND

By letter dated 26 June 2012, the Directorate-General for Health requested the Transparency Committee to reassess the proprietary medicinal product OMACOR in its indication "Adjuvant treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (including statins, platelet aggregation inhibitors, beta-blockers and angiotensin converting enzyme inhibitors)," with particular reference to:

- firstly, the results of a study requested by CEPS in January 2005, with the aim of determining the real-life impact of OMACOR on patient health and on patient mortality in particular, submitted to the HAS methodology and post-registration studies unit.
- secondly, recent publications relating to OMACOR efficacy in secondary prevention.

Consequently, a re-assessment of this proprietary medicinal product was carried out by the Committee pursuant to Article R.163-21 of the Social Security Code.

03 THERAPEUTIC INDICATIONS

"Post myocardial infarction: **"Adjunctive treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (including statins, platelet aggregation inhibitors, beta-blockers and angiotensin converting enzyme inhibitors).**

Hypertriglyceridaemia: Endogenous hypertriglyceridaemia as a supplement to diet when dietary measures alone are insufficient to produce an adequate response:

- Type IV in monotherapy.
- Type IIb/III in combination with statins, when control of triglycerides is insufficient."

04 DOSAGE

"Post myocardial infarction: One soft capsule daily."

05 THERAPEUTIC NEED

Patients with a history of myocardial infarction (MI) have a high risk of recurrence and premature death; in these patients, the risk of recurrence after one year is as high as 8 to 10%.

Secondary prevention after MI relies on comprehensive management, combining:

- Hygiene and dietary measures (smoking cessation, regular physical exercise and dieting with BMI ≥ 30 kg/m^2 and abdominal circumference greater than 102/88 cm (men/women)),
- Taking into account associated risk factors (Diabetes: HbA1c < 6.5%, Hypertension: BP < 140/90 mm Hg, dyslipidaemia: LDL-C < 1 g/l).

Drug treatments:

For secondary prevention of MI, it is recommended to combine:

- a platelet aggregation inhibitor (acetylsalicylic acid 75 to 100 mg/day or clopidogrel 75 mg/day),
- a beta-blocker,
- an angiotensin converting enzyme inhibitor (or an angiotensin receptor antagonist in cases of ACE intolerance),
- a statin.

In most post-MI secondary prevention patients, the therapeutic needs are theoretically covered by the use of the four combined secondary prevention treatments offering a demonstrable benefit in terms of morbidity and mortality (platelet aggregation inhibitors, beta-blockers, ACE inhibitors or ARBs, and statins).

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

OMACOR is an adjuvant treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (including statins, platelet aggregation inhibitors, beta-blockers and angiotensin converting enzyme inhibitors).

There is an omega-3-based proprietary medicinal product – YSOMEGA (Pierre Fabre) – indicated in “isolated or predominant endogenous hypertriglyceridaemia, in patients at risk for coronary artery disease or pancreatitis, as an addition to an appropriate and unrelenting diet, which on its own has proved insufficient to provide an adequate response” (proprietary medicinal product not qualifying for reimbursement).

06.2 Other health technologies

After a myocardial infarction, coronary revascularisation may prove to be necessary in some patients.

06.3 Other available comparators

Omega-3 fatty acids are available as food supplements and in food preparations (margarine, oils, etc.).

◗ Conclusion

The most relevant comparators are YSOMEGA, another omega-3-based proprietary medicinal product used as an adjuvant treatment but not qualifying for reimbursement, and food supplements and preparations containing omega-3 fatty acids.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	Post-myocardial infarction: adjunctive treatment in secondary prevention of myocardial infarction in combination with standard treatments	Endogenous hypertriglyceridaemia: - as an adjunct to diet which alone has proved insufficient −type IV: in monotherapy - type IIb/III: in combination with statins when the triglyceridaemia is not sufficiently controlled
Germany	**yes**	**yes**
Austria	**yes**	**no**
Spain	**no**	**yes**
Estonia	**yes**	**no**
France	**yes**	**no**
Italy	**yes**	**yes**
Latvia	**yes**	**no**
Greece	**yes**	**yes**
Romania	**yes**	**no**
United Kingdom	**yes**	**yes**
USA	**no**	**yes**

08 SUMMARY OF PREVIOUS ASSESSMENTS

Opinion on inclusion: 24 April 2002

Indications	Isolated or predominant endogenous hypertriglyceridaemia, in patients at risk for coronary artery disease and/or pancreatitis, as an addition to an appropriate and unrelenting diet, which on its own has proved insufficient to provide an adequate response. Adjunctive treatment as secondary prevention of myocardial infarction, in combination with standard therapies (including statins, platelet aggregation inhibitors, beta-blockers and angiotensin converting enzyme inhibitors).
AB	**Hypertriglyceridaemia:** Level of actual benefit (AB): Insufficient **Secondary prevention:** The level of actual benefit provided by OMACOR capsules as adjunctive treatment in combination with standard therapies (including statins, platelet aggregation inhibitors, beta-blockers and angiotensin converting enzyme inhibitors) is substantial in secondary prevention of myocardial infarction.
IAB	Secondary prevention of myocardial infarction: the improvement in actual benefit is moderate (level III) in terms of therapeutic efficacy, in light of the small observed reduction in mortality and its place in treatment strategy.

Opinion on renewal of inclusion: 21 October 2009

Indication	Adjunctive treatment as secondary prevention of myocardial infarction, in combination with standard therapies (including statins, platelet aggregation inhibitors, beta-blockers and angiotensin converting enzyme inhibitors).
AB	The actual benefit provided by OMACOR as adjunctive treatment in the prevention of myocardial infarction, in combination with standard treatments, remains substantial. The Committee points out that this actual benefit will be reassessed in 2 years' time in light of the results of the post-inclusion study currently under way.
IAB	Not applicable

09 ANALYSIS OF AVAILABLE DATA

09.1 Efficacy

New data added to the dossier are:

- six meta-analyses with contradictory results, after studying the benefits of omega-3s in terms of cardiovascular prevention,
- a randomised clinical study: OMEGA,[1]
- two retrospective cohort studies conducted in post-MI patients with or without type II diabetes (Poole 2013[2] et Macchia 2013[3]),
- a post-inclusion study, the EOLE study,
- analyses by subgroups, according to the secondary prevention treatments combined with the omega-3s, were performed on the data from the GISSI-Prevenzione study (initial study for the Marketing Authorisation dossier). In view of their methodology (*a posteriori* analysis by subgroup), these analyses will not be given in detail in this Opinion.

The data from the literature search are presented in section 9.1.5.

In addition, data previously included in the Committee's Opinions are recapitulated in section 9.1.6.

[1] Rauch et al. OMEGA, a randomized placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Clinical trial registration 2010; 122: 2152-9.
[2] Poole CD et al. Omega-3 fatty acids and mortality outcomes in patients with and without type 2 diabetes after myocardial infarction: a retrospective match cohort study. **Clinical Therapeutics** January 2013: 40-51.
[3] Macchia et al. Exploratary analysis on the use of statins with or without n-3 PUFA and major events in patients discharged for acute myocardial infarction: an observational retrospective study. Plos One May 2013.

9.1.1 Meta-analyses

Study	Inclusion criteria / population	No. of studies / No. of patients	Treatment:	Endpoints	Results
Delgado-Lista[4] et al. 2012	- Adult patients - RCTs published up to 2012 - Duration > 6 months - Study endpoints: total mortality and one of the following CVEs: CV death, MI, angina, revascularisation, stroke, LVD	21 RCTs included n = 45,285	Omega-3 food supplements or medicinal products	Primary: CVEs (stroke, coronary events, MI, angina, disorder of the lower limbs, CV death) Secondary: total mortality, CV death, coronary events	Primary endpoint: **CVEs: OR 0.90 [0.85; 0.96], p = 0.001 (in a heterogeneous population: patient with an automatic defibrillator, primary or secondary CVE prevention)** Secondary endpoints: - mortality from all causes: OR 0.95 [0.89; 1.02] NS - CV death: OR 0.91 [0.83; 0.99], p = 0.03 - coronary events: OR 0.82 [0.75; 0.90] p < 0.001
Rizos[5] et al. 2012	- Adult patients - RCTs published up to August 2012 - Study endpoints: total mortality, CV death, sudden death, MI, stroke.	20 RCTs included n = 68,680	Omega-3 food supplements or medicinal products	Primary: CVEs - total mortality, - CV death - sudden death - non-fatal MI - stroke	Primary endpoint: **- total mortality: RR 0.96 [0.91; 1.02], NS** **- CV death: RR 0.91 [0.85; 0.98], S (NS if withdrawn from open-label randomised trials)** **- sudden death: RR 0.87 [0.75; 1.01], NS** **- non-fatal MI: RR 0.89 [0.76; 1.04], NS** **- stroke: RR 1.05 [0.93; 1.18], NS**
Kwak[6] et al. 2012	- adult patients with CV history (PII) - blind RCTs published between 1976 and 2011 - Duration of omega-3 treatments ≥ 1 year, - Endpoints: angina, CVEs, sudden death, CV death or death from all causes, HF, stroke or MI.	14 RCTS included n = 20,485	Omega-3 food supplements or medicinal products Dose of omega-3: 0.4 to 4.8 g/day (EPA or DHA)	Primary: CVEs (angina, HF, TIA, sudden death, CV death, stroke, MI (whether fatal or not), peripheral vascular disease, CV interventions)	Primary endpoint: **CVEs: RR 0.99 [0.89; 1.09] NS**
Chen[7] et al. 2011	- Adult patients with CV history (PII) - RCTs published until December 2010 - Duration > 6 months - Study endpoints: sudden death included	10 RCTS included n = 33,429	Omega-3 food supplements or medicinal products	Primary: Sudden death Secondary: CV death, Total mortality	Primary endpoint: **Sudden death: RR 0.86 [0.76; 0.96], S (NS in studies complying with current guidelines)** Secondary endpoints: - CV death: RR 0.81 [0.69; 0.95], S (NS, in studies complying with current guidelines) - Total mortality: RR 0.89 [0.79; 1.01] NS

[4] Delgado-Lista et al. Long chain omega-3 fatty acids and cardiovascular disease: a systematic review. British Journal of Nutrition 2012; 107: S201-S213.
[5] Rizos et al. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. Journal of the American Medical Association 2012; 308(10): 1024-33.
[6] Kwag et al. Efficacy of Omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease. Archives of Internal Medicine 2012; 172: 686-94.
[7] Chen et al. Effects of omega-3 fatty acid for sudden death prevention in patients with cardiovascular disease: a contemporary meta-analysis of randomized controlled trials. Cardiovasc Drugs Ther 2011; 25: 259-65.

Study	Inclusion criteria / population	No. of studies / No. of patients	Treatments	Endpoints	Results
Filion[8] et al. 2010	- Patients at CV risk with CV disease or diabetes - RCTs published between January 1966 and September 2008 - Study endpoints, at least one of the following two endpoints: total mortality or coronary artery restenosis after angioplasty	29 RCTs included n = 34,501	Omega-3 food supplements or medicinal products	Primary: Total mortality Restenosis	Primary endpoints: **- Total mortality: RR 0.88 [0.64; 1.03], NS** **- Restenosis: RR 0.89 [0.72; 1.05], NS**
Leon[9] et al. 2008	- RCTs published between 1966 and 2006 - Study endpoints: arrhythmia and mortality	12 RCTs included	Omega-3 food supplements or medicinal products	Primary: Arrhythmia (defibrillator implanted) Sudden death	Primary endpoints: **- Arrhythmia: OR 0.90 [0.55; 1.46], NS** **- Sudden death: RR 0.81 [0.52; 1.25], NS**

PII: secondary prevention, CV: cardiovascular, RCT: randomised clinical trial, CVD: cardiovascular disease, CVE: cardiovascular events, HF: heart failure, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, LVD: left ventricular dysfunction.

[8] Filion et al. Omega-3 fatty acids in high-risk cardiovascular patients: meta-analysis of randomized controlled trials. BMC cardiovascular Disorders 2010; 10: 24.
[9] Leon et al. Effect of fish oil on arrhythmias and mortality: systematic review. BMJ 2008; 337: a2931.

9.1.2 Randomised clinical trial: OMEGA study[1]

Method: German randomised, double-blind comparative study of omega-3 versus control in combination with standard recommended treatments, performed in 3804 patients with a history of myocardial infarction (MI) 3 to 14 days previously and followed up for 12 months.

Inclusion criteria: Patients over the age of 18 years, hospitalised following a myocardial infarction.

Treatments:
Omega-3 (1 g capsule), n = 1919
Control (1 g olive oil capsule), n = 1885

Primary efficacy endpoint: Percentage of sudden deaths during 12 months of follow-up.
** unexpected cardiac deaths occurring in the hour following the appearance of the initial symptoms or during the night in the absence of a witness or death within 3 weeks following a resuscitated cardiac arrest.*

Secondary endpoints:
- Mortality from all causes
- Major cardiovascular and cerebrovascular events (MI, stroke and death from all causes) (MACCE).

RESULTS:
The characteristics of the patients on inclusion were comparable.
The secondary prevention treatments on discharge from hospital were: aspirin (95%), statin (94%), beta-blocker (94%) and ACE inhibitor (83%).

After a 12-month follow-up, no significant difference was observed between the two groups in terms of the percentage of **sudden deaths:** 1.5% (28/1919) of patients in the omega-3 group versus 1.5% (29/1885) of patients in the control group, **RR: 0.95 [0.56; 1.60] NS**.

As regards the secondary endpoints:
- no significant difference was observed between the two groups in terms of **deaths from all causes**: 4.6% (88/1919) of patients in the omega-3 group versus 3.7% (70/1885) of patients in the control group, **RR: 1.25 [0.90; 1.72] NS**.
- no significant difference was observed between the two groups in the occurrence of **MACCE**: 10.4% (182/1752) of patients in the omega-3 group versus 8.8% (149/1701) of patients in the control group, **RR: 1.21 [0.96; 1.52] NS**.

9.1.3 Retrospective cohort studies

Poole 2013 observational study:[2]
The aim of this study was to evaluate the impact of the administration of omega-3 in combination with the conventional treatment in post-MI patients in terms of mortality from all causes (primary endpoint).
This was an exposed/non-exposed type of retrospective cohort study, in which each patient exposed to omega-3 was matched[10] to 4 non-exposed patients. This follow-up was carried out on the basis of GPRD data (general practice research database), a database electronically gathering together, in collaboration with the MHRA, treatment information from generalist physicians across the United Kingdom.

[10] Matching criteria: sex, year of birth (± 2 years, year of first MI, smoking, type 2 diabetes, GP, post-MI follow-up period > time between MI and institution of omega-3 for each corresponding exposed patient

Inclusion criteria: patients with a history of recent MI (dating back no more than 180 days).
Exposed patients were treated with 1 g of omega-3[11] and the analysis was confined to patients in whom treatment was instituted within 90 days following the MI, resulting in the exclusion of almost 20% of the eligible population.

On inclusion, treatment with statins, antihypertensives and platelet aggregation inhibitors was more frequently prescribed in patients exposed to omega-3 than in non-exposed patients. These factors in particular were taken into account as covariables in the survival analysis carried out using Cox's model with time-dependent variables.

Results: This study compared 2466 patients exposed to omega-3 with a control group of 9712 non-exposed patients.

In total, 1517 deaths were observed (12.5% of patients): 243/2466 exposed versus 1274/9712 non-exposed. The mortality rates were 36.4/1000 patient-years in the exposed group and 51.1 in the non-exposed group. i.e. a reduction in the adjusted relative risk of death of 0.782 [0.641; 0.995], p = 0.0159.

Macchia 2013 observational study:[3]
The aim of this study was to evaluate the impact of the administration of combined treatments (statins + omega-3) versus statins alone in post-MI patients in terms of major cardiovascular events (mortality, recurrence of MI, atrial fibrillation, heart failure, stroke).
This cohort follow-up included patients after hospitalisation in an Italian hospital for a first MI between January and December 2003 and treated with omega-3 in the 30 days following the MI.
On inclusion, the treated groups were not comparable; in the "combined treatment" group, patients were significantly younger and had fewer cardiovascular antecedents and comorbidities than patients in the group taking only statins. In addition, the proportion of patients treated with aspirin, beta-blockers and ACE inhibitors was higher. These factors in particular were taken into account as covariables in the survival analysis carried out using Cox's model with time-dependent variables.

In total, 11,532 patients were followed up for 4 years: 7230 treated with statins alone and 4302 treated with statins and omega-3.

After 4 years of follow-up, 1591 events were observed with a mortality rate of 3.5/100 patient-years: 4.5/100 patients in the group treated with statins alone and 2/100 patients in the group treated with statins + omega-3 (difference of -2.5/1000 [-2.2; -2.9] p < 0.001), adjusted HR 0.59 [0.52; 0.66], p < 0.001.
A significant difference was also observed, after adjustment, favouring the combined treatment in terms of death or atrial fibrillation, death or heart failure, death or stroke, but not in terms of death or MI.

9.1.4 EOLE post-inclusion study

An exposed/non-exposed type of observational cohort study was performed among private and hospital cardiologists, which over two periods (EOLE 1 and EOLE 2) was to include around 5000 patients with recent MI (≤ 3 months). All included patients were followed up for a period of 6 years, with 6 evaluation times (6 months, 24 months, 3, 4, 5 and 6 years).

The aims of this study were to evaluate the real-life impact of OMACOR on mortality from all causes and on cardiovascular morbidity and mortality in secondary MI prevention, and to

[11] In the form of a medicinal product approved by the United Kingdom health authorities.

ascertain that OMACOR was not leading to any decreased use of concomitant pharmacological treatments or adherence to hygiene and dietary rules.

- **Morbidity and mortality at 3.5 years according to omega-3 exposure**

Morbidity and mortality analyses at 3.5 years relate to the entire population included in EOLE (EOLE1 + EOLE2, n = 5538 patients).

The primary efficacy endpoint (death from all causes) and the secondary morbidity and mortality endpoints were analysed using survival-analysis methods (Cox's models). Three analyses were performed for each endpoint and each treatment:

- without any adjustment (crude analysis),
- after adjusting the score for propensity to exposure to a given treatment, exposure to the other secondary prevention treatments recommended on inclusion and cardiovascular risk factors;
- after pairing off exposed and non-exposed patients according to: age (± 1 year), score for propensity to exposure to a given treatment (± 0.1), exposure to each of the other recommended secondary prevention treatments (omega-3 included).

- Description of included patients according to their exposure or otherwise to omega-3

Patients exposed to omega-3 were on average younger than non-exposed patients (59.2 vs 62.7 years) and more often they were men (81.8% versus 76.8%).
Patients exposed to omega-3 presented overall fewer cardiovascular risk factors than non-exposed patients (diabetes, history of AHT).
The recommended quadruple therapy was more frequently prescribed in patients exposed to omega-3 than patients not exposed to omega-3 (82.1% vs 70.9%).
These differences disappeared after adjustment for the score for propensity to exposure to omega-3.

- Results for mortality at 3.5 years

Vital status ascertainment was carried out by means of the INSEE/INSERM procedure laid down by decree (No. 98-37, January 1998). Individual causes of death were retrieved from the study doctors and validated by an Events Validation Committee.

In all, 421 deaths occurred during the follow-up: 107 coronary deaths, including 58 sudden deaths (25.4%), 36 non-coronary CV deaths (8.6%), 132 deaths from other causes (31.4%), 146 deaths from undetermined causes (34.7%).
Mortality rates at 3.5 years were 7.8% [7.1% - 8.5%], incidence of 23.8% patient-years.

Crude and adjusted analyses relate to all the included patients.[12] For the matching analysis, 823 patients exposed to omega-3 of the initial 867 (94.9%) were paired with non-exposed patients (1 exposed patient paired with a maximum of 3 non-exposed patients).
As the cause of death could not be established for a third of the deaths at the time of the analysis (undetermined cause validated by COVE for 19% and investigation in progress for 15.7%), the incidences of coronary and cardiovascular deaths are underestimates.

Exposure to omega-3	**Adjusted analysis population**		**Matching analysis population**		**Crude HR [95% CI]**	**Adjusted HR [95% CI]**	**Matching HR [95% CI]**
	Evt	**Total**	**Evt**	**Total**			
Mortality from all causes							
- Non-exposed	383	4668	122	2161	1	**1**	**1**
- Exposed	38	867	36	823	0.53 [0.38; 0.74]	**0.82 [0.58; 1.16]**	**0.80 [0.54; 1.16]**
Coronary mortality							

[12] **apart from the 3 patients corresponding to the areas not covered between the 2 groups in the distribution of the scores for propensity for the adjusted analyses**

- Non-exposed	95	4668	32	2161	1	**1**	**1**
- Exposed	12	867	12	823	0.67 [0.37; 1.22]	**1.06 [0.56; 2.00]**	**0.94 [0.48; 1.85]**
CV mortality							
- Non-exposed	124	4668	40	2161	1	**1**	**1**
- Exposed	18	867	18	823	0.77 [0.47; 1.27]	**1.30 [0.77; 2.19]**	**1.14 [0.65; 2.00]**

The results of survival analyses at 3.5 years do not reveal any significant decrease in coronary and cardiovascular mortality or mortality from all causes in patients exposed to omega-3 in comparison to non-exposed patients.

- Coronary and CV morbidity and mortality results at 3.5 years

Gathering morbidity information relies only on following-up patients with the aid of annual self-questionnaires and resuming monitoring in the case of non-responder patients (the patient information source is solely for detecting events that are later documented).
As the patient attrition rate in relation to coronary and cardiovascular morbidity and mortality analyses is high (respectively 36% and 42% at 3.5 years) and in the absence of data that would enable the follow-up durations in each exposure group to be documented, the results of these analyses are not given in detail.

- **Continued prescription of secondary prevention treatments and changes to hygiene and dietary rules at 24 months**

This analysis relates to 64.1% of patients included in the EOLE 1 study (n = 2188 patients) for whom data from the medical inclusion questionnaire, the inclusion self-questionnaire and the patient self-questionnaire after 24 months of follow-up were available.

Exposure to recommended secondary prevention treatments on inclusion was defined as any treatment prescribed by the cardiologist or declared by the patient in a concomitant period of ± 31 days relative to the inclusion consultation date. Exposure to recommended secondary prevention treatments at 24 months is defined as any treatment declared by the patient at 24 months.

A total of 13.3% of patients included in the study were exposed to omega-3 on inclusion (99.7% of whom were treated with OMACOR).
The proportion of patients exposed to the recommended secondary prevention quadruple therapy excluding omega-3 (BASI) was higher among patients exposed to omega-3 (78.8%) than among patients without omega-3 (70.8%) (p = 0.005). Exposure on inclusion was similar in both exposure groups for beta-blockers (89.0%), aspirin (or other platelet aggregation inhibitors) (99.4%) and statins (or other lipid-lowering agents) (96.9%).

The proportion of patients exposed to BASI treatments remained high at 24 months (63.4%).
Persistence of exposure to BASI treatments between inclusion and 24 months remains high, irrespective of whether or not patients are exposed to omega-3s on inclusion (78.3% of patients exposed to omega-3s and 79.1% non-exposed).
On the other hand, almost one-third of patients treated initially with omega-3s are no longer on omega-3s at 24 months.

In order to give an overview of the information concerning how well subjects complied with hygiene and dietary rules, a mean score for compliance with the rules for “healthy” hygiene and diet was built up from variables at 24 months relating to changes in food consumption, smoking and exercise. The score for complying with the rules for “healthy” hygiene and diet ranged from -1 (non-compliance with the rules) to +1 (full compliance).
This score was a median of 0.38 for patients exposed to omega-3s and 0.33 for non-exposed patients, with no significant difference (no data available for 20% of the patients).

- **Conclusion**

Interim analysis of the EOLE 1 study shows that persistence at 24 months of follow-up of recommended secondary prevention treatments (without omega-3) remains high, whether

patients were exposed to omega-3s on inclusion or not. On the other hand, almost one-third of patients treated initially with omega-3s are no longer on omega-3s at 24 months.
The overall change in the rules on hygiene and diet at 24 months showed no difference between patients exposed to omega-3s and those not exposed.
These results, however, relate to only 61.4% of patients in the EOLE1 study, patients for whom data from the medical questionnaire on inclusion, the patient's self-questionnaire on inclusion and the self-questionnaire at 24 months of follow-up were available. Comparison of patients both analysed and not analysed on the entirety of their characteristics on inclusion (200 variables) revealed a dozen or so statistically significant differences. These differences were not systematic and did not exceed 10% for most of the parameters.
The results of the survival analyses (adjusted analyses and matching analyses) at 3.5 years did not show any significant fall in mortality from all causes (adjusted HR analysis: 0.82 [0.58; 1.16], matching HR analysis: 0.80 [0.54; 1.16]), coronaries (adjusted HR analysis: 1.06 [0.56; 2.00], matching HR analysis: 0.94 [0.48; 1.85]) and cardiovascular (adjusted HR analysis: 1.30 [0.77; 2.19], matching HR analysis: 1.14 [0.65; 2.00]) in patients exposed to omega-3s compared to non-exposed patients.
This is an interim analysis at 3.5 years; the final results are expected at 6 years.

9.1.5 Other data from the literature search

A French randomised clinical study conducted in 2501 patients (Galan 2010[13]) was identified.
The aim of this study was to evaluate the benefits of vitamin B or omega-3 supplements in terms of preventing major cardiovascular events in patients with a history of acute coronary syndrome or ischaemic stroke.

Method: Randomised, double-blind, comparative study of vitamin B alone, omega-3 alone, versus a combination of the two versus placebo in combination with the recommended standard treatments, conducted in 2501 patients with a history of acute coronary syndrome or ischaemic stroke, treated for a median 4.7 years.

Inclusion criteria: Patients aged 45 to 80 years with a history of acute coronary syndrome or ischaemic stroke in the 12 months prior to inclusion.

Treatments:
Omega-3, n = 633
Vitamin B, n = 622,
Omega-3 + vitamin B, n = 620,
Placebo, n = 626.

Primary efficacy endpoint: First major cardiovascular event (non-fatal MI, ischaemic stroke, cardiovascular death*).
** including fatal MI, fatal stroke, sudden death, aortic dissection, heart failure or any other fatal event defined as being of cardiovascular origin by the Events Adjudication Committee).*

RESULTS: The patients' characteristics on inclusion were comparable.

After a median follow-up of 4.7 years, no significant difference was observed between patients receiving omega-3 supplements and patients not receiving any omega supplementation in terms of the onset of at least one major cardiovascular event (non-fatal MI, ischaemic stroke, cardiovascular death): 6.5% (81/1253) of patients treated with omega-3s versus 6.1% (76/1248) of patients without omega-3s, **HR: 1.08 [0.79; 1.47] NS**.

[13] Galan P et al. Effects of B vitamins and omega-3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. BMJ 2010; 341: c6273

9.1.6 Summary of previous opinions of the Committee

Opinion of 21/10/2009 (renewal of inclusion): New data

"Verboom 2006 study[14]

In 2006, Verboom et al. published a critical analysis of the results of the GISSI-Prevenzione study.

The authors concluded that the improvement in post-MI patient overall survival observed in the GISSI-Prevenzione study was correlated with the significant reduction in sudden deaths under omega-3s combined with conventional therapies in comparison with the control arm.

GISSI-HF 2008 study:

The GISSI-HF 2008 study {Tavazzi, 2008}[15] compared the effect of the administration of omega-3s (1 g/day) (n = 3494) versus placebo (n = 3481) on mortality from all causes and hospitalisation in 6975 heart failure patients followed up for 3.9 years and treated with rosuvastatin 10 mg (rosuvastatin + omega-3 versus rosuvastatin + placebo).

As OMACOR did not have a validated indication in heart failure, the results of this study will not be elaborated upon in this opinion."

Opinion of 24/04/2002 (inclusion): GISSI-Prevenzione study

"Methodology: Multicentre, open-label, randomised, 4-arm, comparative study (omega-3 1 g/day, vitamin E 300 mg/day, omega-3 1 g/day + vitamin E and a control group) carried out in 11,324 patients having had a myocardial infarction (MI) in the previous 3 months, followed up for 3.5 years. These treatments were administered in combination with conventional post-MI treatments (platelet aggregation inhibitors, ACE inhibitors, beta-blockers and hypolipidaemic agents).

Endpoints: Intention-to-treat analysis

- combined endpoint 1: mortality from all causes combined, non-fatal MI and non-fatal stroke
- combined endpoint 2: cardiovascular mortality, non-fatal MI and non-fatal stroke.

Results:

Frequency of events / Reduction in relative risk versus the control group:

	OMACOR (omega-3 1 g/day) n = 2836	OMACOR + vitamin E n = 2830	Vitamin E n = 2830	Control n = 2828
Endpoint 1: n (%)	356 (12.3%)	359 (12.7%)	371 (13.1%)	414 (14.6%)
Reduction in RR	**15% [2-26]**	14% [1- 26]	11% [-3 – 23]	
Endpoint 2: n (%)	262 (9.2%)	285 (10.1%)	286 (10.1%)	322 (11.4%)
Reduction in RR	**20% (5 – 32)**	12% (-3 – 25)	12% (-4 – 25)	

Conclusion: A significant decrease in cardiovascular events was observed with OMACOR 1 g/day in comparison with the control arm: reduction in RR of 15% [2; 26] or 20% [5; 32] according to the criterion used."

[14] Verboom CN, Critical Analysis of GISSI-Prevenzione Trial. Highly purified omega-3 polyunsaturated fatty acids are effective as adjunct therapy for secondary prevention of myocardial infarction. Herz 2006; 31 Suppl 3: 49-59.

[15] Tavazzi L *et al.* Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008; 372(9645): 1223-30.

09.2 Adverse effects

9.2.1 PSUR data

Analysis of the latest PSUR (5) covering the period from 23 July 2009 to 22 January 2011 shows the estimated number of exposed patients to be 747,029, corresponding to one notification per 93,379 treatments sold.

An analysis of the notifications observed in France was carried out by the applicant for the period from 01 April 2009 to 31 July 2012. During this period, 15 spontaneous notifications for 24 adverse effects were received, including 4 unexpected serious effects (extrasystole, increased gamma-GT, duodenal ulcer, ulceration of the cutaneous mucosa at the injection site).

These observations did not lead to the safety profile of OMACOR being changed and the sections of the SPC dealing with safety of use have not been altered.

9.2.2 SPC data

According to the SPC, the most commonly observed adverse effects are dyspepsia and nausea.

09.3 Usage data

According to IMS-EPPM data (moving annual total for the summer of 2013), OMACOR was prescribed 324,728 times. The mean dosage of 1 or 2 tablets a day is in accordance with the SPC. OMACOR is most often prescribed in ischaemic heart disease (55% of prescriptions) with 12% of prescriptions in recent or old MI and in lipid anomalies, non-refundable indication (18% of prescriptions).

09.4 Summary & discussion

Data filed by the applicant in order to determine the value of OMACOR as adjunctive treatment in the secondary prevention of myocardial infarction, in combination with standard treatments, are based on six meta-analyses published between 2008 and 2012, a randomised clinical study, the OMEGA study and the initial GISSI-Prevenzione study.

Main efficacy results

The GISSI-Prevenzione study, published in 1999, showed the benefit of secondary prevention against myocardial infarction with OMACOR as adjunctive treatment in combination with standard treatments (platelet aggregation inhibitors, ACE inhibitors, beta-blockers and hypolipidaemic agents). However, on inclusion in this study, the percentages of patients treated with the recommended secondary prevention medicines were very small relative to current practice (statin 4.7%, beta-blocker 44.3%, ACE inhibitor 46.9%), though this study was performed in 1999, when the approach to the management of post-infarction patients was very different from that used at the present time. It is therefore not at all applicable to current actual practice.

Several recent randomised clinical trials did not show OMACOR to be effective in preventing major cardiovascular events:

- In the OMEGA study – a French, randomised, controlled, blinded study in 3804 patients who had recently (3-14 days previously) suffered MI – no difference was observed between OMACOR and placebo as regards the occurrence of sudden death at 12 months (RR: 0.95 [0.56; 1.6]), of a first major cardiovascular event (RR: 1.21 [0.96; 1.52]) and mortality from all causes (RR: 1.25 [0.90; 1.72]).

- In the Galan 2010 study – a German, randomised, controlled, blinded study with a median follow-up of 4.7 years in 2501 patients with ACS or ischaemic stroke not more than 12 months previously – no difference was observed between patients treated with OMACOR and patients not receiving OMACOR in terms of onset of a major cardiovascular event (non-fatal MI, ischaemic stroke, death from cardiovascular causes): 81 events versus 76, HR 1.08 [0.79; 1.47], NS.

Meta-analyses published between 2008 and 2012 are conflicting.
Indeed, two meta-analyses concluded that omega-3s were beneficial as adjunctive treatment when combined with standard treatment, compared with their use on their own.

- the meta-analysis by Chen 2011 (10 RCTs included, n = 33,429) concluded that there was a significant effect in terms of sudden death (RR 0.85 [0.76; 0.95]) taking the study population as a whole. This effect is no longer significant when one compares the addition of omega-3s in patients treated in accordance with current guidelines.
- the meta-analysis by Delgado-Lista 2012 (21 RCTs included, n = 45,285) concluded that there was a significant effect in terms of cardiovascular events[16] (OR 0.90 [0.85; 0.96], p = 0.001) in a heterogeneous patient population.

The four other meta-analyses concluded that the combination of omega-3s with standard treatments did not offer any advantage over the standard treatment alone in terms of cardiovascular events and/or mortality:

- Rizos 2012 (20 RCTs included, n = 68,680): total mortality: RR 0.96 [0.91; 1.02], CV deaths: RR 0.91 [0.85; 0.98], sudden death: RR 0.87 [0.75; 1.01], non-fatal MI: RR 0.89 [0.76; 1.04] and stroke: RR 1.05 [0.93; 1.18].
- Kwak 2012 (14 RCTs included, n = 20,485): cardiovascular events:[17] RR 0.99 [0.89; 1.09].
- Filion 2010 (29 RCTs included, n = 34 501): total mortality: RR 0.88 [0.64; 1.03], restenosis: RR 0.89 [0.72; 1.05],
- Leon 2008 (12 RCTs included): arrhythmia: OR 0.90 [0.55; 1.46], sudden death: RR 0.81 [0.52; 1.25].

Interpretation of the results of the meta-analyses is made difficult by the heterogeneity of the populations included in the studies (patients with an implantable automatic defibrillator, primary or secondary prevention), of the form and the dose of omega-3s received and the duration of the studies.

Observational retrospective studies seem to show that the addition of omega-3s to standard treatments has a significant effect in terms of mortality and of impact on certain cardiovascular events:

- in the Poole study, mortality rates fell in patients exposed to omega-3s combined with conventional treatments compared with non-exposed patients: RR 0.782 [0.641; 0.995], p= 0.0159;
- in the Macchia study: mortality rates fell in patients exposed to omega-3s combined with conventional treatments in comparison with patients not exposed to omega-3s: adjusted HR 0.59 [0.52; 0.66], p < 0.001. A significant difference was also observed, after adjustment, in favour of the combined treatment in terms of death or atrial fibrillation, death or heart failure, death or stroke, but not in terms of death or MI.

The results of these studies have not been confirmed in recent randomised clinical studies (OMEGA, Galan, etc.).

In the EOLE study, the interim results of the post-inclusion EOLE study at 3.5 years do not show any significant decrease in mortality from all coronary and cardiovascular causes in patients exposed to omega-3s in comparison with non-exposed patients.

[16] Combined criterion including: stroke, coronary events, MI, angina, disorder of the lower limbs, CV death
[17] angina, sudden death, CV death, HF, TIA, stroke, MI (whether fatal or not), peripheral vascular disease, CV interventions

Main safety results

These observations taken from the analysis in the latest PSUR (5) covering the period from 23 July 2009 to 22 January 2011 did not lead to the safety profile of OMACOR being changed and the sections of the SPC dealing with safety of use have not been altered.

According to the SPC, the most commonly observed adverse effects are dyspepsia and nausea.

09.5 Planned studies

The applicant has not mentioned any other studies that might be in progress or to come apart from the EOLE study.

010 THERAPEUTIC USE[18,19,20]

Patients with a history of MI are at high risk of recurrence (8 to 10% at one year) or premature death.

Secondary MI prevention is based on comprehensive management, combining:

- Hygiene and dietary measures (smoking cessation, physical exercise and diet when the BMI is ≥ 30 kg/m^2 and the abdominal circumference exceeds 102/88 cm (men/women)),
- Management of associated risk factors (Diabetes: HbA1c < 6.5%, AHT: BP < 140/90 mmHg, dyslipidaemia: LDL-C < 1 g/l)

Pharmacological treatments:

For secondary prevention of MI, it is recommended to combine:

- a platelet aggregation inhibitor (acetylsalicylic acid 75 to 100 mg/day or clopidogrel 75 mg/day),
- a beta-blocker, regardless of the blood pressure level or left-ventricular function,
- an angiotensin converting enzyme inhibitor (or an angiotensin receptor antagonist in cases of ACE-inhibitor intolerance),
- a statin.

In the majority of patients receiving treatment as secondary prevention of myocardial infarction, therapeutic needs are theoretically covered by the use of a combination of these four therapeutic classes of secondary prevention that have proved beneficial with respect to morbidity and mortality.

According to the ESC guidelines, omega-3 supplements may only be considered in the event of the failure of statins in a context of associated elevation of triglycerides.

According to the AHA/ACC, omega-3s of dietary origin (fish) or in capsule form (1 g per day) may be suggested as adjunctive treatment.

[18] ESC Guidelines 2008. Acute myocardial infarction in patients presenting with ST-segment elevation.
[19] ACC/AHA 2007. Guidelines for the management of patients with unstable angina/non ST-Elevation myocardial infarction.
[20] ESC guidelines 2012. European guidelines on cardiovascular disease prevention in clinical practice. Eur HJ 2012; 33: 1635-701.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

◗ Events (death or cardiovascular events) that occur after a myocardial infarction are serious and potentially life-threatening.

◗ *This medicinal product is intended as a preventive therapy.*

◗ Where secondary prevention of myocardial infarction is concerned, therapeutic needs are theoretically covered by the use of standard treatments (statins, platelet aggregation inhibitors, beta-blockers, ACE inhibitors or sartans) which have proved to be beneficial in terms of morbidity and mortality.
The GISSI-Prevenzione study had initially shown OMACOR to be beneficial in terms of morbidity and mortality when used as adjunctive treatment for secondary prevention of myocardial infarction, in combination with the standard treatments used in this study (statins, platelet aggregation inhibitors, beta-blockers and ACE inhibitors). This old open-label study from 1998 was based on less than optimal treatment strategies, with in particular only 4.7% of the patients treated with a cholesterol-lowering agent on inclusion and 28.6% at 6 months.
The results of recent studies using a rigorous methodology (randomised clinical studies, meta-analyses), with large patient numbers, have not shown OMACOR to be particularly effective in secondary prevention, in terms of any of the primary or secondary endpoints or in any of the predefined subgroups, in patients treated in accordance with the current guidelines (optimal management).
Thus, within the framework of the optimal management of secondary prevention of myocardial infarction, including, in particular, statins in combination with platelet aggregation inhibitors, beta-blockers, calcium inhibitors, sartans, conversion enzyme inhibitors, the benefits of omega-3s in the management of coronary patients cannot be clearly established.

The efficacy/adverse effects ratio of OMACOR cannot be established.

◗ OMACOR is an adjunctive treatment.

◗ A non-pharmacological alternative does exist (food supplement, food intake).

◗ Public health benefit:
Ischaemic heart disease is a major public health burden.
Improving secondary prevention of MI continues to constitute a public health need which is an established priority (GTNDO priority).
The impact of OMACOR on the secondary prevention of infarction in the occurrence of mortality from all causes was shown in the GISSI-Prevenzione study, an open-label randomised study involving patients included between 1993 and 1995.
Given the considerable expansion in therapeutic management by way of secondary prevention of myocardial infarction, in particular in terms of the percentage of patients treated with statins and in the absence of any demonstrable efficacy of omega-3s under current management conditions, OMACOR is not expected to offer any impact in terms of morbidity or mortality.
Moreover, the EOLE observational study showed that almost one-third of patients had stopped taking OMACOR at 24 months.
Consequently, in the current state of knowledge, it is not expected that OMACOR will benefit public health.

Taking account of these points, the Committee considers that the actual benefit provided by OMACOR in the indication "Adjunctive treatment in secondary prevention of myocardial infarction, in addition to standard therapy," is insufficient to justify reimbursement by National Health Insurance.

The Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use in the stated indication.

Reminder: The actual benefit in the indication "Endogenous hypertriglyceridaemia as a supplement to diet, when dietary measures alone are insufficient to produce an adequate response" remains insufficient.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ **Packaging:** Not appropriate for the prescription conditions. The Committee points out that, in accordance with its deliberations of 20 July 2005, it recommends the harmonisation of pack sizes for treatments lasting one month to the equivalent of 30 days of treatment.