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EMA/303982/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report following the re-examination procedure

Referral under Article 31 of Directive 2001/83/EC

Omega-3 acid ethyl esters – containing medicinal products for oral use in secondary prevention after myocardial infarction

Procedure number: EMEA/H/A-31/1464

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Information on the procedure

Medicinal products containing omega-3 acid ethyl esters have been approved in the majority of the European Union Member States for secondary prevention after myocardial infarction (MI) and in the treatment of hypertriglyceridaemia.

The original approval of Omacor (EU reference medicinal product) was based on an open-label study (GISSI-P) from 1999. In this study, there was a relative risk reduction for one of the two primary MACE endpoint (death, non-fatal MI and non-fatal stroke) of 10% with a rather poor precision (upper CI 0.99), whereas for the other primary endpoint including cardiovascular (CV), instead of all-cause death, statistical significance was not achieved. However, later studies, including meta-analyses[1][2][3] have failed to show a beneficial effect in this condition. The Swedish national competent authority considered that in light of recent clinical trials, the clinical benefit of omega-3 acid ethyl esters containing products in prevention after MI should be re-evaluated.

On 15 March 2018 the Swedish national competent authority therefore triggered a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Omega-3 acid ethyl esters containing medicinal products for oral use in secondary prevention after myocardial infarction and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Omega-3 acid ethyl esters are an ethyl ester of long-chain polyunsaturated fatty acids with an eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) content of no less than 85% and an EPA to DHA ratio of 0.9 to 1.5. These products contain 18 to 22 carbon atoms and a varying number of double bonds, the first of which is in the n-3 position. Therefore omega-3 fatty acids are also termed n-3 polyunsaturated fatty acids (n-3 PUFA). They are essential fatty acids and must be obtained from the diet.

The therapeutic effect of omega-3 fatty acids has been attributed to their possible involvement on eicosanoid balance, lipid metabolism, and cell membranes. They also inhibit very-low-density lipoprotein (VLDL) synthesis in the liver, which reduces triglyceride concentrations.

2.2. Data on efficacy

The marketing authorisation holders (MAHs) were requested to provide scientific evidence related to the therapeutic efficacy of omega-3-acid ethyl esters containing medicinal products for oral use in secondary prevention after myocardial infarction in adults. These data consists of prospective randomised clinical trials, meta-analysis, retrospective cohort studies, other observational studies and references to guidance documents. An overview of the main clinical trials is presented below.

[1] Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA. 2012;308(10):1024-1033
[2] Kotwall et al. Omega 3 Fatty acids and Cardiovascular Outcomes Systematic and Meta-Analysis, Circ Cardiovasc Qual Outcomes 2012;5:808-818
[3] Kwak et al. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and decosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Arch Intern Med. 2012 May 12;172(9):686-694

Table 1 - Overview of key efficacy data – Clinical trials

Study ID and design / reference	Key objectives / endpoints	Population	Inclusion / exclusion criteria	Treatment	Main results
Secondary prevention after myocardial infarction in adults					
GISSI-P Multicentre, randomized, open-label	Co-primary endpoints: 1. Cumulative rate of all-cause death + non-fatal MI + non-fatal stroke. 2. Cumulative rate of CV death + non-fatal MI + non-fatal stroke.	11,324 patients with recent (≤3 months) myocardial infarction. No age limit.	Eligible patients: - No contraindications to the dietary supplements - No unfavourable short-term outlook (eg, overt congestive heart failure, cancers, etc.).	Omega-3-acid ethyl esters (1 g daily, n=2836); vitamin E (300 mg daily, n=2830); both (n=2830); or none (control, n=2828).	Two-way analysis (n-3 PUFA groups vs Control groups): 1. RR 0.90; 95%CI 0.82-0.99; p=0.048 2. RR 0.89; 95% CI 0.8-1.01, p=0.053
OMEGA Randomized, placebo-controlled, double-blind multicentre	Primary endpoint: Rate of sudden cardiac death in survivors after acute myocardial infarction. Secondary end points: total mortality, major adverse cerebrovascular and cardiovascular events.	3851 patients (female, 25.6%; mean age, 64.0 year) within 3 to 14 days after myocardial infarction.	Inclusion Criteria: Myocardial infarction 3-14 days before randomisation (STEMI and NSTEMI); ability to take Ω-3-FAE or olive oil without risk. Exclusion Criteria: Premenopausal women who are not surgically sterile, who are pregnant or nursing, who are of child-bearing potential and are not practising acceptable means of birth control; known hypersensitivity to study medication; dislike of fish oil; haemorrhagic diathesis; unwillingness to	1 gram of omega-3-acid ethyl esters or placebo	The event rates were (omega and control groups) as follows: sudden cardiac death, 1.5% and 1.5% (P=0.84); total mortality, 4.6% and 3.7% (P=0.18); major adverse cerebrovascular and cardiovascular events, 10.4% and 8.8% (P=0.1); and revascularization in survivors, 27.6% and 29.1% (P=0.34)

			discontinue other medications containing fish oil; history of drug or alcohol abuse within 6 months; any investigational therapy within one month of signing informed consent form.		
GISSI-HF Randomized, double-blind, placebo-controlled	Co-primary endpoints: 1. time to death 2. time to death or admission to hospital for cardiovascular reasons.	6,975 patients with chronic heart failure of New York Heart Association class II–IV, irrespective of cause and left ventricular ejection fraction.	Major exclusion criteria included specific indication or contraindication to n-3 PUFA; known hypersensitivity to study treatments; presence of any non-cardiac comorbidity (e.g., cancer) that was unlikely to be compatible with a sufficiently long follow-up; treatment with any investigational agent within 1 month before randomisation; acute coronary syndrome or revascularisation procedure within the preceding 1 month; planned cardiac surgery, expected to be done within 3 months after randomisation; significant liver disease; and pregnant or lactating women or women of childbearing potential who were not adequately protected against becoming pregnant.	Treatment with 1 g/day of n-3 fatty acids EPA and DHA (N=3494) or placebo (N=3481)	1. Unadjusted HR 0.93 (95.5% CI 0.852–1.021); p=0.124; Adjusted HR 0.91, 95.5% CI 0.83–0.99, p=0.041 2. Unadjusted HR 0·94 (99% CI 0·869–1·022); p=0·059 ; Adjusted HR 0·92, 99% CI 0·84–0·99], p=0·009
ORIGIN	Primary outcome:	12,536 patients	Eligibility criteria	Either Omega-3-	1. 9.1% vs.

Randomised, double-blind, placebo controlled	death from cardiovascular causes. Secondary outcomes: combined endpoint of cardiovascular death, myocardial infarction and stroke.	who were at high risk for cardiovascular events and had impaired fasting glucose, impaired glucose tolerance	were an age of at least 50 years; a diagnosis of diabetes with receipt of no more than one oral glucose-lowering drug, impaired glucose tolerance, or impaired fasting glucose; a history of myocardial infarction, stroke, or revascularization; angina with documented ischemia; a ratio of urinary albumin to creatinine of more than 30 mg per gram; left ventricular hypertrophy; 50% or more stenosis of a coronary, carotid, or lower-limb artery on angiography; or an ankle–brachial index of less than 0.9. Participants were excluded if they were unwilling to discontinue use of a non-study preparation of n–3 fatty acids, had a locally measured glycated haemoglobin level of 9% or more, had undergone coronary-artery bypass grafting within the previous 4 years with no intervening cardiovascular event, had severe heart failure, or had a cancer that might affect survival.	acid ethyl esters (1g/day) or placebo.	9.3%; HR 0.98; 95% CI 0.87 - 1.10; P = 0.72 2. 16.5% vs. 16.3%; HR, 1.01; 95% CI, 0.93- 1.10; P = 0.81

SU.FOL.OM3 Double blind, randomized, placebo controlled	Primary endpoint: Major cardiovascular events	2501 patients with a history of myocardial infarction, unstable angina, or ischaemic stroke	Men and women aged 45–80 years who had had an acute coronary or cerebral ischaemic event within the 12 months before randomisation were eligible to participate. Exclusion criteria included age (<45 years or >80 years), ill-defined diagnosis of cardiovascular disease, inability or unwillingness to comply with study treatment, and disease or treatment that might interfere with metabolism of homocysteine or omega 3 fatty acids, in particular methotrexate for treating cancer or rheumatoid arthritis and chronic renal failure (plasma creatinine concentration >200 µmol/l or creatinine clearance <40 ml/min).	Vitamin B, Omega 3 fatty acids, both or placebo	HR 1.08, 95%CI 0.79-1.47, P=0.64
Alpha Omega Multicenter, double-blind, placebo-controlled	The primary end point was the rate of major cardiovascular events, which comprised fatal and nonfatal cardiovascular events and the cardiac interventions PCI and CABG.	4837 patients, 60 through 80 years of age (78% men) who had a MI and were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy	N/A	One of four trial margarines: - a margarine supplemented with a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (with a targeted additional daily intake of 400 mg of EPA–	HR 1.01, 95%CI 0.87-1.17, P=0.93

				DHA), - a margarine supplemented with plant-derived alpha-linolenic acid (ALA) (with a targeted additional daily intake of 2 g of ALA), - a margarine supplemented with EPA–DHA and ALA, or - a placebo margarine.	
JELIS Prospective, randomized, open label, blinded endpoint evaluation	The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting.	18 645 patients Some but not all patients had coronary artery disease as defined as previous myocardial infarction, coronary interventions, or confirmed angina pectoris.	The key inclusion criterion was a total cholesterol level of a least 6·5 mmol/L with LDL of at least 4.4 mmol/L. Among the exclusion criteria were a myocardial infarction within the past 6 months, unstable angina pectoris, a history or complication of serious heart disease.	Patients were assigned to receive either 1800 mg of EPA daily (600 mg tid) with statin (EPA group; n=9326) or statin only (controls; n=9319)	HR 0.81, 95%CI 0.69-0.95, P=0.011
DOIT trial	The primary endpoints in the DOIT were changed in carotid intima–media thickness, circulating biomarkers, and peripheral pulse wave propagation.	563 Norwegian men, 64-76-year old and 72% without overt cardiovascular disease.	Inclusion Criteria: Elderly men with long standing hypercholesterolemia (cholesterol > 6.45 mmol/L and < 8.00 mmol/L) with or without coronary heart disease. Exclusion Criteria: Cholesterol > 8.00 mmol/L, blood pressure > 170/100; uncontrolled hypertension;	Four groups: - controls (no dietary counseling and placebo, n=142), - diet only (dietary counseling and placebo, n=139), - n-3 PUFA only (no dietary counseling and n-3 PUFA supplementation	The unadjusted hazard ratios of all-cause mortality and cardiovascular events were 0.57 (95% confidence interval: 0.29-1.10) and 0.86 (0.57-1.38), respectively

			socially or otherwise unsuitable subjects; anticipated non-compliance; other major non cardiac illness expected to reduce life expectancy or interfere with study participation.	, n=140), and combined (dietary counseling and n-3 PUFA supplementation , n=142	
Risk and Prevention trial Randomized, double-blind, placebo-controlled	Composite of death or hospitalization from cardiovascular cause.	12,505 patients at high risk for a cardiovascular event but without a history of myocardial infarction	Inclusion Criteria Multiple risk factors: diabetes, age => 65 years, male sex, hypertension, hypercholesterolemia, smoking, obesity, family history of premature cardiovascular disease; Previous manifestations of atherosclerotic disease Exclusion Criteria Contraindications or indications for the treatment with n-3 PUFA, serious comorbidity with an unfavourable prognosis over the short term, expected non-compliance over a long period of time, pregnancy	1 g/day of omega-3 fatty acids versus olive oil placebo	Adjusted HR= 0.97; 95% [CI], 0.88 to 1.08; P = 0.58
AREDS-2 Multicenter, randomized, double-blinded, placebo-controlled phase 3 study	The primary end point was a composite of time to the first event: CVD mortality and CVD morbidity.	4203 participants aged 50 to 85 years at risk for progression to advanced age-related macular degeneration (AMD). Approximately	Enrolment was restricted to people determined to be at high risk of progression to advanced AMD with either bilateral large drusen or non-foveal geographic atrophy (no advanced AMD) or large drusen or	Patients were treated with daily supplementation with long-chain ω-3 polyunsaturated fatty acids, macular xanthophylls, combination of	Unadjusted HR, 0.95; 95% CI, 0.78-1.17

		19% had a history of CVD; 44% reported taking a statin medication; and 14% reported taking any type of medication for congestive heart failure, CVD, or cerebrovascular disease.	non-foveal geographic atrophy in one eye and advanced AMD in the fellow eye (AREDS Simple Scale Score of 2, 3 or 4).	the two, or matching placebos.	
ASCEND study Randomized 2x2 Factorial Phase 4 Study	Primary outcome: serious vascular event Secondary outcome: Serious vascular event or any arterial revascularizatio n	15,480 patients with diabetes but without evidence of atherosclerotic cardiovascular disease	Inclusion Criteria: Males or females with type 1 or type 2 diabetes mellitus; aged ≥ 40 years; no previous history of vascular disease; no clear contra-indication to aspirin; no other predominant life-threatening medical problem. Exclusion Criteria: definite history of myocardial infarction, stroke or arterial revascularisation procedure; currently prescribed aspirin, warfarin or any other blood thinning medication	1g capsules containing either n−3 fatty acids (fatty acid group) or matching placebo (olive oil) daily	Primary outcome: rate ratio, 0.97; 95% CI, 0.87 to 1.08; p=0.55 Secondary outcome: rate ratio, 1.00; 95% CI, 0.91 to 1.09
VITAL trial Randomized , placebo-controlled trial, with a two-by-two factorial design	Primary endpoint: MACE and invasive cancer of any type	25,871 participants Men 50 years of age or older and women 55 years of age or older in the United States	Inclusion criteria: men aged 50 or older or women aged 55 or older; no history of cancer (except non-melanoma skin cancer), heart attack, stroke, transient ischemic attack, angina	Eligible participants were assigned to one of four groups: (1) daily vitamin D and omega-3; (2) daily vitamin D and omega-3 placebo; (3) daily vitamin D	Hazard ratio, 0.92; 95% confidence interval [CI], 0.80 to 1.06; p = 0.24

			pectoris, CABG, or PCI. Exclusion criteria: history of renal failure or dialysis, hypercalcemia, hypo- or hyperparathyroidism, severe liver disease (cirrhosis), or sarcoidosis or other granulomatous diseases such as active chronic tuberculosis or Wegener's granulomatosis; allergy to fish or soy; serious illness that would preclude participation; be consuming no more than 800 IU of vitamin D; be consuming no more than 1200 mg/d; not be taking fish oil supplements	placebo and omega-3; or (4) daily vitamin D placebo and omega-3 placebo	

2.2.1. Prospective randomized clinical trials

GISSI-P study (GISSI-Prevenzione Investigators, 1999)

The original approval of omega-3 acid ethyl esters in secondary cardiovascular disease prevention was based on the GISSI Prevenzione study (GISSI-P).

Overall, the treatment effect was modest for the co-primary endpoints: 12.6% in n-3 PUFA group vs. 13.9% in the control group had a Major Adverse Cardiac Event (MACE) (death, non-fatal MI, and non-fatal stroke: RR 0.90; 95%CI 0.82-0.99). For the second co-primary endpoint including CV death instead of all-cause death, the upper CI was just above 1 (9.7% vs. 10.8%, RR 0.89; 95% CI 0.80 – 1.01). In a secondary two-way analyses of fatal events, a reduction of sudden death events was seen (RR 0.74; 0.58-0.93). An effect on sudden death was seen after only 4 months of treatment which lead to a hypothesis of an antiarrhythmic effect.

Figure 1 – Overall efficacy profile of n-3 PUFA treatment

	All (n=11 324)	Two-way analysis			Four-way analysis		
		n-3 PUFA (n=5666)	Control (n=5668)	Relative risk (95% CI)	n-3 PUFA (n=2836)	Control (n=2828)	Relative risk (95% CI)
Main endpoints							
Death, non-fatal MI, and non-fatal stroke	1500 (13·3%)	715 (12·6%)	785 (13·9%)	0·90 (0·82–0·99)	356 (12·3%)	414 (14·6%)	0·85 (0·74–0·98)
Cardiovascular death, non-fatal MI, and non-fatal stroke	1155 (10·2%)	547 (9·7%)	608 (10·8%)	0·89 (0·80–1·01)	262 (9·2%)	322 (11·4%)	0·80 (0·68–0·95)
Secondary analyses							
All fatal events	1017 (9·0%)	472 (8·3%)	545 (9·6%)	0·86 (0·76–0·97)	236 (8·3%)	293 (10·4%)	0·80 (0·67–0·94)
Cardiovascular deaths	639 (5·6%)	291 (5·1%)	348 (6·2%)	0·83 (0·71–0·97)	136 (4·8%)	193 (6·8%)	0·70 (0·56–0·87)
Cardiac death	520 (4·6%)	228 (4·0%)	292 (5·2%)	0·78 (0·65–0·92)	108 (3·8%)	165 (5·8%)	0·65 (0·51–0·82)
Coronary death	479 (4·2%)	214 (3·8%)	265 (4·7%)	0·80 (0·67–0·96)	100 (3·5%)	151 (5·3%)	0·65 (0·51–0·84)
Sudden death	286 (2·5%)	122 (2·2%)	164 (2·9%)	0·74 (0·58–0·93)	55 (1·9%)	99 (3·5%)	0·55 (0·40–0·76)
Other deaths	378 (3·3%)	181 (3·2%)	197 (3·5%)	0·91 (0·74–1·11)	100 (3·5%)	100 (3·5%)	0·99 (0·75–1·30)
Non-fatal cardiovascular events	578 (5·1%)	287 (5·1%)	291 (5·1%)	0·98 (0·83–1·15)	140 (4·9%)	144 (5·1%)	0·96 (0·76–1·21)
Other analyses							
CHD death and non-fatal MI	909 (8·0%)	424 (7·5%)	485 (8·6%)	0·87 (0·76–0·99)	196 (6·9%)	259 (9·2%)	0·75 (0·62–0·90)
Fatal and non-fatal stroke	178 (1·6%)	98 (1·7%)	80 (1·4%)	1·21 (0·91–1·63)	54 (1·9%)	41 (1·5%)	1·30 (0·87–1·96)

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.

Several serious shortcomings in the conduct and results of the clinical trial were identified:

- The study had an open label design in which the control group did not receive placebo. This is considered as a major concern since placebo effects were not controlled and clinical decision making, diagnoses and treatment adherence are influenced by the knowledge about treatment. Treatment adherence (to placebo) *per se* has been shown to reduce cardiovascular mortality (*Zhao Yue et al., The effect of placebo adherence on reducing cardiovascular mortality: a meta-analysis, Clinical Research in Cardiology 2014; 103, 229–235*). Only the patients who were taking active medication got reminded of their inclusion in the study every day, which may have influenced their behaviour during the study. Receiving a study drug and encouragement to take it may improve overall treatment adherence and thereby improve outcome when compared to not receiving a study drug at all.

  This seems to be the case in GISSI Prevenzione as although the result for Vitamin E did not reach statistical significance compared to untreated controls, there was little difference between the three active treatment arms, one including administration of Vitamin E only. The result in the control arm was numerically inferior to all of these treatment arms.

  After the GISSI-P trial was published, it became evident in large scale placebo controlled studies that Vitamin E supplementation had no effect on MACE endpoints. This was supported by the results in the Women's Angiographic Vitamin and Estrogen (WAVE) trial, where the supplementation with Vitamin E and C also had no beneficial cardiovascular effect with a trend towards worsening. (*JAMA 2002; 288: 2432–2440*). When eliminating the negative “no treatment” effect of the control arm by post hoc comparing efficacy in the Omega-3-acid ethyl ester arm with the Vitamin E arm, the difference was less than 0.5%.

- Standard of care for prevention after myocardial infarction (not only concomitant medical treatments but also invasive treatment procedures) has substantially evolved since the time the study was performed. Baseline therapy, in particular statin and beta-blocker use was not consistent with current treatment recommendations.

  At baseline only about 5% of the patients received lipid lowering medication and after 42 months the rate of patients on lipid lowering therapy was about 25%. Mean LDL-C levels were about 137 – 138 mg/dL which is considerably higher than the target of <70 mg/dL which is recommended by current treatment guidelines for very high risk patients. Furthermore, beta-blockers were used in about 40% of the patients only, although beta-blockers are known to reduce all-cause mortality in patients with a recent myocardial infarction (*Andersson et al., J Am Coll Cardiol. 2014 Jul 22;64(3):247-252*).

- The effect of n-3 PUFA on the co-primary endpoints was exclusively driven by fatal cardiovascular events whereas there was no effect on non-fatal cardiovascular events. This is an unexpected result in a cardiovascular outcome study.
- The post-hoc analysis of GISSI-P trial reported early protection against sudden death and all-cause death. All included participants had a recent (≤3 months) MI. This would explain the lack of efficacy in trials where omega-3 treatment was initiated >3 months after MI.

In summary, it is considered that the level of evidence resulting from the GISSI-P trial, to support a beneficial effect of Omega-3 for secondary prevention after myocardial infarction at the dose of 1 g/day is weak.

OMEGA trial, Rauch et al 2008

This was a randomized, placebo-controlled, double-blind multicentre trial conducted in Germany between 2003 and 2007.

The primary objective was to study the rate of sudden cardiac death in survivors after acute myocardial infarction, testing one of the postulated mechanisms of action (antiarrhythmic) of Omega-3 in GISSI-P. Sudden cardiac death occurred in 1.5% of the patients in both Omega and control groups OR 0.95(0.56-1.60). No difference in total mortality (OR 1.25, CI 0.90-1.72) or MACE (OR 1.21, CI 0.96 – 1.52) was found between the study groups.

Omega-3 was given in addition to standard of care treatment; 81% in the treated group were on a statin, 86% on a beta-blocker, 94% on aspirin, and 88% on clopidogrel, 78% underwent acute percutaneous coronary intervention.

Figure 2 – Primary and secondary endpoints for the OMEGA trial

	Omega Group	Control Group	*P*	OR* (95% CI)	RD, % (95% CI)
Total patients analyzed, n	1919	1885			
Sudden cardiac death, % (n)	1.5 (28/1919)	1.5 (29/1885)	0.84	0.95 (0.56–1.60)	−0.1 (−0.9–0.7)
Total mortality, % (n)	4.6 (88/1919)	3.7 (70/1885)	0.18	1.25 (0.90–1.72)	0.9 (−0.4–2.1)
MACCE, % (n)	10.4 (182/1752)	8.8 (149/1701)	0.10	1.21 (0.96–1.52)	1.6 (−0.3–3.6)
Revascularization: PCI+CABG in survivors, % (n)	27.6 (466/1686)	29.1 (482/1654)	0.34	0.93 (0.80–1.08)	−1.5 (−4.6–1.6)
ICD–terminated ventricular tachycardia or fibrillation in survivors, % (n)	0.5 (9/1705)	0.1 (2/1689)	0.06	4.47 (0.97–20.74)	0.4 (0.0–0.8)

The OMEGA trial started 10 years after the GISSI-P trial, and the management of MI patients have advanced considerably over this period. Dissimilar to GISSI-P, almost all patients received statins, beta-blockers and antiplatelet drugs in line with current treatment guideline recommendations. 78% underwent coronary intervention.

There were several strengths of this study when compared to GISSI-P, including administration of study drug within few days of a myocardial infarction, placebo control, double-blind design and optimal baseline therapy. The results of the OMEGA trial with a numerically negative trend for all-cause mortality and MACE indicate a lack of efficacy within the approved indication in patients treated with optimal baseline therapy according to current treatment guidelines. This study is therefore considered as key evidence for the lack of clinical benefit of omega-3 in secondary prevention after myocardial infarction.

The one year event rate (all-cause mortality, sudden cardiac death, MACE) was comparable or slightly higher in OMEGA compared to the GISSI-P study. The duration of the study was shorter (12 months) but this does not impair the interpretation of the results, since no additional efficacy was seen after 12 months in the GISSI-Prevenzione trial.

One limitation, of the OMEGA trial, was that the event rate was lower than expected and the expected power to show an effect on sudden death was not achieved. However, in the OMEGA trial the OR was 1.25 (0.90-1.72) for total mortality and 1.21 (0.96 – 1.52) for MACE numerically favouring placebo 0.95 (0.56-1.60) for sudden death; so it is considered by the CHMP very unlikely that a beneficial effect could have been shown with a larger trial.

In summary, the results from this clinical trial did not confirm the beneficial effects, in secondary prevention after myocardial infarction at 1 g/day, of n-3 PUFA seen in the GISSI-P trial. The results of the OMEGA study show a lack of efficacy of n-3 PUFA in the secondary prevention in patients after an acute myocardial infarction on appropriate baseline therapy according to current treatment guidelines including (e.g. percutaneous coronary intervention, statins and beta-blockers).

GISSI-HF , Tavazzi et al (2008)

The GISSI-HF was a randomized, double-blind, placebo-controlled study designed to investigate the effects of EPA–DHA and rosuvastatin on mortality and morbidity in patients with symptomatic heart failure. This trial was performed to verify whether the results obtained in patients with prior myocardial infarction could also be obtained in those with heart failure. Two endpoints were defined: time to death, and time to death or admission to hospital for cardiovascular reasons.

The GISSI-HF trial compared efficacy of omega-3 PUFA 1 g daily vs. placebo in 3494 vs. 3481 patients with heart failure. A limited benefit (adjusted HR for death 0.91, 95.5% CI 0.83–0.99, p=0.041) was observed.

Only about 50% of the patients had ischemic heart disease and only 41 – 42% of patients had a previous myocardial infarction. In a predefined subgroup analysis in patients with ischemic heart disease the HR for the composite co-primary endpoint was 0.95 (0.97 – 1.03, NS) numerically favouring 3-n PUFA but this subgroup comprised more patients (about 50%) than the 41- 42% with a previous MI at baseline.

Observed effects were only small, overall of borderline clinical relevance, and the p values for both co-primary endpoints were just below the predefined significance levels. P values were calculated based on HRs adjusted for post hoc baseline imbalances with p<0.1. These adjustments for overall minor imbalances (admission to hospital during the preceding year for heart failure, pace maker and aortic stenosis) had a major impact on the p value. Without the adjustments the p values for both primary endpoints (p=0.124 and p=0.059) were clearly above the pre-specified significance levels of p=0.045 and p=0.001. Although this procedure was pre-specified, such an adjustment based on post hoc observed imbalances is discouraged by the *EMA Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013)* and should only be used for exploratory analyses. It is also not clear from the publication, to which degree the different categories of baseline characteristics to be analysed were pre-specified. Therefore, the statistical significance is in question.

ORIGIN, Bosh et al 2012

In the ORIGIN trial, Omacor was investigated in a mixed population at increased cardiovascular risk (a history of MI, stroke, or revascularization; angina with documented ischemia; a ratio of urinary albumin to creatinine of more than 30 mg per gram; left ventricular hypertrophy; 50% or more stenosis of a coronary, carotid, or lower-limb artery on angiography; or an ankle–brachial index of less than 0.9). The study focussed on patients with diabetes or impaired glucose tolerance, 60% of patients

had established underlying cardiovascular disease and a part of these had a myocardial infarction ≥ 5 days prior to randomization. The incidence of the primary outcome of death from cardiovascular causes was not decreased among patients receiving omega-3 acid ethyl esters, as compared with those receiving placebo (9.1% vs. 9.3%; HR 0.98; 95% CI 0.87 - 1.10; p=0.72). There was no beneficial effect on MACE endpoints in the overall population and in the subgroup of patients with a previous cardiovascular event [HR 0.99, (0.86 – 1.14), NS].

Even though this study is not fully representative of the target population discussed in the referral, i.e. patients who had a MI, 59% of the study population had established coronary or cerebrovascular disease in form of myocardial infarction, coronary revascularisation or stroke and the dose used was identical to the dose approved for post MI patients. Although only a subgroup of the study population had a prior MI in line with the current indication for omega 3-containing medicinal products, a relevant effect in secondary prevention appears unlikely in the absence of any effect in an overall high CV risk population and in the subgroup of patients with a previous cardiovascular event.

SU.FOL.OM3, Galan et al 2010

The SU.FOL.OM3 trial included 2501 patients with a history of myocardial infarction, unstable angina, or ischaemic stroke. Allocation to omega 3 fatty acids was not associated with significant effect on MACE (6.5% vs 6.1%, HR 1.08, 95%CI 0.79-1.47, p=0.64) or on all-cause mortality (HR 1.03, 95%CI 0.72-1.48, p=0.88).

Even though the studied dose (600 mg of eicosapentanoic acid and docosahexaenoic acid at a ratio of 2:1) is lower than the content for Omacor (1 mg), the study population is representative of the target population subject to this referral and therefore it is considered that the results are relevant for assessment of omega 3 acids esters efficacy in secondary cardiovascular prevention. Despite of the lower dose, a relevant overlap with the target EPA/DHA level achieved with the approved dose is expected, considering the variability in eating habits and daily fish intake by meal. Therefore, the lack of efficacy observed cannot be entirely explained by the lower dose used in this study.

In summary, the results of the SU.FOL.OM3 trial study are indicative of lack of efficacy of EPA/DHA in the secondary prevention in patients with a history of an acute myocardial infarction or other cardiovascular events at appropriate current baseline therapy.

Alpha Omega trial, Kromhout, et al. (2010)

The randomised double-blind Alpha Omega study did not show a beneficial effect [HR 1.01, (0.87 – 1.17), NS] of the administration of an average of 226 mg of EPA and 150 mg of DHA per day in patients with a history of myocardial infarction when added to a baseline therapy including antithrombotic drugs, statins and antihypertensive drugs.

JELIS Study, Yokoyama et al (2007)

The Japan EPA lipid intervention study (JELIS) was a prospective, randomized, open label, blinded endpoint evaluation (PROBE) study conducted in Japan between November 1996 and November 1999.

The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. Secondary endpoints were all-cause mortality, mortality and morbidity of coronary artery disease, stroke, peripheral artery disease and cancer.

At mean follow-up of 4.6 years, major coronary events occurred in 262 (2·8%) patients in the EPA group and 324 (3·5%) in control group; i.e. a 19% relative reduction in major coronary events (p=0·011) between the 2 groups.

In the stratum of patients with coronary artery disease there was a statistically significant reduction in major coronary events as defined above [HR 0.81 (0.66 – 1.00)]. The results for this endpoint were largely driven by the reductions in unstable angina events and in coronary procedures (CABG and PTCA). There was a neutral effect on sudden cardiac death and a numerical reduction in fatal and non-fatal MIs. No data for stroke, all cause mortality or cardiovascular death (defined as all deaths not confirmed to be non-cardiovascular) were presented for this stratum. There was a small numerical decrease in triglycerides in the EPA group compared to the control group and no relevant difference regarding the effect on cholesterol levels (total, LDL, HDL).

The study results suggest that there may be a beneficial coronary effect of EPA 1800 mg daily in patients with hypercholesterolemia treated with low dose statins that is mainly related to a reduction in coronary procedures and to angina pectoris. The EPA dose was 4 fold higher than what is administered with Omacor, whereas the study medication did not contain DHA. The authors of the study indicated that this high dose was important for the effect on non-fatal coronary events. The driving components of the primary efficacy endpoint (coronary procedures and unstable angina pectoris) are generally not accepted to demonstrate efficacy in a primary analysis, and are particularly not considered appropriate in an open label study.

The data are inconclusive for patients after myocardial infarction. Only 5% of the patients included in the study had a previous myocardial infarction. No patients with a myocardial infarction that occurred less than 6 months prior to randomization were included. Key efficacy information (such as all-cause mortality, stroke) is not available for these patients but the neutral effect for stroke and the numerical increase in all-cause mortality by 9% (HR 1.09) in the whole group of patients raises doubts about an overall beneficial effect in these patients.

In conclusion, the results of the study are not suitable to support an indication in patients post myocardial infarction on appropriate baseline therapy.

DOIT Trial, Einvik et al

In the Diet and Omega-3 Intervention Trial (DOIT), 563 Norwegian men, 64-76-years old and 72% without overt cardiovascular disease, were randomized to a 3-year 2×2 factorial designed clinical trial of diet counseling and/or 2.4 g omega-3 PUFA supplementation of which about 49% were EPA and about 35% were DHA. The omega-3 PUFA arm was placebo-controlled (corn oil) and double blinded. Randomization occurred from 1997 to 1998.

Deaths and cardiovascular events were recorded through 3 years, and the effects of omega-3 PUFA-intervention on these outcomes were evaluated in pooled groups of the omega-3 PUFA-arm (Table 2).

Table 2 – Efficacy of n-3 PUFA supplementation on all-cause mortality and cardiovascular events

	Placebo $n=281$	n-3 PUFA $n=282$	Unadjusted HR (95% CI)	Adjusted model 1 HR (95% CI)[a]	Adjusted model 2 HR (95% CI)[b]	P
All-cause mortality (n)	24	14	0.57 (0.29–1.10)	0.54 (0.28–1.05)	0.53 (0.27–1.04)	0.063
Cardiovascular	11	7				
Noncardiovascular	13	7				
Cardiovascular events (n)	36	32	0.86 (0.57–1.38)	0.90 (0.56–1.47)	0.89 (0.55–1.44)	0.624
Fatal	11	7				
Nonfatal	25	25				

Cox regression proportional hazard analyses. CI, confidence interval; HR, hazard ratio; PUFA, polyunsaturated fatty acid. [a]Adjusted for age and serum glucose at baseline. [b]Adjusted for age, serum glucose, body mass index, systolic blood pressure, and current smoking at baseline.

Whilst not statistically significant, the authors concluded that a tendency toward reduction in all-cause mortality in the omega-3 PUFA groups was observed despite a low number of participants.

However, although the results regarding all-cause mortality, cardiovascular mortality and cardiovascular fatal events were in favor of n-3 PUFA treatment, no reliable conclusions can be drawn with respect to efficacy of Omacor in the post MI indication, due to:

- Small absolute numbers of events
- The dose of the study medication was higher (2.4 Gr EPA/DHA/day) than the dose of Omacor approved for patients post myocardial infarction (1 Gr EPA/DHA /day).
- Only a small number of patients had underlying coronary artery disease, only a part of these patients had a previous myocardial infarction. Most patients were at high cardiovascular risk due to other risk factors.
- MACE endpoints were not the primary analysis and it is not clear from the publication whether the analysis was predefined. Cardiovascular events included components that usually are not considered in a primary efficacy analysis and an observation that fatal but not non-fatal cardiovascular events are reduced poses questions on the reliability of the result.

The results of the study, although indicating a non-statistically significant trend towards efficacy of a higher than approved dose of n-3 PUFA in patients at high cardiovascular risk, are considered inconclusive for patients post myocardial infarction on baseline risk prevention therapy.

Risk and Prevention (R&P) trial (The Risk and Prevention Study Collaborative Group)

This double blind placebo (1 g olive oil) controlled large scale study in 12,505 patients at high risk for a cardiovascular event but without a history of myocardial infarction did not show any beneficial effect or trend in relevant MACE endpoints and cardiovascular mortality.

The primary endpoint was originally the cumulative rate of death, non-fatal MI, and non-fatal stroke; however, following intermediate blinded analyses that revealed low event rates, the primary endpoint was changed to the composite of death or hospitalization from cardiovascular cause.

The primary endpoint occurred in 1,478 patients (11.8%), including 733 of 6,239 who received n−3 fatty acids (11.7%) and 745 of 6,266 who received placebo (11.9%). The incidence of the primary endpoint was not significantly reduced by n−3 fatty acids (adjusted hazard ratio, 0.97; 95% confidence interval [CI], 0.88 to 1.08; P = 0.58).

Although the study population (mainly primary prevention) was different from the population as defined in the wording of the post myocardial infarction indication, it casts doubts that efficacy can be achieved in patients with prior MI in the absence of any effect in an overall high CV risk population.

Overall this prospective double blind placebo controlled study can be considered as a negative study in patients at increased cardiovascular risk without a previous myocardial infarction. Since this is not the patient population included in the wording of the indication (patients post MI), no definite conclusions can be drawn based on this study. However, the study indicates that different levels of fish consumption in the normal range were not relevant for efficacy of Omacor in this population.

AREDS-2 trial Bondes et al. (2014)

This double blinded placebo controlled trial using EPA/DHA at the strength approved in patients after myocardial infarction did not provide evidence for efficacy in a primarily ophthalmologic population. Only 405 (9.7%) of the 4,203 patients in AREDS-2 had prior coronary heart disease (CHD). Patients with a cardiac event during the preceding 12 months or in unstable condition were excluded.

Therefore, no conclusion from the results of this study can be inferred to patients after myocardial infarction.

ASCEND and VITAL Manson et al. (2018)

Two recent very large studies ASCEND (2018) and (VITAL 2018) investigated administration of n−3 Fatty Acids in primary prevention at the same dose level and composition as the medicinal product concerned in this referral. Both studies were negative with respect to their primary endpoints: a reduction in serious vascular events and MACE, respectively. However, there was a positive effect on the risk of MI (one of the secondary endpoints) in the VITAL study, raising a question of potential differences between results from primary and secondary prevention trials. The results of these studies do not support the use of omega-3-containing products in the secondary prevention after MI.

Reduce-IT (2018)

REDUCE-IT was a randomized, double blind, placebo-controlled trial treating high CV risk patients (N = 8,179) with hypertriglyceridemia with EPA 4 g/day vs. placebo, for a median of 4.9 years. Results were published in November 2018.

The risk of ischemic events, including cardiovascular death, was significantly lower among those who received treatment. The results of the study are of limited relevance for this referral procedure as a considerably higher dose than the authorised dose was investigated and the active substance was different (icosapent ethyl, a highly purified and stable EPA ethyl ester). In addition, the study may be relevant only in the context of an indication for the treatment of patients with hypertriglyceridemia since all of the included patients had hypertriglyceridemia. The indication for the treatment of hypertriglyceridemia is not affected by this referral.

2.2.2. Meta-analyses

During the last ten years, a large number of meta-analyses assessing the effect of n-3 PUFA on cardiovascular events have been published.

The meta-analyses have included small and large clinical trials assessing the associations of omega-3 fatty acid supplements (intended as fish intake, dietary advice, fish oil supplements and omega-3 fatty acids-containing medicinal products) with the risk of fatal and non-fatal coronary heart disease and major vascular events in primary prevention, secondary prevention or mixed primary and secondary.

The CHMP has carefully reviewed all the available meta-analysis, the most relevant is described below.

Aung et al 2018

The most recent meta-analysis to investigate association of omega-3 fatty acid supplement use with cardiovascular disease risks was performed by Aung et al 2018, published in January 2018. Ten large randomized trials involving 77,917 individuals were identified comparing the associations of treatment with omega-3 FA supplementation vs. placebo or no treatment for at least 12 months in populations with prior CHD, stroke, or at high risk of cardiovascular disease (CVD).

Of the 77 917 individuals participating in the 10 trials, 47 803 (61.4%) were men, and the mean age at entry was 64.0 years; the trials lasted a mean of 4.4 years. The associations of treatment with outcomes were assessed on 6273 coronary heart disease events (2695 coronary heart disease deaths and 2276 nonfatal myocardial infarctions) and 12 001 major vascular events. Randomization to omega-3 fatty acid supplementation (eicosapentaenoic acid dose range, 226-1800mg/d) had no significant associations with coronary heart disease death (rate ratio [RR], 0.93; 99%CI, 0.83-1.03; P = .05), nonfatal myocardial infarction (RR, 0.97; 99%CI, 0.87-1.08; P = .43) or any coronary heart

disease events (RR, 0.96; 95%CI, 0.90-1.01; P = .12). Neither did randomization to omega-3 fatty acid supplementation have any significant associations with major vascular events (RR, 0.97; 95% CI, 0.93-1.01; P = .10), overall or in any subgroups, including subgroups composed of persons with prior coronary heart disease, diabetes, lipid levels greater than a given cutoff level, or statin use.

Table 3 – Characteristics of included trials

Study (Year)	Patients, No.	Dose of EPA/ DHA (mg/d)	Male, No. (%)	Mean Trial Duration, y	Mean (SD) Age, y	No. (%)			
						Prior CHD	Prior Stroke	Prior Diabetes	Statin Use
DOIT (2010)	563	1150/800	563 (100)	3	70 (3)	133 (23.6)	37 (6.6)	46 (8.2)	NA
AREDS-2 (2014)	4203	650/350	1816 (43.2)	4.5	74 (NA)	405 (9.7)	211 (5.0)	546 (13.0)	1866 (44.4)
SU.FOL.OM3 (2010)	2501	400/200	1987 (79.4)	4.7	61 (NA)	1863 (74.5)	638 (25.5)	440 (17.9)	2079 (83.1)
JELIS (2007)[a,b]	18 645	1800/NA	5859 (31.4)	4.6	61 (8)	NA	NA	3040 (16.3)	18 645 (100.0)
Alpha Omega (2010)	4837	226/150	3783 (78.2)	3.3	69 (6)	4837 (100.0)	345 (7.2)	1014 (21.0)	4122 (85.2)
OMEGA (2010)	3818	460/380	2841 (74.4)	1	64 (NA)	796 (22.5)	192 (5.5)	948 (27.0)	3566 (94.2)
R&P (2013)	12 505	500/500	7687 (61.5)	5	64 (NA)	Not stated (30)	594 (4.8)	7494 (59.9)	12 505 (100.0)
GISSI-HF (2008)	6975	850/950	5459 (78.3)	3.9	67 (11)	3614 (51.8)	346 (5.0)	1974 (28.3)	NA
ORIGIN (2012)	12 536	465/375	8150 (65.0)	6.2	64 (8)	8094 (64.6)	10 877 (86.8)	11 081 (88.4)	6739 (53.8)
GISSI-P[b] (1999)	11 334	850/1700	9658 (85.2)	3.5	59 (11)	11 334 (100.0)	NA	2139 (18.9)	NA
Total	77 917	NA	47 803 (61.4)	4.4	64	31 076/46 767 (66.4)	13 240/47 938 (27.6)	28 722 (36.9)	49 522 (83.4)

Abbreviations: AREDS-2, Age-Related Eye Disease Study 2; DOIT, Diet and Omega-3 Intervention Trial; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure; GISSI-P, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione; JELIS, Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Study; NA, not available; OMEGA, Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction; ORIGIN, Outcome Reduction With Initial Glargine Intervention; SU.FOL.OM3, Supplémentation en Folates et Omega-3; R&P, Risk and Prevention Study.

[a] All trials used eicosapentaenoic acid and docosahexanoic acid supplements, with the exception of the JELIS trial (eicosapentaenoic acid only).

[b] All trials were blind, placebo-controlled randomized clinical trials with the exception of JELIS and GISSI-P, which were open-label without placebo.

Figure 3 - Associations of Omega-3 Fatty Acids with Major Vascular Events

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Coronary Heart Disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87-1.08)
Coronary heart disease death	1301 (3.3)	1394 (3.6)	0.93 (0.83-1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90-1.01)
			P = .12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88-1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76-1.51)
Unclassified/Other	142 (0.4)	135 (0.3)	1.05 (0.77-1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93-1.13)
			P = .60
Any major vascular event	3230 (15.2)	6071 (15.6)	0.97 (0.93-1.01)
			P = .10

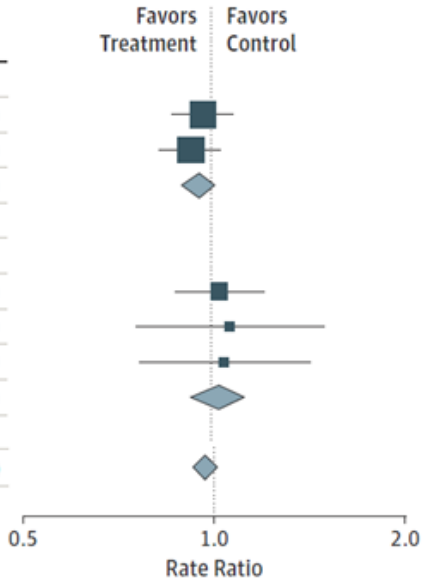
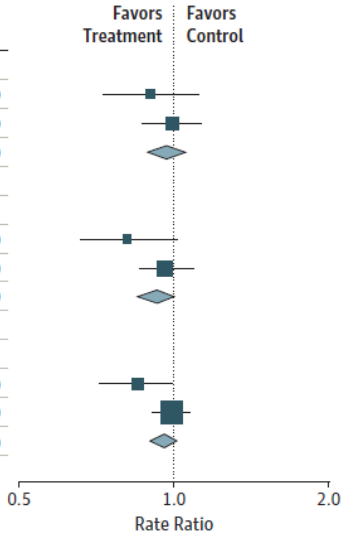


Figure 4 - Associations of Omega-3 Fatty Acids with Fatal and Nonfatal Vascular Events, by Trial Design

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Nonfatal myocardial infarction			
Open	285 (1.9)	316 (2.1)	0.90 (0.73-1.11)
Blind	836 (3.5)	839 (3.5)	0.99 (0.87-1.13)
All	1121 (2.9)	1155 (3.0)	0.97 (0.89-1.05)
			P = .40
Coronary heart disease death			
Open	276 (1.8)	337 (2.2)	0.81 (0.66-1.01)
Blind	1025 (4.3)	1057 (4.4)	0.96 (0.86-1.09)
All	1301 (3.3)	1394 (3.6)	0.93 (0.85-1.00)
			P = .05
Any coronary heart disease			
Open	512 (3.4)	598 (4.0)	0.85 (0.72-0.99)
Blind	2573 (10.7)	2590 (10.8)	0.99 (0.91-1.07)
All	3085 (7.9)	3188 (8.2)	0.96 (0.90-1.01)
			P = .12



Symbols and conventions as in Figure 1. Heterogeneity between trial designs (χ^2_1 in all cases) was 1.05 (*P* = .31) for nonfatal myocardial infarction, 3.26 (*P* = .07) for coronary heart disease death, and 4.81 (*P* = .03) for any coronary heart disease.

Even though the meta-analyses by Aung et al. includes clinical trials with products, doses and populations not exactly representing the approved secondary prevention indication, all studies include patients with cardiovascular disease and therefore, the results are considered relevant and are supportive of lack of efficacy.

2.2.3. Retrospective cohort trials in patients after an acute myocardial infarction

Three retrospective cohort trials (published in 2013 and 2016) in patients who had experienced acute MI have been submitted.

The study by Poole and colleagues (2013) compared survival rates after treatment with omega-3-acid ethyl esters in routine clinical practice in individuals with or without diabetes who survived their first MI, adjusting for other clinical variables and CV risk modifying medications. The study population

comprised 2,466 eligible patients diagnosed with a first MI. Patients initiating treatment with omega-3 fatty acids 1 g/day within 90 days after their MI were identified and each matched to 4 patients non-exposed to omega-3 fatty acid treatment. Patients initiating omega-3 treatment > 90 days after MI were excluded, as were patients who were prescribed a daily dose of > 1 g. In adjusted analysis, for those initiating omega-3-acid ethyl esters within 90 days of first MI, the hazard ratio for all-cause mortality was 0.782 (95% CI, 0.641–0.995; P = 0.0159). Adjustment for measured covariates in a time-dependent Cox model attenuates the risk estimate to 0.78 (HR; [95% CI 0.64 to 0.96]). Since this study focused on mortality, impact on other relevant coronary and general cardiovascular morbidity outcomes are not available. The importance of adherence to standard of care was also reflected in this study, in which a sensitivity analysis among subjects receiving dual antiplatelet therapy and those achieving low levels of LDL-C did not show a beneficial effect of *n*-3 fatty acid exposure on mortality.

The study by Macchia and colleagues (2013) was a retrospective cohort study conducted in Italy, using administrative databases of drug prescriptions and hospitalizations from 117 Coronary Care Units covering an overall population of 7.5 million across 22 health regions of Italy. A cohort of up to 14,704 patients discharged following their first MI between January 1, 2003 and December 31, 2003 was established. A total of 11,532 (78,4%) filled a prescription for a statin, with (N=4,302) or without (7,230) prescription for omega-3-acid ethyl esters during the first 30 days of hospital discharge. As compared with patients treated only with statins, patients who received combination therapy were significantly younger, with a higher proportion of males, lower prevalence of CV and non-CV comorbidities at baseline and higher probability of receiving aspirin, beta-blockers and ACE-inhibitors at hospital discharge. Over the four years of follow-up there were 1,591 fatal events, representing an overall death rate of 3.5 per 100 patients/year. In this study it is further noted that while there is a reduced all-cause mortality (adjusted HR 0.59 [95% CI 0.52 to 0.66]) the estimated association is notably attenuated looking at the combined outcome of death and myocardial infarction (adjusted HR 0.94 [95% CI 0.86 to 1.02], NS).

The study by Greene et al. (2016) was a retrospective cohort-based integrated analysis based on administrative databases maintained by 5 local health units in Italy with a combined population of approximately 4.3 million. Patients discharged from hospital between January 1, 2010 and December 31, 2011, with primary diagnosis of acute MI were identified. 11,269 patients met study inclusion criteria, of whom 2,425 patients received ≥ 2 prescriptions for omega-3-acid ethyl esters at a daily dose of 1 g/day. The other 8,844 patients comprised the non-exposed comparator group. Patients treated with omega-3-acid ethyl esters tended to be younger, men, and less likely to have baseline chronic kidney disease or heart failure. Further they were more likely to be prescribed medications for diabetes and to receive guideline-recommended post-acute MI medical therapy. Approximately half of the patients treated with omega-3 fatty acids during follow-up had an adherence related of > 80%. There was a total of 1,198 deaths (10.6%) and 494 acute MIs (4.4%) during follow-up (4 years after the date of hospital discharge). After adjusting for patient characteristics and concurrent therapies, omega-3 acid ethyl esters treatment was associated with reduced all-cause mortality with a hazard ratio of 0.76 (95% CI 0.59 - 0.97; P=0.029) and recurrent MI with a hazard ratio of 0.65 (95% CI 0.49-0.87; P=0.004).

Intrinsic to observational studies, there is an inevitable selection bias. In this case, the choice to initiate treatment with omega 3 can be expected to be correlated with patient, prescriber, and site characteristics that are related to the outcome of interest. While attempts can be made to adjust for such factors in the analyses, it can only apply to accurately measured characteristics. The likelihood for residual bias is substantial. Observational studies in this context are challenging to interpret, may only provide supportive evidence and cannot substitute results of clinical studies with a more robust design (such as randomised controlled clinical trials) which provide a higher level of evidence.

2.2.4. Effect of n-PUFA on atrial fibrillation and flutter

In a review of Schacky, C.v. (Front Physiol. 2012; 3: 88.) the data available at that time did neither show a proarrhythmic effect nor an antiarrhythmic efficacy in postoperative AF, recurrent AF and new-onset AF. However, in the recently published large scale REDUCE-IT trial comparing icosapent ethyl 4g/day vs. placebo, a larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, p = 0.004). The relevance of this proarrhythmic finding for the lower approved dose of EPA/DEA after myocardial infarction is unclear.

2.2.5. Effect of n-PUFA on ventricular arrhythmias

In GISSI-P, a reduction of sudden death events was seen (RR 0.74; 0.58-0.93) in secondary two-way analyses of fatal events. The primary objective OMEGA trial was to study the rate of sudden cardiac death in survivors after acute myocardial infarction, testing one of the postulated mechanisms of action (antiarrhythmic) of Omega-3 in GISSI-P. The OMEGA trial is the only large prospective, double blind, randomized study that used sudden cardiac as a primary endpoint. The study failed to show a beneficial effect of n-PUFA. Sudden cardiac death occurred in 1.5% of the patients in both Omega and control groups OR 0.95(0.56-1.60). No difference in total mortality (OR 1.25, CI 0.90-1.72) was found between the study groups.

In the double blind randomized study by *Leaf et al.* a higher dose of fish oil (2.6 gr) per day was compared with 1 gr of olive oil. 402 patients with an ICD were included. The rate of discontinuation of prescribed supplements was high (35%, 142 subjects). There was no difference in all cause death (fish oil n = 13, olive oil n = 12) or in cardiac deaths between the groups. For the primary endpoint (time to first ICD event) there was a non-significant trend (ITT P=0.057 and on treatment analysis P=0.11) favoring fish oil. Overall, the study does not provide clear evidence for a clinically relevant antiarrhythmic effect of the approved dose. When a higher dose was used, neither all-cause mortality nor cardiovascular mortality or arrhythmia associated mortality showed any difference between the two groups. The primary endpoint did not reach statistical significance and the high discontinuation rate decreases the robustness of the results. No information is provided in the study for the rate and the time from last event of ICD events before randomization. The time from ICD implant was numerically longer in the placebo arm (1.77 ± 0.16 years vs. 1.45 ± 0.13 years) which may have some influence on the event rate. In summary, the study raises the possibility of an antiarrhythmic efficacy of fish oil at higher doses (2.6 g daily), although these results are inconclusive. In the absence of an effect on all-cause mortality, cardiovascular mortality and arrhythmia associated mortality, the clinical relevance of such a possible effect is unclear.

In the SOFA trial (Brouwer et al. 2006) 2 g/d of fish oil vs. placebo (n=273 in each group) for a median period of 356 days) did not have a significant effect on the primary endpoint (appropriate ICD intervention for VT or VF, or all-cause death). The primary end point occurred in 81 (30%) patients taking fish oil vs 90 (33%) patients taking placebo (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.64-1.16; p=0.33).

In the study from *Raitt et al.* (2005) in 200 patients with an implantable cardioverter defibrillator (ICD) and a recent episode of sustained VT or VF (fish oil, 1.8 g/d, 72% omega-3 PUFAs, vs. placebo, follow up for a median of 718 days (range, 20-828 days) the rate of ventricular tachycardia and ventricular fibrillation events was numerically higher in the fish oil group. At 6, 12, and 24 months after randomization, respectively, 46% (SE, 5%), 51% (5%), and 65% (5%) of patients assigned to fish oil had ICD therapy for VT/VF compared with 36% (5%), 41% (5%), and 59% (5%) of patients assigned to placebo (p=0.19). The group assigned to fish oil tended to have a shorter time to first episode of ICD therapy for VT/VF than those assigned to placebo. All-cause mortality and cardiac mortality were

numerically lower in the fish oil group (n = 4 and 2, respectively) than in the placebo group (10, and 5), sudden deaths were observed only in the fish oil group (n = 2). This study did not indicate a beneficial effect of fish oil (1.8 g) on ventricular tachycardias.

In a placebo controlled blinded study published by *Weisman et al. 2017* 105 ICD recipients with ischemic cardiomyopathy were treated with 3.6 mg of EPA and DHA (the active gel capsule consisted of 400-mg EPA, 200-mg DHA, 40-mg oleic acid, 2-mg tocopherolvitamin E as an anti-oxidant, and 3–30 mg of other omega-3 fatty acids, 6 times per day) vs. placebo (half sunflower oil and half corn oil) for 6 months respectively (cross over design with 4 months washout). Among 87 patients who completed the study protocol, a total of 18 (21%) patients experienced appropriate ICD therapies. A significantly lower rate of VTEs was reported for the fish oil group vs. placebo (1.7 vs 5.6; p = 0.035, primary endpoint). There was no difference in VTE terminated by ICD shocks, (0.11 ± 0.6 vs. 0.10 ± 0.4), a trend towards a lower rate of VTEs terminated by antitachycardic pacing was reported (2.8 ± 13.7 vs. 0.5 ± 2.1, respectively; p = 0.077)

Overall, the study indicates the possibility of an antiarrhythmic effect of n-PUFA at doses considerably higher than the currently approved dose. However, this study has some limitations. The number of patients is small. Also, no information was provided on the number of events in each period (overall and in each group), on the rate of events prior to inclusion into the study, abd for the 18 patients that dropped out during the study.

A meta-analysis (Khoueiry et al. 2013) overall did not show a statistically significant effect of n-PUFA on ventricular arrhythmias. The results became statistically significant after exclusion of the study with the most negative result (Raitt et al. 2005) favouring placebo. Of note, the negative OMEGA trial with sudden cardiac death as the primary endpoint was also not included in this meta-analysis, whereas the GISSI study was.

Overall, the studies showed inconsistent results and no robust conclusions can be drawn on whether there are clinically relevant antiarrhythmic effects of n-PUFA on atrial or ventricular tachycardic events. All of the studies (except GISS and OMEGA) used higher doses than the 1 g that is currently approved for the treatment in patients after a myocardial infarction.

Some studies show that there might be some antiarrhythmic efficacy of n-PUFA at higher doses on ventricular tachycardia but the results are inconsistent.

A Cochrane Database systemic review from November 2018 reported that a total of 3788 people experienced arrhythmia in 28 RCTs with 53,796 participants, and omega-3 intervention did not have any effect on this outcome (RR 0.97, 95% CI 0.90 to 1.05.) In summary, a clinically relevant antiarrhythmic efficacy of n-PUFA 1 g qd has not been demonstrated. Demonstration of beneficial antiarrhythmic efficacy of omega-3 acid ethyl esters would have been relevant for those patient populations at increased cardiovascular risk. Since this was not the case, these can be considered supportive for a lack of efficacy.

2.2.6. Therapeutic guidelines

Since 2016, the European Society of Cardiology and European Atherosclerosis Society state in their guidelines for prevention on cardiovascular disease that the effect of omega-3 fatty acids supplement on all cause coronary heart disease (CAD) and stroke mortality is questionable. This is also reflected in the guidelines for the management of dyslipidaemia which no longer recommend use of omega-3 fatty acids supplements for prevention of cardiovascular disease in people who have experienced a cardiovascular event, in view of the recent evidence showing a lack of benefit. The 2017 ESC Guidelines for the management of acute MI in patients presenting with ST-segment elevation

recommends a diet similar to the Mediterranean diet but no recommendations are made for omega-3 supplementation.

The American College of Cardiology / American Heart Association guideline for management of blood cholesterol to reduce atherosclerotic CV risk in adults states that non-statin therapies (e.g. OM3EE) do not provide acceptable atherosclerotic CV disease risk reduction benefits compared to their potential for adverse effects in the routine prevention of atherosclerotic CV disease. However, these non-statin drugs may be useful as adjuncts to statin therapy in some circumstances, e.g. for high-risk patients who are completely intolerant to statin therapy.

In contrast, a science advisory from the American Heart Association (majority of co-authors) concluded in 2017 that use of omega-3 fatty acid supplements is reasonable for secondary prevention of coronary heart disease.

The CHMP noted these clinical recommendations.

2.2.7. Discussion on efficacy

The approval of omega-3 acid ethyl esters containing products in secondary prevention after myocardial infarction is based on the results of the GISSI-P study performed in 1999. In this study, there was a relative risk reduction for one of the two co-primary MACE endpoints of 10% with a rather poor precision (upper CI 0.99) with the second co-primary endpoint just failing to show a significant result. The study is associated with some methodological limitations - this was an open label study where the control group did not receive study medication which may have influenced patient motivation and behaviour and consequently the results. The issue is highlighted by the fact that omega-3 acid ethyl esters had little effect when compared to the Vitamin E arm in the same trial. Vitamin E being considered not beneficial in the prophylaxis of cardiovascular events.

In more recent prospective randomised clinical trials (OMEGA study, GISSI-HF, ORIGIN study and SU.FOL.OM3 performed between 2003 and 2012), the results from the GISSI-P study have not been reproduced.

In GISSI-P, a reduction of sudden death events was seen in secondary two-way analyses of fatal events in the absence of an effect on non-fatal events. The primary objective of the OMEGA trial was to study the rate of sudden cardiac death, one of the postulated mechanisms of action (antiarrhythmic) of Omega-3 in GISSI-P. The OMEGA trial is a large prospective, double blind, randomized study that used sudden cardiac death as a primary endpoint. In a more robust study design (double blind and placebo controlled setting), it aimed at rechecking the finding of GISSI-P of a decrease in fatal cardiovascular events in the absence of an effect on non-fatal cardiovascular events. From all the available data, OMEGA and GISSI-P are considered as the most relevant studies for the discussion regarding treatment with Omega-3 containing medicinal products in secondary prevention after myocardial infarction (MI). In GISSI-P, at the most 5% of the patients were on lipid lowering therapy over the whole period of the first year. Although statin use increased during the study, it was only 28 – 29% at 6 months and 44 – 46% at 42 months. Beta-blockers that are indicated in most patients post MI were only used in 37 – 44% in GISSI-P.

CHMP considered that the OMEGA trial has a more adequate design and enrolled a higher number of patients that correctly reflect the population using omega-3 for secondary prevention of MI, when compared with GISSI-P. As such, it is considered that the negative results in the OMEGA trial outweighs the evidence obtained from GISSI-P. A Cochrane Database systemic review from November 2018 reported that a total of 3,788 people experienced arrhythmia in 28 RCTs with 53,796 participants, and omega-3 intervention did not have any effect on this outcome (RR 0.97, 95% CI 0.90 - 1.05.).

Thus, CHMP considered that the GISSI-P clinical trial suffers from some methodological limitations and that the evidence in support of the indication of secondary prevention after MI is weak. OMEGA trial based on a more robust and adequate design did not reproduce these findings and did not demonstrate efficacy in this indication.

It is acknowledged that the population in the ORIGIN study was not exactly representative of the target population for this referral, but the population was at high risk of CVD and therefore, the results are considered as relevant. It is also acknowledged that the dose in the SU.FOL.OM3 trial was somewhat lower than the one proposed in this referral. However, since patients in addition to the study medication were eating variable amounts of fish, an overlap in intake of PUFA can be assumed and a gradual rather than an all-or-nothing difference would be more likely. Furthermore, in the GISSI-HF trial about 50% of the patients had ischemic heart disease, most of these (about 41 – 42 % overall) had a history of myocardial infarction. In the subgroup of patient with established ischemic heart disease, no relevant efficacy results were seen. Therefore, the results of these additional studies have some relevance in the context of omega-3 in secondary prevention after MI and similar to OMEGA trial, a lack of effect of in this indication was observed.

Several meta-analyses have been performed but the strength of the results are dependent on the conduct and relevance of the studies included. The CHMP evaluated all available meta-analysis, in particular 4 meta-analyses (Aung, 2018; Rizos, 2012; Kotwal 2012 and Kwak 2012) which was also the focus of the MAHs in their responses. In these analyses, the data did not support a beneficial effect on all-cause mortality (RR approx. 0.95, upper CI above 1). Such meta-analyses do not reflect the details of the individual studies as discussed above e.g., the meta-analysis by *Aung et al.* illustrates also that the evidence of beneficial effects of omega-3 fatty acids comes mainly from open label studies, and is driven by the large GISSI studies. The included studies are discussed above.

The CHMP reviewed the results of the 3 submitted cohort studies, including subjects who had experienced a MI, which seem to be in line with the results of the GISSI-P study. Two of the studies (Greene and Macchia) included a large number of subjects and for the latter, the documented risk reduction for all-cause mortality was rather impressive (RR 0.63 CI 0.56-0.72). These results should, however, be interpreted with caution. All these studies carry the risk of a selection bias, which is supported by baseline data provided. In the retrospective cohort study by Polle (2013) only 1 % of post MI patients who were screened were included in the analysis. No attempts have been made to adjust for likely differences between centres regarding strategies and ambition for secondary prevention, likely creating correlations within centres. Some of the results cast doubts on whether the associations seen actually reflect biologically plausible effects or more likely reflect a selection bias problem. Only a limited amount of parameters in these retrospective analyses were available. These were not rich enough to allow for a full adjustment of differences in risk profiles or to mirror real life post MI situations (e.g. no data regarding smoking history, BMI/obesity, physical exercise were reported in the Macchia study). Thus, retrospective data in these studies did not allow for appropriate statistical adjustment for confounding. Based on these limitations, the results of the cohort studies are not considered to override the results of the randomized trials referred to above.

It is also noted that no relevant beneficial antiarrhythmic efficacy of omega-3 acid ethyl esters was demonstrated. Antiarrhythmic efficacy has been discussed in the context of the GISSI-P trial. Since this was not confirmed, these can be considered supportive for a lack of efficacy.

The CHMP took also into consideration the outcome of a consultation with the cardiovascular scientific advisory group.

In view of all the available data, the CHMP considered that the evidence that supported the authorisation of omega-3 in secondary prevention after MI suffered from some methodological

limitations and was weak. The efficacy in this indication was not demonstrated in subsequent and more robust clinical trials.

During the oral explanation in front of the CHMP, one of the MAHs proposed a new indication;

'Post Myocardial Infarction. Adjuvant treatment in secondary prevention, initiated within 3 months after myocardial infarction, in addition to other standard therapy (e.g. statins, antiplatelet medicinal products, betablockers, ACE inhibitors / Angiotensin receptor blockers)'.

Treatment should be particularly considered in patients having high residual risk, such as

- *No acute Percutaneous coronary intervention (PCI) after MI*
- *Impaired systolic function (EF < 50%)*
- *Type 2 diabetes*
- *Known intolerance or low adherence to one or more guideline recommended cardiovascular medications*

Treatment should continue until 12-18 months after myocardial infarction

The CHMP carefully reviewed this proposal but did not consider that this specification of the target population was supported by the submitted data and could not agree that a benefit was shown in the proposed population.

2.3. Data on Safety

With respect to safety, no new data has emerged since the last PSUSA (January 2017) in which the PRAC concluded that the benefit-risk balance was unchanged.

Omega-3-fatty acid should be used with caution in patients with known sensitivity or allergy to fish. Because of the moderate increase in bleeding time, patients receiving anticoagulant therapy must be monitored and the dosage of anticoagulant adjusted if necessary.

The most frequent undesirable effects (Common ≥ 1/100 to < 1/10) are gastrointestinal disorders including abdominal distension, abdominal pain, constipation, diarrhea, dyspepsia, flatulence, eructation, gastro-esophageal reflux disease, nausea or vomiting.

In general, it can be concluded that the safety profile seems well characterized.

In the last PSUSA for omega-3-acid-ethyl esters, "increase in bleeding time in patients with haemorragic diathesis or receiving treatment with anticoagulants" and "increase in hepatic enzymes that require monitoring in hepatic patients" was included as identified risks. The increase in bleeding time may be of particular relevance for patients post MI, most of who are on single or dual antiplatelet therapy and/or on anticoagulants post MI or for associated diseases.

3. Consultation with the Cardiovascular Scientific Advisory Group

Upon request from the CHMP, a Cardiovascular Scientific Advisory Group meeting was convened on 10 October 2018.

The experts discussed in depth strengths and limitations of prospective, randomised controlled trials (RCT) (eg GISSI-P, OMEGA study, GISSI-HF, ORIGIN study and SU.FOL.OM3), meta-analyses (eg

Aung et al 2018) and retrospective cohort studies (eg Macchia, Poole, Green). Two additional clinical trials, the Japan EPA Lipid Intervention study (JELIS) and ASCEND trial, were also considered.

The RCTs were considered most relevant for the discussion regarding treatment with Omega-3 containing medicinal products in secondary prevention after myocardial infarction (MI), in particular the results of GISSI-P and OMEGA studies. The strengths and limitations of these studies were noted. The experts expressed concern regarding the lack of mechanistic explanation for the mortality benefit in positive studies and pointed to the various definitions of sudden cardiac death in the literature.

It was admitted that the OMEGA study was relatively smaller and shorter compared to other discussed clinical trials and the mortality in this trial was overestimated in the planning phase. The population studied in the OMEGA and the dose of the drug tested was considered relevant for the currently discussed indication (1 g/day of Omega-3 containing medicinal products for 1 year in survivors of acute MI, given in addition to current guideline-adjusted treatment). Also, the primary endpoint in this study was sudden cardiac death (SCD) testing one of the postulated mechanisms of action (antiarrhythmic) of Omega-3 containing medicinal products. In addition, it was suggested that a study in patients with ICDs would be an ideal setting to verify the arrhythmia-reducing hypothesis as possible mechanism of action of Omega-3 containing medicinal products. The background therapy in the OMEGA study was more in line with current standard of care (SoC) in the population of MI patients compared to GISSI-P study, considering that this study was conducted just over 10 years after GISSI-P in 2003 - 2007.

The GISSI-P study was considered relevant for the currently discussed indication with dose of 1g/day of Omega-3 containing medicinal products tested in population of patients early (within 90 days) after MI. The study had however an open label design while events were adjudicated by blinded events committee. The background therapy was different compared to current SoC (in particular the proportion of patients on statins was much lower compared to the proportions observed in recent RCT or in similar populations of patients as also reported in the EUROASPIRE V survey [*https://www.eas-society.org/news/399857/EAS2018-Late-Breaking-Clinical-Trial-EUROASPIRE-V.htm*]). Although the MAH presentations drew attention to poor adherence with preventive therapy, particularly statins, this was felt to be much less of an issue in the first 12 months after MI. Also, the frequency of revascularisation procedures during the course and after MI and the use of drug eluting stents is currently much higher than when GISSI-P was conducted. Also more patients are subjected to implantation of medical devices (ICDs). The standards of reporting of clinical trials have changed as well (for example the definition of the mode of death would have been recorded and reported more precisely; subgroup analysis by sex would be pre-specified and conducted; survival analyses accounting for competing events would have been performed).

The remaining RCTs were seen as less relevant for the currently discussed indication (SU.FOL.OM3 study: different product formulation and lower dose of Omega-3 containing medicinal products, patients included within 12 months after acute coronary or cerebrovascular event; GISSI-HF and ORIGIN studies: patients included were not fully representative for discussed indication of secondary prevention after MI; the number of patients who had experienced a MI was lower than 50 % in these studies and the time from MI to enrolment in the study was heterogeneous and generally far from the acute event).

Meta-analysis (Aung et al 2018) did not provide confirmatory evidence of a beneficial effect of Omega-3 - containing medicinal products when used in secondary prevention after MI but there were many limitations of this meta-analysis, in the context of the indication currently discussed, that were noted. Among others the experts flagged: (1) the heterogeneity of the studies included in this meta-analysis (with more or less relevant population of patients), (2) the variability of different doses of omega-3 products tested, (3) different lengths of follow up in studies included and (4) aggregated study-level

data but not individual patients-level data included in this meta-analysis. Also, a random effect meta-analysis would have been more appropriate. It was agreed that the meta-analysis of OMEGA and GISSI-P studies would have been more relevant for the indication currently discussed, specifically if conducted on total mortality and on sudden cardiac death.

The experts noted that the retrospective cohort studies were performed in populations of patients in post MI-cohorts with treatment onset <90 days post MI in line with the GISIS-P study. However, the limitations of retrospective cohort studies (eg Macchia, Poole, Green) were also identified. Propensity score matching were not systematically performed (used in one study only). Only limited amount of parameters in these retrospective analyses were available. These were useful to characterise the patient population that was looked at, but were not rich enough to allow for a full adjustment of differences in risk profiles or to mirror real life post MI situations (eg no data regarding smoking history, BMI/obesity, physical exercise in Macchia study). Thus, retrospective data in these studies did not allow for appropriate statistical adjustment for confounding. Also, in the retrospective cohort study by Polle (2013) only 1 % of post MI patients who were screened were included in the analysis and the experts did not consider this to reflect the "real-life" population of post MI patients.

The recommendations of the learned societies were discussed including some discrepancies. Patients' representatives considered recommendations regarding healthy diet valuable as well as availability of products with relatively mild safety profile. They expressed an opinion that the adherence rate to Omega-3 containing medicinal products should be at least comparable if not better to statin therapy.

The expert felt that there might have been evidence supporting the indication discussed at the time the GISSI-P was finalised in the late nineties but new data were subsequently generated that should be currently considered. Based on the results of studies available today the experts did not see a place for therapy with Omega-3 containing medicinal products at a dose of 1g/day in the context of secondary cardiovascular prevention after MI given the considerations regarding RCTs (particularly OMEGA and GISSI-P studies), meta-analysis and retrospective cohort studies described above.

Further studies with Omega-3 containing medicinal products in this population of patients were encouraged by the group especially including studies with higher doses of these agents. Also it was recognized that more data with higher doses will soon be available (REDUCE-IT in November 2018 and STRENGTH early 2019).

4. Benefit-risk balance

4.1. Initial benefit-risk balance assessment

The aim of the current referral procedure is to evaluate the benefit-risk balance of omega-3 acid ethyl esters containing products in secondary prevention of patients having experienced a myocardial infarction based on all currently available data.

The current approval of omega-3 acid ethyl esters containing products in secondary prevention after myocardial infarction is based on the results of the GISSI-P study performed in 1999. In this study, there was a relative risk reduction for one of the two the co-primary MACE endpoints of 10% with a rather poor precision (upper CI 0.99) with the second co-primary endpoint just failing to show a significant result. The study is associated with some methodological limitations - this was an open label study where the control group did not receive study medication which may have influenced the results. The issue is highlighted by the fact that omega-3 acid ethyl esters had little effect when compared to the Vitamin E arm in the same trial. Vitamin E is not considered beneficial in the prophylaxis of cardiovascular events.

In addition, it may be questioned if the results are relevant in the context of current MI standard of care which has substantially evolved since the time the study was performed and secondary prevention of CVD. In GISSI-P at the most, 5% of the patients received lipid lowering therapy over the whole period of the first year. Although statin use increased during the study, it was only 28 – 29% at 6 months and 44 – 46% at 42 months. Beta-blockers that are indicated in most patients post MI were only used in 37 – 44% in GISSI-P. Therefore, at the most about 1/3 of the 11,324 randomized patients received appropriate baseline medication at any time during the first year and not more than 5% over the entire first year. In conclusion, the level of evidence resulting from the GISSI-P trial to support a beneficial effect of Omega-3 for secondary prevention after myocardial infarction at the dose of 1 g/day is weak. This study suffers from some methodological limitations and results should be interpreted with caution.

In GISSI-P, a reduction of sudden death events was seen in secondary two-way analyses of fatal events. The primary objective of the OMEGA trial was to study the rate of sudden cardiac death testing one of the postulated mechanisms of action (antiarrhythmic) of Omega-3 in GISSI-P. The OMEGA trial was a large prospective, double blind, randomized study including a population highly representative of the target population including the use of standard of care treatment. Even though the incidence of sudden death may have been too low to draw firm conclusions, the OR was 1.25 (0.90-1.72) for total mortality and 1.21 for MACE (0.96 – 1.52), so it is considered unlikely that a beneficial effect could have been shown with a larger trial. Therefore, these results do not support an effect in secondary prevention after MI. It has also been argued that the OMEGA trial had a too short duration (12 months) to observe beneficial effects. However, in the GISSI-P trial, the effect was most pronounced at earlier time points (<12 months) with no increase thereafter. OMEGA trial was based on a more robust and adequate design than GISSI-P. It did not reproduce these findings and did not demonstrate efficacy in this indication.

In addition, in other prospective randomised trials performed after the original approval (GISSI-HF, ORIGIN study and SU.FOL.OM3 performed between 2003 and 2012), as well as in meta-analyses (e.g. by Aung et al. 2018), the results from the GISSI-P study could not also be reproduced. Even though doses and populations in these studies do not fully represent the approved secondary prevention indication, all studies include patients with cardiovascular disease and therefore, these studies are relevant in the context of omega-3 in secondary prevention after MI. Similar to OMEGA trial, a lack of effect of in this indication was observed. If there was a relevant beneficial antiarrhythmic efficacy of omega-3 acid ethyl esters, as has been stated, it should also have been relevant for those patient populations at increased cardiovascular risk included in these studies. Since this was not the case, these can be considered supportive for a lack of efficacy.

The results of the meta-analyses by Aung et al. and the recent Cochrane review, even though includes trials with products, doses and populations not exactly representing the approved secondary prevention indication, are considered relevant as all studies include patients with cardiovascular disease and therefore are supportive of lack of efficacy.

The CHMP reviewed the results of 3 submitted cohort studies, including subjects who had experienced a MI, which seem to be in line with the results of the GISSI-P study. Two of the studies (Greene and Macchia) included a large number of subjects and for the latter, the documented risk reduction for all-cause mortality was 37% (RR 0.63 CI 0.56-0.72). These results should, however, be interpreted with caution. All these studies carry the risk of a selection bias, which is supported by baseline data provided, e.g. in the retrospective cohort study by Polle (2013) only 1 % of post MI patients who were screened were included in the analysis. No attempts have been made to adjust for likely differences between centers regarding strategies and ambition for secondary prevention, likely creating correlations within centers. Some of the results cast doubts on whether the associations seen actually reflect biologically plausible effects or more likely reflect a selection bias problem. Only a limited

amount of parameters in these retrospective analyses were available. These were not rich enough to allow for a full adjustment of differences in risk profiles or to mirror real life post MI situations (e.g. no data regarding smoking history, BMI/obesity, physical exercise were reported in the Macchia study). Thus, retrospective data in these studies did not allow for appropriate statistical adjustment for confounding. Based on these limitations, the results of the cohort studies are not considered to override the results of the randomized trials referred to above.

Studies investigating the effect of Omega-3 acid ethyl esters medicinal products on atrial and ventricular arrhythmias did not demonstrate a clinically relevant antiarrhythmic efficacy. Treatment with Icosapent ethyl 4g/day was associated with an increase in hospitalization for atrial fibrillation of flutter in the REDUCE-IT trial. Studies in patients with an implantable cardioverter defibrillator (ICD) showed inconsistent results regarding antiarrhythmic efficacy (Leaf et al., 2005; Brouwer et al. 2006, Raitt et al., 2005; Weisman et al., 2017).

In view of all the available data, the CHMP considered that the evidence that supported the authorisation of omega-3 in secondary prevention after MI suffered from some methodological limitations and was weak. The efficacy in this indication was not demonstrated in subsequent and more robust clinical trials.

It should also be noted that the current European guidelines no longer recommend omega-3 supplementation in this indication.

Upon request from the CHMP, a SAG CVS meeting was convened on 10 October 2018 (see details above). Based on the results of studies available today the experts did not see a place for therapy with Omega-3 containing medicinal products at a dose of 1 g/day in the context of secondary cardiovascular prevention after MI given the considerations regarding RCTs (particularly OMEGA and GISSI-P studies), meta-analysis and retrospective cohort studies.

With respect to safety, the PRAC concluded in the last PSUSA (January 2017) that no new safety issues had emerged. In general, it can be concluded that the safety profile seems well characterized. As discussed above, in the last PSUSA for omega-3-acid-ethyl esters, “increase in bleeding time in patients with haemorragic diathesis or receiving treatment with anticoagulants” and “increase in hepatic enzymes that require monitoring in hepatic patients” was included as identified risks. The increase in bleeding time may be relevant for patients post MI most of which are on single or dual antiplatelet therapy and/or on anticoagulants post MI or for associated diseases.

Based on the totality of the data emerging after the original approval as well as the serious limitations of the GISSI-P trial, the CHMP concluded that efficacy is not established in secondary cardiovascular prevention at the dose of 1 g/day and whereas the safety profile of Omega-3 -acid ethyl esters is unchanged, the CHMP concluded that the benefit-risk balance in this indication is no longer favourable.

4.2. Re-examination procedure

Following the adoption of the CHMP opinion in December 2018, a re-examination request was received from two of the MAHs involved in the procedure, BASF AS and ALFASIGMA S.p.A (on behalf of DOC GENERICI S.r.l., EG S.p.A., IBSA FARMACEUTICI ITALIA S.r.l., PFIZER ITALIA S.r.l., SPA SOCIETÀ PRODOTTI ANTIBIOTICI S.p.A.).

It is noted that the CHMP is a scientific committee and that while it operates within the framework of the Union legislation regulating medicinal products, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the CHMP, and therefore the re-examination of the

referral procedure under Article 31 of Directive 2001/83/EC focuses only on the scientific grounds for re-examination.

4.2.1. Detailed grounds for re-examination submitted by the MAH

The grounds for re-examination of the CHMP recommendation as submitted by the MAHs are summarised below.

Grounds submitted by BASF AS (*representing Mylan Hrvatska D.O.O, BGP Products Ltd, Ferrer-Galenica S.A and Strides Arcolab International Limited)*

i. Omacor is an authorised medicinal product without any known safety concerns

In their first argument the MAHs pointed out that Omacor has been authorised and placed on the market in the European Union ("EU") since 2001 and the MA was renewed in 2006 on the basis of a re-evaluation of the risk-benefit balance of the medicinal product by the competent authorities in EU Member States, with no new safety concerns identified related to treatment of patients with Omacor.

The MAHs also argued that removal of a therapeutic indication from the marketing authorisation for Omacor may be justified only after demonstration that the use of medicinal product for this indication is harmful, lacks therapeutic efficacy or the risk-benefit balance of the medicinal product is not favourable according to Article 116 of Directive 2001/83/EC and that these conditions have not been met.

ii. Available scientific evidence supporting the favourable risk-benefit balance of Omacor as an adjuvant treatment in secondary prevention after myocardial infarction

For this second ground the MAHs presented a list of arguments based on the scientific data assessed by the CHMP and listed their points of disparity. Their argumentation is listed and summarised below.

GISSI Prevenzione ("GISSI-P") demonstrated clinically and statistically significant mortality benefits

The MAHs argued that the GISSI-P trial generated robust clinical data that demonstrates the efficacy of Omacor as an adjuvant treatment in secondary prevention after myocardial infarction. The first main endpoint of GISSI-P, a composite of cardiovascular death, non-fatal MI and non-fatal stroke, was reduced by 10% in the two-way analysis and 15% in the four-way analysis, both with statistical significance. After analysing the secondary endpoints, it can be observed that the benefit was driven by reduction in mortality, more specifically by sudden death, which was reduced by 26% in the two-way analysis and by 46% in the four-way analysis.

The MAHs also pointed out that although in the initial Opinion the CHMP focused on the two-way analysis the main strategy defined in the protocol was to conduct a four-way analysis and therefore this should be acknowledged in the assessment. The MAHs also defended the validity and wide acceptance of the PROBE design and how an open label design did not significantly influenced adherence to post-MI medication or dietary behaviours.

The MAHs discussed the post-hoc analyses from GISSI-P that have been conducted to investigate the validity of the data under changing clinical treatment standards. These analyses demonstrated that concomitant treatment with antiplatelet agents, beta-blockers, ACE inhibitors, and statins did not alter the therapeutic benefit of Omacor.

The MAHs also criticised the comparison of vitamin E results in GISSI-P with results from the WAVE and HOPE trials which is not according to scientific and regulatory principles.

The risk-benefit balance of Omacor remains favourable over time

The MAHs defend that the GISSI-P trial demonstrated the benefit of the use of Omacor in patients with a recent MI and highlighted that the experts of the SAG conducted in October 2018 acknowledged that GISSI-P provided evidence supporting the efficacy of Omacor as an adjuvant treatment in secondary prevention after myocardial infarction "at the time the GISSI-P was finalized".

The MAHs consider that a number of key questions were not addressed by CHMP in order to properly conclude on the validity of the data generated in the GISSI-P Trial and the related conclusions concerning the efficacy of Omacor. The MAHs argue that although the diagnostic criteria for cardiac disease and myocardial infarction have changed slightly over the years, the clinical characteristics of an individual MI patient have not changed and although new treatment standards are utilised in many post-MI patients today, this does not disqualify the potential benefit of an existing treatment option for certain patients who, for various reasons, are or cannot be treated according to these new treatment standards. As such, the efficacy of Omacor as an adjuvant treatment in secondary prevention after myocardial infarction remains unquestioned and the available data reviewed by CHMP does not suggest that the clinical effects or characteristics of Omacor have changed over time, or that Omacor is not effective.

The OMEGA Trial was severely underpowered and the data generated in this Trial could not be deemed statistically valid

The MAHs questioned the validity and reliability of the data generated in OMEGA clinical trial and highlighted that the trial was essentially, severely underpowered to detect a potential benefit of Omacor on sudden cardiac death and total mortality and therefore, cannot be used for any regulatory purposes whether it is an application or a withdrawal of an indication.

Design and statistical considerations in relevant regulatory guidelines – the need for adequately powered clinical trials to demonstrate the efficacy of a drug

The MAHs also highlighted that the OMEGA study does not comply with CHMP guidelines that establish the adequate approach to demonstrate the quality, safety and efficacy of medicinal products, especially the principles for statistical evaluations and sample size determination. The MAHs pointed out that the OMEGA trial failed to ensure adequate sample size and power calculations, and as such reduced the value of the trial to such a degree that it cannot be used as convincing evidence to support a claim.

As a consequence the MAHs argued that the results of the OMEGA trial could not be relied upon by the CHMP as the clinical trial is severely underpowered and the data generated were not statistically valid.

Retrospective cohort trials as supportive evidence for GISSI-P outcomes

Three retrospective cohort studies conducted in the last 6 years generated additional data concerning the efficacy of Omacor as an adjuvant treatment in secondary prevention after myocardial infarction. The MAHs pointed out that these results confirmed the data generated in the GISSI-P trial as well as related findings and conclusions concerning the efficacy of Omacor in the secondary prevention of MI, and that these data remain valid in light of the developments in the treatment standards.

The MAHs highlighted that the findings from these three retrospective cohort studies cannot be considered to be inconsistent. The studies consistently demonstrate mortality reductions in the range of 22-41% following treatment of patients with Omacor. The results of all three retrospective cohort studies are statistically significant, in the MAHs' view.

Recent data failing to show benefit of omega-3 acid ethyl esters is unspecific

The MAHs have pointed out that the scientific conclusions included in the initial CHMP Opinion and the related CHMP Assessment Report, appeared to rely on arguments that are based on data not relevant for Omacor and its specific use as an adjuvant treatment in secondary prevention after myocardial infarction. The initial CHMP opinion and the related CHMP Assessment Report state that recent clinical trials and meta-analyses results have failed to show a beneficial effect in patients after myocardial infarction. The MAHs still have strong reservations concerning the relevance and reliability of the data generated in the abovementioned meta-analyses and clinical trials.

Meta-analysis

The MAHs pointed out that the data generated in the meta-analysis is not relevant or reliable and therefore cannot support a conclusion by the CHMP that the risk-benefit balance of Omacor is negative for use in secondary prevention after MI.

The Rizos EC et al. meta-analysis reviewed 20 studies with significant differences regarding patient populations. While the discussed indication is intended for patients with history of myocardial infarction, some studies in this review included as little as 5% of post-MI patients, in some cases, even excluding patients with early events. The assessed studies by Rizos et al weren't specific regarding outcomes since 6 of them didn't have MI as an outcome.

Regarding the Kotwal S. et al. meta-analysis, when the studies were selected for this meta-analysis, no criteria were established regarding the dosage or source of omega-3. In addition, the proportion of included patients with previous MI varied from 5 to 100%. The difference regarding the follow up duration of the included trials contributed as well to the heterogeneity of the meta-analysis, with a range from 6 months to 6 years.

The 14 studies included in the Kwak et al meta-analysis, were conducted using a very variable dose of omega-3 supplementation, ranging from 0.4 to 4.8 g/d, since only 4 studies were conducted using the post-MI prescription product Omega-3-acid ethyl esters 90 and in one of the included studies the intervention was made with enriched food. Regarding the history of MI, only 4 trials assessed this type of event and the proportion of post-MI patients varied from 12 to 100% among the studies. It is worth mentioning that GISSI-P was not reviewed in this meta-analysis for having an open-label design.

The Aung T et al. meta-analysis included 10 trials from which only 4 were conducted using omega-3 acid ethyl esters. From the remainder ones, 4 were conducted using dietary supplements, 1 with an EPA product and 1 was conducted using enriched food. The dose of supplementation was also very different among the studies. Regarding the proportion of post-MI patients included, it was as low as 5% in one of the assessed studies and another study even excluded this type of patients.

The Cochrane review (2018) was a meta-analysis assessing 79 trials, but this extensive database increases the risk of heterogeneity. Regarding the intervention, most studies assessed long chain omega-3 (LCn3) supplementation with capsules but some used LCn3- or ALA rich or enriched foods or dietary advice compared to placebo or usual diet. The included population was also heterogeneous, including not only 100% post-MI patients, but also subjects with no history of cardiovascular disease.

Other studies

The MAHs also discussed other studies.

The MAHs also criticised the CHMP argument that cardiovascular disease is a continuum, and that if Omacor is effective one would expect to observe cardiovascular benefits also in other cardiovascular patient populations and not only with early treatment onset after an MI.

The MAHs also considered that data generated in three single studies data is not relevant for Omacor and the specific therapeutic indication of the medicinal product, and therefore, cannot support a

conclusion concerning the lack of efficacy of Omacor or a negative risk-benefit balance for Omacor when used as an adjuvant treatment in secondary prevention after myocardial infarction.

Regarding GISSI-HF study the MAHs pointed out that even if the intervention was carried out using omega-3 acid ethyl esters in the same dose of the indication under discussion, the population was different. Heart failure normally develops after other condition weakens or stiffens the heart and its function becomes affected. Myocardial infarction is among the list or risk factors that can lead to heart failure, but it is not the only one. Other chronic diseases such as diabetes or myocarditis after infections can lead to heart failure as well.

The ORIGIN study intended to evaluate whether omega-3 acid ethyl esters could reduce cardiovascular mortality among patients with diabetes or at risk for this condition. Even though the occurrence of myocardial infarction was assessed among the secondary endpoints when analysing the baseline characteristics of ORIGIN, patients with history of myocardial infarction were included in a subgroup, together with those with stroke or revascularization history. No analysis has been carried out among post-MI patients, and, therefore, no conclusion can be drawn from this trial to conclude on an indication for post-MI subjects. So in the ORIGIN trial once again the study population was not comparable with a post-MI population.

Despite the history of cardiovascular disease that the participants should have to be included in the SU.FOL.OM3 study, the population remained imprecise for the discussed indication as it included patients with cerebral ischaemic events and acute coronary syndrome, in addition to those with history of myocardial infarction. With regard to the intervention, the omega-3 used was a dietary supplement containing 600mg of EPA+DHA and not a pharmaceutical product containing 1 gram which is the dose of the post-MI indication.

Therapeutic guidelines: generally beneficial for cardiovascular risk prevention

The MAHs argued that the most important limitation of therapeutic guidelines is the lack of specificity. In the MAHs' view, guidelines are not designed for individual patients but intended to treat wide groups of patients to reduce outlays for hospitalisation, prescription drugs, surgery, and other procedures. Guidelines are recommendations made by various societies to assist the clinician in his/her everyday clinical practice. However, they are not linked to approval of indications by regulatory bodies and therefore the MAHs states that the citation of guidelines is less relevant.

iii. A modified text for the current therapeutic indication to treat post-MI patients with Omacor

The MAHs maintained the view that the Committee should consider regulatory alternative actions including a more precise wording for the therapeutic indication for Omacor that ensures the medicinal products are used for the treatment of those patients under a higher risk.

To that effect, they proposed the following indication:

> *Adjuvant treatment in secondary prevention, initiated within 3 months after myocardial infarction, in addition to other standard therapy (e.g. statins, antiplatelet medicinal products, betablockers, ACE inhibitors).*
>
> *Treatment should be particularly considered in patients having high residual risk, such as:*
>
> - ✓ *Type 2 diabetes*
> - ✓ *No acute PCI after MI*
> - ✓ *Impaired systolic function (EF < 50%)*
> - ✓ *Known intolerance to one or more guideline recommended cardiovascular medications*

To support the above, the GISSI-P investigators conducted new *post-hoc* analyses on high-risk patient subgroups based on the data generated in the GISSI-P Trial. The purpose of the new subgroup post-hoc analyses on high-risk patients' groups was to demonstrate that Omacor is particularly efficacious in patients with high risk after having had a myocardial infarction. The company maintained the view that these patient groups would benefit from Omacor and thus the existing indication with a modified text is highly relevant and addresses a medical need that is currently unmet.

Grounds submitted by ALFASIGMA S.p.A *(on behalf of DOC GENERICI S.r.l., EG S.p.A., IBSA FARMACEUTICI ITALIA S.r.l., PFIZER ITALIA S.r.l., SPA SOCIETÀ PRODOTTI ANTIBIOTICI S.p.A.)*

The grounds from Alfasigma S.p.A. (on behalf of the abovementioned group of companies) are also summarised below.

i. GISSI-P study, GISSI-P Investigators, 1999

The MAHs consider the GISSI-P as the most relevant study to support the secondary cardiovascular prevention indication, particularly in patients in which full adherence to current guidelines recommendation is not achievable.

The MAHs pointed out that although the result for Vitamin E did not reach statistical significance compared to untreated controls in the two-way analysis, there was little difference between the three active treatment arms, one including administration of Vitamin E only in the four-way analysis. In their opinion, the four-way analysis provides a clearer profile of the effects of n-3 PUFA, without any possible interaction.

Regarding the design of the trial the MAHs maintained the opinion that this did not represent a major concern being sudden cardiac death, a fatal outcome that traditionally has proven to be largely resistant to medical intervention; therefore it is considered a hard clinical endpoint in post-MI patients. Also, the MAH argued that the observed reduction of cardiovascular mortality cannot be ascribed to adherence to placebo *per se*, but rather to adherence to all recommended treatment strategies.

In the GISSI-P trial, the control group patients were not taking placebo but they received baseline drugs and other nonpharmacological recommendation, as well as the n-3 PUFA group of patients. Amongst control and n-3 PUFA groups, there were patients either adherent or not adherent to all the recommended therapies; however the dietary habits, recommended secondary prevention treatments, and revascularization procedures at baseline and during the study, were well balanced across both groups. For all these reasons, the open design of GISSI-P trial does not represent, in the MAHs opinion, a bias for the obtained results.

ii. OMEGA trial, Rauch et al 2008

The MAHs are of the opinion that the OMEGA trial is statistically underpowered and should not be considered to provide unequivocal evidence on the lack of efficacy of omega-3 acid ethyl esters containing medicinal products in the secondary cardiovascular prevention indication; furthermore the population under study is not representative of a real life setting.

iii. Adherence to standard care therapy

The MAHs pointed out that in a real life setting low treatment adherence is an important barrier to achieve optimal treatment targets. Also the MAHs was of the opinion that the treatment with n-3 PUFA

still represents a therapeutic opportunity for high risk patients in whom, despite any effort put in place, the complete adherence to the guideline-driven therapies cannot be reached.

Moreover, the MAHs highlighted that in a recent trial (REDUCE-IT), conducted in patients under baseline current standard of care, statistically significant results have been obtained by higher doses of n-3 PUFA.

iv. Recent clinical trial evidence (ASCEND, VITAL, REDUCE-IT)

The MAHs supported the fact that studies recently published bring new information on the role of n-3 PUFA.

The results of ASCEND trial, very recently published (The ASCEND Study Collaborative Group, 2018), demonstrate that, among patients with diabetes without evidence of cardiovascular disease there was a trend toward a reduced rates of deaths from any cause in the n-3 fatty acid group in comparison to the group assigned to receive placebo. Deaths were reported in 752 patients (9.7%) and 788 patients (10.2%), respectively (rate ratio, 0.95; 95%CI, 0.86 to 1.05). Moreover, additional sub-groups analyses ("Vascular Death") showed that there were significantly fewer vascular deaths in the n-3 fatty acid group than in the placebo group (196 patients [2.5%] vs. 240 [3.1%]) Rate Ratio (95% CI) 0.82(0.68–0.98).

In November 2018, the results of VITamin D and omega-3 TriaL (VITAL) were published in N. Engl. J. Med. The VITAL trial examined the effects of omega-3 fish oil supplementation (1 g/day containing 460 mg EPA and 380 mg DHA) with or without 2,000 IU/day vitamin D for a median of 5.3 years (Manson et al 2018). The study population consisted of 25,871 men aged 50 and older and women aged 55 and older with no previous heart attacks, strokes, or cancer. Participants taking the omega-3 treatment experienced a statistically significant 28% reduction in total myocardial infarction rates (including a 40% reduction among those who consumed less than 1.5 servings of fish *per* week). Omega-3 treated group had significant reductions in rates of fatal myocardial infarction, total coronary heart disease, and percutaneous coronary intervention (PCI). No significant reductions in stroke or death rates from cardiovascular causes were observed.

The REDUCE-IT study showed that purified n3-PUFA reduced the primary end-point by 25 % and the secondary end point by 26%. The primary end point was a composite of cardiovascular death, non-fatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end-point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

v. Meta-analyses

The MAHs discussed why meta-analyses, due to combined types of participants with different level of risk ranging from low risk in primary prevention to patients with high mortality risk, heterogeneous conditions and products, lead to debatable statistical results.

Aung et al 2018

The MAHs pointed out several limitations of the meta-analysis: both primary and secondary prevention studies were included; underlying medical conditions and different grade of risk of the patient population; variable doses of ω-3 PUFAs were used; it involved the use of aggregated study level data rather than individual-level data; also, the authors stated that the 95% CIs cannot exclude a 7% lower risk of major cardiovascular events and a 10% lower risk of ischemic events, associated with ω-3 PUFA supplementation.

Other meta-analysis

On the other hand, the MAHs pointed out that other meta-analyses demonstrated the favourable effects of n-3 PUFA supplementation on mortality, including work by Alexander et al. (2017) and Maki et al (2017).

However, the MAHs criticised a Cochrane Systematic Review performed in 2018. The MAHs considered that the Cochrane meta-analysis is based on old data and does not provide the final answer on the omega-3 question.

vi. Retrospective cohort trials in patients after an acute myocardial infarction

The MAHs argued that these real life studies (mainly by Greene and colleagues; 2016) supported the efficacy of n-3 PUFA in secondary prevention.

The MAHs pointed out that regarding the Poole CD et al. study (2013), the real-world evaluation of clinical practice complemented randomised trial data by demonstrating that treatment with n-3 fatty acids was associated with reduced all-cause mortality when initiated early post-MI. These data are in the MAHs' view concordant with the 20% reduction in all-cause mortality reported in the GISSI-P investigators 1999 trial.

The MAHs also highlighted that in Greene et al. study (2016), which was a large, contemporary observational study of Italian patients hospitalised for AMI, the use of n-3 PUFA was independently associated with a relevant reduction in all-cause mortality and recurrent AMI. This large study demonstrated the influence of n-3 PUFA use on post-AMI clinical outcomes in a "real-world" situation.

vii.Therapeutic guidelines

The MAHs pointed out that recommendations from European guidelines cannot be considered relevant in this context.

The role of omega-3 fatty acids ethyl esters containing medicinal products as therapeutic option in secondary prevention is reported in the: 2016 European Guidelines on cardiovascular disease prevention in clinical practice and the AHA Science Advisory - Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease - A Science Advisory From The American Heart Association (Siscovick et al. 2017).

Regarding omega-3 fatty acids, the 2016 European Guidelines on cardiovascular disease prevention in clinical practice, state that "…it is debatable whether they exert a favourable effect on all-cause, CAD and stroke mortality" and " A recent meta-analysis of 20 trials, mostly prevention of recurrent CV events and mostly using fish oil supplements, showed no benefit of fish oil supplementation on CV outcomes."

However, the above European guideline position is based on meta-analysis that are not considered relevant in this setting. Wen's meta-analysis, that was aimed at investigating the effects of omega-3 fatty acids on major cardiovascular events and mortality in patients with coronary heart disease from the early-phase (e.g. in primary prevention before MI and HF). By contrast, subgroups analysis demonstrated beneficial effects in reducing death from cardiac causes (OR= 0.88; 95% CI, 0.80 to 0.96), sudden cardiac death (OR, 0.86; 95% CI, 0.76 to 0.98) and death from all causes (0.92; 95% CI, 0.85 to 0.99). Also, Rizos' meta-analysis due to combined types of participants, heterogeneous conditions and products, resulting in debatable statistical results.

viii. Data on safety

The MAHs further discussed the safety profile of n-3 PUFA with special focus on bleeding events.

In their view, the safety profile of n-3 PUFA is well known and the products, administered at authorized dosages, are recognized as safe and well tolerated. The potential increase in bleeding time, especially in patients receiving treatment with anticoagulants, has been analysed in the post marketing setting as well as in clinical trials and publications. Bleeding-related evidence was infrequently reported in the MAHs' post-marketing databases and no significant difference in the occurrence of the adverse events, relevant to bleeding, between the intervention and control groups, resulted from the relevant clinical trials and publications.

4.2.2. CHMP discussion on grounds for re-examination

CHMP considered the detailed grounds as submitted by the MAHs within this re-examination procedure and the scientific data underlying these grounds.

GISSI-P study

The approval of the post-MI indication was based on the outcomes from the GISSI-P trial, which was initiated in 1993 and published in 1999. GISSI-P is a multicentre, open-label design study (PROBE design) in which 11,324 patients after (≤ 3 months) myocardial infarction were randomly assigned to receive omega-3 acid ethyl (1 g daily, (n=2836); vitamin E (300 mg daily, n=2830); both (n=2830); or none (control, n=2828), for 3.5 years.

The analysis was done with the 'intent to treat' samples and according to two predefined strategies: first, a two-way (omega-3 groups vs. control groups); and second a four-way (all four groups) analysis. In the two-way factorial analysis, a 10% relative decrease in risk for the first co-primary endpoint (all-cause death, non-fatal MI and non-fatal stroke) was found (95% CI 0.82-0.99, p=0.048), but the decrease in risk for second co-primary endpoint (CV death, non-fatal MI and non-fatal stroke) was not statistically significant (11% [95% CI 0.80-1.01], p=0.053). In the four-way analysis, both co-primary endpoints showed statistically significant relative decreases of 15% ([95% CI 0.74-0.98, p=0.023) and 20% (0.68-0.95, p=0.008), respectively. Based on these results, the MAHs considered that GISSI-P demonstrated clinically and statistically significant mortality benefits.

Since the two-way analysis was the first predefined test procedure according to the publications by GISSI-P investigators (1999) and Marchioli (1999), the beneficial effect is considered borderline by the CHMP. The study did not provide a statistically significant difference on both co-primary endpoints with the primary analysis and the study failed. In the grounds the MAHs mentioned that the four-way analysis should also be fully acknowledged. However, this analysis was defined as secondary, and in a hierarchical testing sequence the co-primary endpoints would not have been analysed using the secondary four-way method because the primary analysis failed on one of the co-primary endpoints. Furthermore, the effect of omega-3 on the co-primary endpoints was exclusively driven by fatal cardiovascular events, while there was no risk reduction observed on non-fatal cardiovascular events. This is not expected in a cardiovascular outcome study.

A key concern in today's context with this study is that standard of care for the treatment after MI has intensified since the GISSI-P, in particular use of statins, beta-blockers and invasive treatment including PCI. In GISSI-P, at baseline only about 5% of the patients received lipid lowering medication and after 42 months the proportion of patients on lipid lowering therapy was only approx. 25%. With regard to invasive treatment, 5% of patients had coronary artery bypass graft or angioplasty procedures before recruitment and after 42 months 24% of patients had received invasive treatment. The observation that patients were not on optimal current standard of care has also been underlined by the mean LDL-C levels at baseline of 137 mg/dL, which is much higher than the LDL-C target of < 70 mg/dL recommended in the current ESC EAS guideline.

Therefore, the GISSI-P study does not support the current wording of the indication of omega-3 acid ethyl esters *"treatment of secondary prevention after myocardial infarction in addition to other standard therapy (e.g. statins, antiplatelet medicinal products, beta-blockers, ACE inhibitors)*".

Another concern of this study was its open-label design (PROBE) and that the control group did not receive placebo. It is agreed that the open-label design did not seem to influence adherence to post-MI medication or dietary behaviours, since these were well-balanced between the groups. In addition, it is agreed that it can be assumed that the evaluation of the endpoints by the Blinded endpoint committee are not influenced by this design since it concerns hard clinical endpoints. However, as previously mentioned in the initial assessment, this design raises serious concerns since placebo effects were not controlled and clinical decision making and diagnoses are influenced by the knowledge about treatment, which could have an effect at the endpoints. Moreover, the control group could not experience a placebo effect as they knew that they did not receive any treatment.

Furthermore, the MAHs claimed that *post-hoc* analysis (Marchioli et al 2007) conducted on GISSI-P showed no evidence that concomitant pharmacological interventions with statins, anti-platelet medicinal products, beta-blockers or ACE-inhibitors altered the therapeutic benefit of omega-3 treatment. To assess the benefit of Omacor in patients with or without statins, information was collected in 4271 GISSI-P patients who came to the 6-month follow-up visit with total blood cholesterol >200 mg/dl and who accepted to be included in the nested clinical trial testing the efficacy of pravastatin (20 mg) daily vs. no treatment. The results showed that, among those patients under treatment with Omacor, there was no difference in mortality rates whether they were allocated to statins or not. According to the MAHs, this analysis confirms and validates the fact the Omacor remains efficacious for secondary prevention in post-MI patients with modern guideline-adjusted background therapy and that the risk-benefit balance of the medicinal product remains favourable.

This argument is not endorsed by the CHMP. First, 20 mg of pravastatin is considered a low-intensity statin regimen, whereas a high-intensity statin regimen is defined as atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg daily. Therefore, it can be concluded that subjects in this subgroup analysis where not on optimal statin therapy. Secondly, not observing a difference is not the same as concluding there is no difference. Thirdly, although this *post-hoc* analysis did not show differences in benefit with or without concomitant statin therapy, potential differences could not be excluded since the study was not sufficiently powered to detect such differences. The latter concern also applies to *post-hoc* analyses in patients with or without anti-platelet medicinal products, beta-blockers or ACE-inhibitors. Overall, the CHMP considered that there is no evidence that concomitant pharmacological interventions did not alter the therapeutic benefit of omega-3 treatment. Therefore, the key concern that standard of care after MI has intensified since the time of the GISSI-P study, in particular statin therapy, beta-blockers and invasive treatment, still remains.

Based on the above CHMP considers that the results of the GISSI-P do not support the current indication "in addition to other standard therapy" while several studies have been published after approval, in particular the OMEGA trial, in the context of current standard of care failing to show benefit.

The MAH's argument that the GISSI-P population differed significantly from the populations of WAVE (postmenopausal women with at least one 15-75% coronary stenosis) and HOPE (cardiovascular disease, or diabetes mellitus) since neither of these studies systematically randomized recruited patients immediately after MI and consequently comparing Vitamin E results in GISSI-P with results from the WAVE and HOPE trials cannot be carried out is acknowledged.

In the grounds the MAHs highlighted that the Scientific Advisory Group (SAG) of October 2018 acknowledged that GISSI-P provided evidence supporting the efficacy of Omacor as an adjuvant treatment in secondary prevention after myocardial infarction at the time the GISSI-P was finalized

(minutes from SAG CVS meeting, 10 October 2018). Furthermore, the MAHs mentioned that the beneficial effects of omega-3 acid ethyl ester have not changed with time, as compared to 20 years ago there are no differences in the clinical characteristics of an individual MI patients and no differences in the formulation and mode of administration of the omega-3 product. The CHMP considered that the report from the SAG is misinterpreted since it is stated that "The expert felt that there might have been evidence supporting the indication discussed at the time the GISSI-P was finalised in the late nineties but new data were subsequently generated that should be currently considered". As mentioned above, the GISSI-P trial has several substantial limitations which also have been subject to criticism at the time of MAA. Since the GISSI-P trial showed beneficial effects, although inconclusive, and there were no major side effects, MA has been granted at that time in many Member States. However, after approval of omega-3 containing products, several RCTs have become available that failed to show benefits. Although these studies have limitations (see below), it is still considered that the results are more relevant than GISSI-P in the context of current standard of care for patients with a MI.

The standard therapy has been intensified since the GISSI-P trial, especially with respect to statin therapy, beta-blockers therapy and invasive treatment. Therefore, the results of the GISSI-P trial do not support the wording of the approved indication of Omacor "treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (e.g. statins, anti-platelet medicinal products, beta-blockers, ACE inhibitors)" since Omacor has not been evaluated on top of current standard of care in this study.

According to the data that are available, both endpoints in the two-way analyses (MACE and MACE/all-cause mortality) were considered in the primary endpoint and equally important. This raises a multiplicity issue for which no solution is discussed. If the endpoints are co-primary, according to today's standards, for a positive result both endpoints would be tested at p=0.05 and both should have been positive – which is not the case; in other scenarios, a statistical strategy (e.g hierarchy or Bonferroni) should have been pre-defined. In all these approaches, the trial outcome is considered inconclusive and the secondary endpoints only have hypothesis-generating strength.

OMEGA study

The CHMP acknowledged that the assessment should be based on indication specific studies using the approved pharmaceutical omega-3 acid ethyl ester product at the relevant dose (1 g/day) and conducted in patients with the approved indication, i.e. MI. In this respect, the OMEGA trial is considered most relevant in terms of studied population.

OMEGA was a randomised, placebo-controlled, double-blind multicentre trial conducted in 3,851 patients with myocardial infarction (NSTEMI/STEMI) between October 2003 and June 2007. The study drug was given over a period of 12 months in addition to guideline-adjusted treatment after AMI; 81% in the treated group were on statins, 86% on a beta-blocker, 94% on aspirin, and 88% on clopidogrel, 78% underwent acute percutaneous coronary intervention. The primary objective was to study the effects of Omega-3-acid ethyl esters (1 g/day for 1 year) on the rate of sudden cardiac death. No difference was observed between the two treatment arms for the primary endpoint sudden cardiac death (OR: 0.95; 95% CI 0.56-1.6, p=0.84)). Moreover, all-cause mortality and MACCE (major adverse cerebrovascular and cardiovascular events were numerically in favour of the control group (OR: 1.25; 95% CI 0.90-1.72, p=0.18 and OR: 1.21; 95% CI 0.96-1.52, p=0.10, respectively).

According to the MAHs, the OMEGA trial was severely underpowered from a statistical perspective, since the cohort size was too small to allow for sound statistical analyses. The OMEGA trial failed to prove a reduction in the primary endpoint and the event rates were substantially lower than anticipated. An *a posteriori* calculation, included in the main publication of the trial demonstrated that

the trial had only 44% power to prove a 45% risk reduction in the main endpoint, and only 19% for a risk reduction of 25%.

The CHMP acknowledges the fact that the study is underpowered, but in line with the outcome of the SAG on 19 March 2019 did not discount the study results. The OMEGA study had several strengths compared to GISSI-P, e.g. administration of study drug within few days of an MI, a placebo-controlled double-blind design and improved baseline therapy. The MAHs quote of relevant guideline "*included clinical trials need to be long-term controlled (usually 12 months or longer), parallel and preferably double-blind*" is correct. However, ignoring double-blind by using no treatment as comparator (as in GISSI-P) ignores another important concept in clinical trials, i.e. the use of a (blinded) comparator in order to control the other effects than the investigational drug, and deviation of this principle should only be needed or suitable "when it is difficult or impossible to avoid", according to ICH E10 (Choice of control group in clinical trials). The OMEGA study included close to 2,000 patients in both arms and over 300 MACE events were reported, more in the Omega group than in the placebo group OR 1.25 (0.96-1.52). The narrow confidence interval excludes any clinically relevant beneficial effects. Total mortality was also numerically higher in the omega-3 fatty acids group OR 1.25 (0.90-1.72). Despite the lack of statistical power for the specific “sudden cardiac death” endpoint, the lack of substantial benefit can be concluded from this trial in a statistically valid way, as evidenced by the narrow confidence intervals. Based on the results, there is only a 2.5% chance that the relative risk reduction for MACE exceeds 4%.

Based on above, the OMEGA trial is considered important evidence, by CHMP to establish a lack of clinically relevant efficacy of omega-3 acid ethyl esters in the approved indication at the approved dose.

Retrospective cohort studies

In support of the efficacy of Omacor as an adjuvant treatment in secondary prevention after MI, the MAHs provided the results of three retrospective cohort studies (Poole et al. 2013, Greene et al. 2016 (sponsored by Sigma), and Macchia et al. 2013) which have been conducted in the UK and Italy in the last 6 years. These three studies are considered to have sufficiently large populations of subjects diagnosed with acute MI, studied omega-3-fatty acids in the relevant dose of 1 g and evaluated all-cause mortality as main endpoint. Although the retrospective cohort studies confirmed the results of the GISSI-P study, they should be interpreted with caution given the known limitations of retrospective cohort studies. Especially selection bias is of concern as it can be envisaged that omega-3 fatty acids will be prescribed to certain patients (not needing strict treatment immediately). Furthermore, residual bias will always be present. Therefore, CHMP agrees with the MAHs that they can only be considered supportive.

Meta-analysis

The provided meta-analyses showed both positive and negative effects of omega-3 fatty acid treatment on the risk of cardiovascular events. The CHMP acknowledged that the studies included in the different meta-analysis are heterogeneous with respect to study population (e.g. patients with or without history of cardiovascular disease), study design (open-label or RCT), source of omega-3 fatty acid intake (dietary or medication intervention), dose and composition of omega-3 fatty acid. A meta-analysis using individual participant data (IPD), selecting patients with a history of MI and treated with the same dose as for the indication under review (1 g) would have been more appropriate. Therefore, it is considered that the validity of the meta-analyses is rather limited and that the meta-analysis can only be interpreted as being indicative, but not conclusive, with regards to potential efficacy or the lack of efficacy of omega-3 fatty acids in reducing the risk of cardiovascular events. For this, RCT data are available which included a sufficient number of patients and resulted in estimates of treatment effect with sufficient precision.

Other studies

The CHMP recognises that although the GISSI-P and the OMEGA trials are considered the most relevant for evaluating the effect of omega-3 containing products in the secondary prevention after MI, the CHMP considers that RCTs (GISSI-HF, ORIGIN, SU.FOL.OM3) conducted in other CV risk populations (e.g. coronary revascularisation, angina pectoris, ischaemic stroke) still provide relevant data. The CHMP still considers that cardiovascular disease is a continuum. Acute coronary syndrome (ACS) associated with typical coronary artery disease (atherosclerosis) is the most common cause of a MI. In addition to MI, ACS is also associated with unstable angina. Furthermore, ischaemic stroke is also most often caused by atherosclerosis. Therefore if Omacor is effective in reducing cardiovascular events after an MI, cardiovascular benefits in other CV risk populations (e.g. coronary revascularisation, angina pectoris ischaemic stroke) can be anticipated. The MAHs did not provide neither a plausible mechanism of action nor plausible (pre-)clinical data to support that omega-3 containing products would only be beneficial in the post MI-setting. Based on above, the CHMP believes that RCTs conducted in other CV risk populations are relevant in support of the efficacy or lack of efficacy of Omacor in secondary prevention of cardiovascular disease.

In GISSI-HF (Tavazzi et al. 2008) the observed beneficial effects are considered borderline with p-values just below the predefined significance levels. Furthermore, it is noted that MI is only one of the risk factors which can lead to heart failure and that the population is different compared to the indication under discussion. This is confirmed by the fact that only 42% of the patients included in this study had prior MI of which subgroup analyses are not available. Overall, this study is considered inconclusive with respect to the efficacy of omega-3 fatty acids secondary prevention in patients with myocardial infarction.

In the ORIGIN study (Bosh et al. 2012) no effect of omega-3 fatty acids on the primary or secondary cardiovascular endpoints was observed. Strengths of the study are the double-blind placebo-controlled design, the choice of the cardiovascular endpoints, the same dose as that for indication under review, the study size and the long observation period. However, the study population is not fully representative for the target population under review, i.e. post MI, since approx. 60% of the patients had established cardiovascular disease and only a part of these had a history of myocardial infarction. Nevertheless, as stated above, considering that cardiovascular disease is a continuum, a relevant effect in secondary prevention appears unlikely in the absence of any effect in an overall high CV risk population (primary and secondary prevention). Moreover, the subgroup analysis in those patients with a previous cardiovascular event also showed no efficacy (HR 0.99, (0.86 – 1.14). Overall, the ORIGIN study can be considered as a negative study for patients at increased cardiovascular risk including patients with myocardial infarction on baseline therapy according to current treatment recommendations.

In SU.FOL.OM3 (Galan et al 2010) no effect of omega-3 fatty acids on the primary or secondary cardiovascular endpoints was observed. However, the daily dose of omega-3 fatty acids used in the study (400 mg EPA and 200 mg DHA) is slightly lower than the dose recommended for the indication under review (460 mg EPA, 380 mg DHA). It is questionable whether the lack of efficacy can be attributed to this small difference. Furthermore, the study population, consisting of 46% patients with prior MI, is not fully representative for the target population under review and subgroup analysis are not available. However, as stated above cardiovascular disease is considered a continuum. Overall, the SU.FOL.OM3 study can be considered indicative for the lack of efficacy of omega-3 fatty acids in the secondary prevention in patients after a MI, but not conclusive on itself.

Guidelines

CHMP acknowledged that the ESC/EAS guidelines are recommendations made by various societies in consultation with task forces, expert groups or consensus panels, with the aim of assisting physicians

in selecting the best management strategies for an individual patient with a given condition taking into account the impact on outcome as well as the risk-benefit ratio of particular diagnostic or therapeutic means. The recommendations in these guidelines are, therefore, developed after careful consideration of the scientific and medical knowledge and evidence available at the time of coming into effect. As the European guidelines do not recommend omega-3 fatty acid medicinal products, they, apparently, consider the level of evidence and the strength of the recommendation of omega-3 fatty acids in prevention of cardiovascular events both in patients after MI and in patients with other cardiovascular conditions rather weak.

Moreover, the American Heart Association states that use of omega-3 fatty acid supplements is 'reasonable' for patients with prevalent coronary heart disease such as MI - The strength of recommendation is therefore low (Class IIa/IIb Recommendation).

Modified indication

The MAHs proposed a modification of the indication for use in high-risk patients in case the CHMP considers that there are concerns regarding the efficacy of Omacor as follows:

Adjuvant treatment in secondary prevention, initiated within 3 months after myocardial infarction, in addition to other standard therapy (e.g. statins, antiplatelet medicinal products, beta-blockers, ACE inhibitors).

Treatment should be particularly considered in patients having high residual risk, such as:

- *Type 2 diabetes*
- *No acute PCI after MI*
- *Impaired systolic function (EF < 50%)*
- *Known intolerance to one or more guideline recommended cardiovascular medications*

Considering that the high-risk groups of patients with type 2 diabetes, patients with no acute PCI after MI, and patients with impaired systolic function (EF < 50%) have been identified based on *post-hoc* subgroup analyses conducted on GISSI-P and that these specific groups were not treated according to the current standard of care, the results of these subgroups are not representative and therefore do not support the proposed indication. Additionally, the level of evidence in these post-hoc subgroup analyses is not strong.

With respect to the high risk group of known intolerance to one or more guideline recommended cardiovascular medications, there is no data available supporting better adherence to omega-3 fatty acids compared to other pharmacological interventions. Moreover, there is no evidence of beneficial effect for omega-3 fatty acids in this specific population.

Based on above, the CHMP considered that the proposed modification of the indication is not acceptable.

Adherence to standard care therapy

The MAHs referred to several clinical studies and the ESC 2017 in order to demonstrate that adherence to medication in patients with CVD is low and claimed that omega-3 fatty acids still represents a therapeutic opportunity for high risk patients in whom, despite any effort put in place, the complete adherence to guideline-driven therapies cannot be reached. Although it is acknowledged that non-adherence is a ubiquitous problem, evidence for efficacy in this specific group of patients is not available. The GISSI-P trial does not represent the clinical setting of non-adherence to current standard therapies and, as such, direct extrapolation is not justified. Moreover, there is no data available supporting better adherence to omega-3 fatty acids compared to other pharmacological interventions.

With respect to the reference of the MAHs to the REDUCE-IT trial, the results of this study are of limited relevance since the daily dose was much higher than the dose of the indication under review (4 g vs. 1 g) and the active substance was icosapent ethyl, a highly purified EPA ethyl ester, instead of a mixture of EPA and DHA.

Recent clinical trial evidence (ASCEND, VITAL, REDUCE-IT)

Three large studies (ASCEND, VITAL and REDUCE-IT) investigating the effect of omega-3 fatty acids in reduction of cardiovascular events have been published and submitted by the MAHs as support of clinical benefit of omega-3 fatty acids in the secondary prevention indication. It should be noted that although these trials have been recently published, the results were already discussed in detail during the previous phase of the referral procedure.

ASCEND is a randomized placebo-controlled trial to assess the efficacy of daily supplementation with omega-3 fatty acids (1 g daily), as compared with placebo (olive oil), in 15,480 patients with diabetes without evidence of cardiovascular disease at trial entry. Using a factorial design in the same trial, it is also assessed whether aspirin prevents CVD and cancer. The mean follow-up was 7.4 years (adherence rate 76%). Treatment with omega-3 fatty acids had no effect on the primary endpoint of first serious vascular event defined as nonfatal myocardial infarction or stroke, transient ischemic attack, or vascular death, excluding confirmed intracranial haemorrhage (RR: 0.97; 95%CI 0.87-1.08, p = 0.55). There was also no significant between group difference in the secondary outcome of serious vascular events or revascularization (RR: 1.00; 95%CI 0.91-1.09) or death from any cause (RR: 0.95; 95%CI 0.86-1.05). In exploratory subgroup analyses, there were fewer vascular deaths in the fatty acid group (196 patients [2.5%] than in the placebo group (240 [3.1%] (RR 0.82; 95% CI 0.68-0.98).

To conclude, no effect of omega-3 fatty acids on the primary or secondary cardiovascular endpoints was observed. Incidences in vascular death were numerically in favour of the omega-3 group, however, these results were based on exploratory subgroup analyses. Overall, the ASCEND study can be considered as a negative study.

VITAL is a randomized placebo-controlled trial with a two-by-two factorial design, of vitamin D3 (at a dose of 2000 IU per day) and marine omega-3 fatty acids (at a dose of 1 g per day) in the primary prevention of cardiovascular disease and cancer among men 50 years of age or older and women 55 years of age or older in the United States. A total of 25,871 patients were randomized and the median follow-up was 5.3 years. Primary endpoints were major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes) and invasive cancer of any type. Treatment with omega-3 fatty acids had no effect on the primary endpoint of major cardiovascular event (HR 0.92; 95%CI 0.80-1.06, p= 0.24). In the analyses of key secondary end points, the hazard ratios were as follows: for the expanded composite end point of cardiovascular events (including coronary revascularization), 0.93 (95% CI, 0.82- 1.04); for total myocardial infarction, 0.72 (95% CI, 0.59 to 0.90); for total stroke, 1.04 (95% CI, 0.83- 1.31); for death from cardiovascular causes, 0.96 (95% CI, 0.76 to 1.21).

To conclude, no effect of omega-3 fatty acids on the primary or secondary cardiovascular endpoints was observed. Overall, the VITAL study can be considered as a negative study.

REDUCE-IT is a randomized, double blind, placebo-controlled trial conducted in 8,179 patients with patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg/dL and a LDL-C of 41 to 100 mg/dL. The mean follow-up was 4.9 years. The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary endpoint (composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina) occurred in 17.2% of the patients in the icosapent ethyl group compared with 22% in the placebo group (HR:

0.75; 95% CI 0.68- 0.83; p<0.001). The secondary endpoint (composite of CV death, non-fatal MI, or non-fatal stroke) occurred in 11.2 of the patients in the icosapent ethyl group compared with 14.8% in the placebo group (HR: 0.74; 95% CI, 0.65- 0.83; p<0.001). The rates of secondary efficacy end points, as assessed according to a pre-specified hierarchical schema, were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%; hazard ratio, 0.80; 95%CI, 0.66 to 0.98; P=0.03).

It can be concluded that among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily (total daily dose 4 g) than among those who received placebo. However, the results of this study are of limited relevance since the daily dose was much higher than the dose of the indication under review (4 g vs. 1 g) and the active substance was icosapent ethyl, a highly purified EPA ethyl ester, instead of a mixture of EPA and DHA. Moreover, the population included in the REDUCE-IT trial is not comparable with the population of the GISSI-P trial and the indication under review (patients with history of MI), since in addition to established cardiovascular disease or diabetes and other risk factor the patients in the REDUCE-IT trial had also hypertriglyceridemia (> 60% of the patients had TG levels ≥ 200 mg/dL).

Overall, it can be concluded that these published trials do not provide evidence for the efficacy of omega-3 administration (1 g daily) for the indication under review.

Safety

CHMP took into consideration all available safety data and noted that no new safety issues had emerged. In general, it can be concluded that the safety profile seems well characterized.

Expert group consultation during the re-examination

During the re-examination procedure the MAHs requested a second Cardiovascular Scientific Advisory Group meeting. The request was acknowledged by CHMP and the meeting took place on the 19th March 2019.

The Group discussed the results of the available RCTs, meta-analyses and retrospective cohort studies. In particular a long discussion took place regarding the strengths and weaknesses of the GISSI-P trial. The preference for 2-way vs. 4-way analysis was discussed even if the MAHs confirmed that the study was powered to take the 4-way analysis into account. The results of GISSI-P were considered borderline significant. It was mentioned that from the formal viewpoint the trial could be considered non-conclusive. The benefit regarding mortality without reduction in other events (myocardial infarction, ischaemic stroke) was of concern and pointed to the lack of plausible mechanism of action (MoA).

Post-hoc analyses of GISSI-P study submitted regarding patients with reduced ejection fraction, patients with diabetes and patients who did not undergo PCI were considered of limited value to support the efficacy in those particular subgroups.

In addition to weak evidence of efficacy coming from the GISSI-P trial for omega-3 -containing medicinal products in dose of 1 g/day in secondary prevention after MI, it was also underlined that the Standards of Care (SoC) for background therapy has intensified since the time GISSI-P was conducted. Although the GISSI-P trial might have been an adequate study at time it was conducted, the lack of optimal background therapy together with the borderline results is of concern. In addition, the open-label design (PROBE) was an additional weakness as was the fact that the control group did not receive placebo.

The strengths and limitations of OMEGA trial were also noted by the Group. The statistical power was a concern. The confidence intervals were wide, but most of the experts were of opinion that this does not

discount the results of this study. The study was conducted in the population of patients representative for the indication of secondary prevention after MI subject to this review. A significant part of these patients received complete/near complete revascularization. However, not all of the patients had a history of acute coronary syndrome (ACS). Patients in Omega study were treated with the corresponding dose of Omega-3 medicinal products and were on baseline treatment as per current SoC. Contrary to the results of the older GISSI-P, in OMEGA study no effect on primary efficacy endpoint of sudden cardiac death (SCD) was observed (OR: 0.95; 95% CI 0.56-1.6, p=0.84). Also, the study did not show any reduction in all-cause mortality (OR: 1.25; 95% CI 0.90-1.72, p=0.18) and major adverse cerebrovascular and cardiovascular disease (CVD) events (MACCE) (OR: 1.21; 95% CI 0.96-1.52, p=0.10).

If omega-3-containing medical products were effective, the majority of experts would expect that subsequent trials in primary- and secondary prevention would yield similar OR's, albeit with wide confidence intervals in some studies. In a sequential meta-analysis the OR should stabilise and the confidence intervals should become narrower. This was not observed, which weakens the findings of GISSI-P. It was noted by some of the experts that the distinction between primary- and secondary prevention is artificial. It should be seen as prevention of CVD events in patients at lower (primary) or higher (secondary) levels of risk.

The unknown mechanism of action (MoA) of omega-3 containing medicinal products adds to the uncertainty. It was of concern that over years the science did not provide mechanistic explanation for the postulated beneficial effects of products containing Omega-3. The experts pointed out that the speculated MoA of Omega-3 medicinal products following GISSI-P was antiarrhythmic (observed reduction of SCD in this study). Two subsequent studies specifically designed to analyse the anti-arrhythmic effect of Omega-3 are inconclusive. Other possible MoA mentioned by the MAHs are related to plaque development and to the risk for reinfarction and stroke. However these events were not reduced neither in GISSI-P nor in OMEGA.

The experts considered the performed meta-analyses of different trials were not very relevant for the indication at stake as the included studies were conducted (a) in heterogeneous populations of patients at any level of risk and with different clinical conditions, (b) with very different doses of omega-3 and products of different composition and (c) in different period of time with different background therapies. However, this heterogeneity and variation in dose would give the opportunity to analyse the effect of Omega-3 in relation to the spectrum of risk of the patients and in relation to the dose provided. Unfortunately such a meta-analysis using individual patient data which would potentially allow clarification of these issues has not been provided. While the results of the meta-analyses do not support the results of GISSI-P; at the same time their results cannot discount the GISSI-P results.

Retrospective cohort studies were seen as less relevant given their inherent selection bias but it was acknowledged that these provided supportive results to the GISSI-P study. These data base driven studies in real life situation showed that patients treated with Omacor had better survival pattern. The unbalance of cardiovascular risk at baseline between exposed and non-exposed patients could have been partly solved using propensity scores to select and compare exposed and non-exposed groups with similar risk factors at baseline. This could be done if new data based studies could be performed.

The experts discussed GISSI-HF, ORIGIN, SU.FOL.OM3 and R&P trials. They agreed that CVD should be seen as a continuum. Given that in these studies Omega-3-containing medicinal products were tested in different population of patients compared to patients after MI (patients at high risk for CVD events and impaired fasting glucose, impaired glucose tolerance or diabetes in ORIGIN and R&P) and/or different dose (600 mg/day EPA/DHA in SU-FOL-OM3), they were considered less relevant for the indication of secondary prevention after MI.

Other RCTs were discussed as well. In particular, the experts discussed positive (for omega-3 containing medicinal products) results of the REDUCE-IT trial in patients with established CVD with diabetes and other risk factors. It was acknowledged that the dose of omega-3 used in this trial (4 g/day of icosapent ethyl) was higher than the recommended dose in secondary prevention indication (1g/day). Accordingly, the majority of experts agreed that this study is not relevant for the current indication, but rather supports the other indication for omega-3: treatment of patients with hypertriglyceridaemia, who may or may not have a previous myocardial infarction. REDUCE-IT demonstrated CVD benefits of Omega-3 medicinal products added to optimal background therapies in patients with hypertriglyceridaemia.

One expert also commented that 40% of the population of REDUCE-IT had a fasting triglyceride levels below 200 mg/dl, thus in a range common for CAD patients. Comparison of baseline triglyceride levels (≥150 vs. <150 mg *per* deciliter or ≥200 or <200 mg *per* deciliter) revealed no relation with the efficacy endpoints. In his opinion GISSI-P, retrospective studies and REDUCE-IT support the use of omega-3 medicinal products in patients after ACS.

The opinion of the Group was splitted: most experts believed that the level of evidence from GISSI-P together with the results from OMEGA is not supportive for using these products in secondary prevention after MI in addition to current standard of care. They noted that this treatment is not recommended in the current guidelines for prevention of CVD by the European Society of Cardiology and the European Atherosclerosis Society. However, some experts in the SAG saw a place in therapy for omega-3–containing medicinal products in secondary prevention after MI. Patient representative considered there was value to having these products available and not to discourage this aspect of patients' choice given the long history of the use of fish oils in adjunctive medicine and as dietary supplements particularly as there was no evidence of harm with omega-3 supplementation.

The experts agreed that there is no sign of harm in the totality of data, but that the beneficial effect of omega-3s may be questioned as discussed above. This needs to be considered in the review of the indication originally granted.

The experts acknowledged the continuity of CVD risk and that the potential benefits with omega-3s could be demonstrated more easily in a high risk population where the relative risk reduction is expected to be higher. However, the majority of experts believed that the subgroup analyses of GISSI-P provided within the re-examination procedure do not support narrowing of the proposed indication to high-risk subgroups, namely patients with type 2 diabetes, no acute PCI after MI or those with impaired systolic function (EF < 50%).

The observation in various registries that some patients with CVD do not receive the recommended preventive therapy is not a reason to add another agent (omega-3) to the armamentarium, but rather requires better education of physicians to promote adherence to the guidelines. Intolerance to one or more guideline recommended CVD medication was seen as an unmet need in the field of CVD. However omega-3 containing medicinal products was not tested in a population of patients intolerant to guideline recommended medications.

4.2.3. Conclusion on the benefit-risk balance following the re-examination procedure

Grounds for re-examination have been submitted by BASF AF and ALFASIGMA S.p.A, representing eleven MAHs. Both submissions discussed the available data sources and their interpretation. The MAHs disagreed with the CHMP that the evidence that supported the authorisation of omega-3 in secondary prevention after MI suffered from some methodological limitations and was weak and that the efficacy in this indication was not demonstrated in subsequent and more robust clinical trials.

The MAHs have described the results from different RCTs to support the beneficial effect of omega-3 fatty acids in secondary prevention after an MI. In particular the GISSI-P and OMEGA trials, which were considered most relevant, have been extensively discussed by the MAHs.

In the MAHs' view, GISSI-P represented the mainstay of evidence in favour of the use of omega-3 fatty acids in the secondary prevention after MI and it is a valid and robust study. However CHMP still considered that the results of the GISSI-P trial are inconclusive, since the study has several limitations. The key concern of this study is that standard of care for the treatment of MI has evolved since the outcome of the GISSI-P trial in particular statin therapy, beta-blocker therapy and invasive treatment. Another concern for this study was its open-label design and that the control group did not receive placebo treatment. The statistical analysis and interpretation were not robust according to current standards. It is considered that the study had co-primary endpoints and hierarchical primary and secondary endpoint analyses. The study formally failed because the primary analysis of one of the co-primary endpoints did not show a statistically significant difference. With any other interpretation about the primary endpoints, multiplicity should have been controlled, which was not the case. With respect to the GISSI-P trial, no new issues have been identified, with the exception of the statement of the MAHs that *post-hoc* analyses conducted on GISSI-P demonstrated that concomitant treatment with anti-platelet agents, beta-blockers, ACE inhibitors and statins did not alter the therapeutic benefit of Omacor. However, with respect to statin therapy, CHMP concluded that subjects in this subgroup analysis were not on optimal statin therapy. Furthermore, although this *post-hoc* analysis did not show differences in benefit with or without concomitant statin therapy, potential differences could not be excluded since the study was underpowered for demonstrating such differences. The latter concern also applies to *post-hoc* analyses in patients with or without anti-platelet medicinal products, beta-blockers or ACE-inhibitors. Therefore, the key concern that standard of care after MI has intensified since the time of the GISSI-P study, in particular statin therapy, beta-blockers and PCI, still remains. In this regard, the results of the GISSI-P trial are not in line with the current standard of care and therefore with the approved indication of Omacor "in addition to other standard therapy (e.g. statins, antiplatelet medicinal products, beta-blockers, ACE inhibitors".

Regarding the OMEGA study, the CHMP considered that although the trial could be considered to be underpowered this does not invalidate the study results entirely, in line with SAG on 19 March 2019. The OMEGA study has several strengths compared to the GISSI-P study, e.g. administration of study drug within few days of a MI, a placebo-controlled double-blind design, optimal baseline therapy and endpoints investigated. The MAHs citation of relevant guideline "*included clinical trials need to be long-term controlled (usually 12 months or longer), parallel and preferably double-blind*" is correct. However, ignoring double blind by using no treatment as comparator (as in GISSI-P) ignores another important concept in clinical trials, i.e. the use of a (blinded) comparator in order to control the other effects than the investigational drug, and deviation of this principle should only be needed or suitable *"when it is difficult or impossible to avoid"* (ICH E10 guideline on Choice of control group in clinical trials). The OMEGA study included close to 2000 patients in both arms and over 300 MACE events were reported, more in the omega-3 group than in the placebo group OR 1.25 (0.96-1.52). The narrow confidence interval excludes any clinically relevant beneficial effects. Total mortality was also numerically higher in the omega-3 fatty acids group OR 1.25 (0.90-1.72). Despite the lack of statistical power for the specific "sudden cardiac death" endpoint, the lack of substantial benefit can be concluded from this trial in a statistically valid way, as evidenced by the narrow confidence intervals. Based on the results, there is only a 2.5% chance that the relative risk reduction for MACE exceeds 4%.

Although CHMP considers that the GISSI-P and the OMEGA trials are the most relevant for evaluating the effect of omega-3 containing products in the secondary prevention after MI, it is also acknowledged that RCTs (GISSI-HF, ORIGIN, SU.FOL.OM3) conducted in other CV risk populations (e.g. coronary revascularisation, angina pectoris, ischaemic stroke) are as well relevant, as CV disease is still

considered a continuum. Acute coronary syndrome (ACS) associated with typical coronary artery disease (atherosclerosis) is the most common cause of a MI. In addition to MI, ACS is also associated with unstable angina. Furthermore, ischaemic stroke is also most often caused by atherosclerosis. Therefore if omega-3 fatty acids are effective in reducing cardiovascular events after an MI, cardiovascular benefits in other CV risk populations (e.g. coronary revascularisation, angina pectoris, ischaemic stroke) can be anticipated. Based on the above, the CHMP reiterates that RCTs conducted in other CV risk populations are relevant in support of the efficacy (GISSI-HF although borderline and inconclusive) or lack of efficacy (ORIGIN and SU.FOL.OM3) of omega-3 fatty acids in secondary prevention of cardiovascular disease.

Recently published RCTs (ASCEND by Bowman et al. 2018, VITAL by Manson et al. 2019, REDUCE-IT by Bhatt et al. 2019) do not provide evidence for the efficacy of omega-3 administration (1 g daily) for the indication under review. The ASCEND and VITAL studies did not show an effect of omega-3 fatty acids on the primary or secondary cardiovascular endpoints and, as such, were considered as negative studies. The results of RECUCE-IT study results are of limited relevance since the daily dose was much higher than the dose of the indication under review (4 g vs. 1 g) and the active substance was icosapent ethyl, a highly purified EPA ethyl ester, instead of a mixture of EPA and DHA. Moreover, the population included in the REDUCE-IT trial is not comparable with the population of the GISSI-P trial and the indication under review (patients with history of MI), since in addition to established cardiovascular disease or diabetes and other risk factor the patients in the REDUCE-IT trial had also hypertriglyceridemia (> 60% of the patients had TG levels ≥ 200 mg/dL).

The three retrospective studies (Poole et al 2013, Greene et al 2016, Macchia et al 2013) are considered to have sufficiently large populations of subjects diagnosed with acute MI and studied omega-3-fatty acids in the relevant dose of 1 g daily with all-cause mortality as the main endpoint. However, although the retrospective cohort studies seem to confirm the results of the GISSI-P study, they should be interpreted with caution given the known limitations of retrospective cohort studies. Especially selection bias is of concern, as it can be envisaged that omega-3 fatty acids will be prescribed to certain patients (not needing strict treatment immediately). Propensity score matching was incomplete or even not attempted. Furthermore, residual bias will always be present. Therefore, it is considered that these studies are only supportive.

The provided meta-analyses showed both positive and negative effects of omega-3 fatty acid treatment on the risk of cardiovascular events. Studies included in the different meta-analysis are heterogeneous with respect to study population (e.g. patients with or without history of cardiovascular disease), study design (open-label or double-blind), source of omega-3 fatty acid intake (dietary or medication intervention), dose and composition of omega-3 fatty acid. A meta-analysis using individual participant data (IPD), selecting patients with a history of MI and treated with the same dose as for the indication under review (1 g), would have been more appropriate. Therefore, the CHMP considers that the validity of the meta-analyses is rather limited and that the meta-analyses can only be interpreted as being indicative, but not conclusive, with regards to potential efficacy or the lack of efficacy of omega-3 fatty acids in reducing the risk of cardiovascular events. For this, RCT data are available which included sufficient number of patients and resulted in estimates of treatment effect with sufficient precision.

ESC/EAS guidelines are recommendations made by various societies in consultation with task forces, expert groups or consensus panels, with the aim of assisting physicians in selecting the best management strategies for an individual patient with a given condition taking into account the impact on outcome as well as the risk/benefit ratio of particular diagnostic or therapeutic means. The recommendations in these guidelines are therefore developed after careful consideration of the scientific and medical knowledge and evidence available at the time of coming into effect. As the European guidelines do not recommend omega-3 fatty acid medicinal products, they apparently

consider the level of evidence and the strength of the recommendation of omega-3 fatty acids in prevention of cardiovascular events both in patients after MI and in patients with other CV conditions rather weak. Moreover, the American Heart Association states that use of omega-3 fatty acid supplements is 'reasonable' for patients with prevalent coronary heart disease such as MI, indication that strength of recommendation is therefore low (Class IIa/IIb Recommendation). As stated above, RCT data are available which included sufficient number of patients and resulted in estimates of treatment effect with sufficient precision.

During the re-examination procedure, a second Cardiovascular Scientific Advisory Group meeting took place on the 19th March 2019. The outcome of the SAG is fully acknowledged by the CHMP.

The MAHs proposed, as part of their grounds for re-examination, a modification of the indication for use in high-risk patients, i.e. type 2 diabetes, no acute PCI after MI, impaired systolic function (EF < 50%), known intolerance to one or more guideline recommended cardiovascular medications. Considering that the high-risk groups of patients with type 2 diabetes, patients with no acute PCI after MI, and patients with impaired systolic function (EF < 50%) have been identified based on *post-hoc* subgroup analyses conducted on GISSI-P and that these specific groups are not treated according to the current standard of care, the results of these subgroups are not representative and therefore do not support the proposed indication. Additionally, the level of evidence in these post-hoc subgroup analyses is not strong. With respect to the high risk group of known intolerance to one or more guideline recommended cardiovascular medications, there is no data available supporting better adherence to omega-3 acid ethyl esters compared to other pharmacological interventions and evidence for efficacy of Omacor in this specific population is lacking. Therefore, the proposed modification of the indication is not acceptable by the CHMP.

The randomised controlled trials were considered most relevant for the evaluation of the efficacy of omega-3 fatty acids, in particular the results of the GISSI-P and OMEGA trials. The registration of Omacor was based on the GISSI-P study, however, the results of the GISSI-P trial are considered rather weak, since the study has methodological limitations. The OMEGA trial was conducted in patients with the approved indication, i.e. MI and used the approved dose of Omacor (1 g/day). Despite the lack of statistical power for the specific sudden cardiac death endpoint, the lack of substantial benefit can be concluded from this trial in a statistically valid way, as evidenced by the narrow confidence intervals. The efficacy of omega-3 fatty acids in the claimed indication has also not been demonstrated by other relevant RCTs conducted in other CV risk populations (e.g. coronary revascularisation, angina pectoris, ischaemic stroke), including ORIGIN, SU.FOL.OM3, ASCEND, and VITAL. The results of the recently published REDUCE-IT trial are of limited relevance since the daily dose was much higher than the dose of the indication under review (4 g vs. 1 g) and the active substance was icosapent ethyl, a highly purified EPA ethyl ester, instead of a mixture of EPA and DHA.

In conclusion, the totality of data does not support the efficacy of omega-3 fatty acids in prevention after myocardial infarction, including in high-risk patients.

5. Risk management

5.1. Risk minimisation activities

5.1.1. Amendments to the product information

The CHMP considered that amendments to sections 4.1, 4.2 and 5.1 of the SmPC were necessary.

- Section 4.1 Therapeutic indications "Secondary prevention after myocardial infarction" should be deleted

- Section 4.2 Posology and method of administration: Information related to the “secondary prevention after myocardial infarction” indication should be deleted.
- Section 5.1 Pharmacodynamic properties: Information related to the “secondary prevention after myocardial infarction” indication should be deleted.

The Package Leaflet was amended accordingly.

6. Grounds for Opinion following the re-examination procedure

Whereas,

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 31 of Directive 2001/83/EC for Omega-3 acid ethyl esters – containing medicinal products for oral in use in secondary prevention after myocardial infarction.
- The CHMP considered the totality of the data submitted for Omega-3 acid ethyl esters medicinal products with regard to their use in secondary prevention after myocardial infarction. This included the responses submitted by the marketing authorisation holders in writing and during an Oral Explanation, as well as the outcome of the consultation with the Cardiovascular Scientific Advisory Group on the 10 of October 2018. CHMP also considered the grounds submitted by the MAHs as basis for their request for re-examination of the CHMP recommendation as well as the views of a second Cardiovascular Scientific Advisory group held on the 19 of March 2019.
- The CHMP considered that, even though it is acknowledged that the GISSI-P clinical trial was the basis for the original approval of the secondary prevention indication in the light of more recent data and information, the study is considered to have some serious limitations that cast doubts on the results. These limitations include the open-label study design with no study medication in the control arm, the small magnitude of effect, the unusual and unexpected observation of an effect on fatal cardiovascular events only in the absence of any effect on non-fatal events and poor precision of the results. In addition, less than 5% of the patients included in this study received optimal baseline therapy over the whole study period which questions the results in the context of current secondary therapy recommendations.
- It has been hypothesised that the results of the GISSI-P trial was driven by a reduced risk of sudden death, potentially based on an antiarrhythmic effect of omega-3. This potential positive effect on mortality has not been reproduced in subsequent trials and the antiarrhythmic effect has not been confirmed in trials examining patients with ICD.
- The OMEGA trial (performed in 2010 after the original approval of the secondary prevention indication) was a well performed, double blind trial evaluating a population well representative of the currently approved secondary prevention indication, including the use of standard of care treatment. Even though the incidence of sudden death may have been too low to draw firm conclusions, the OR for MACE and total mortality was above 1.21 and 1.25 respectively. with lower CI close to 1 not supporting an effect in the approved indication.
- Even though the meta-analyses by Aung et al. and the recent Cochrane review includes trials with products, doses and populations not exactly representing the approved secondary prevention indication, all studies include patients with cardiovascular disease and therefore, the results are considered as supportive of lack of efficacy.

- Whilst the results of the submitted retrospective cohort studies seemed to be in line with the results of the GISSI-P study, they suffered from methodological limitations which prevent drawing definite conclusions, in particular the lack of randomisation, selection bias and residual confounding.
- Based on the totality of the data emerging after the original approval as well as the limitations of the GISSI-P trial, the CHMP concluded that efficacy is not established in secondary prevention after myocardial infarction at the dose of 1 g/day and, although the safety profile of omega-3 -acid ethyl esters is unchanged, the CHMP concluded that the benefit-risk balance in this indication is no longer favourable.
- As a consequence, the CHMP considered that the indication “Secondary prevention after myocardial infarction” at the dose of 1 g/day should be deleted with additional consequential changes in the product information.

The Committee, as a consequence, considers that the benefit-risk balance of Omega-3 acid ethyl esters medicinal products for oral use in secondary prevention after myocardial infarction is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the variation of the marketing authorisations.

References

Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, et al. Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77917 Individuals. JAMA Cardiol. 2018 Mar 1;3(3):225-34.

Bosch J, Gerstein HC, Dagenais GR, Díaz R, Dyal L, Jung H, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012 Jul 26;367(4):309-18.

Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effect of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989 Sep; 30: 757-61.

Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S. Effects of B vitamins and omega 3 fatty acids

Greene SJ, Temporelli PL, Campia U, Vaduganathan M, Degli Esposti L, Buda S.Effects of Polyunsaturated Fatty Acid Treatment on Post discharge Outcomes After Acute Myocardial Infarction.Am J Cardiol. 2016 Feb 1;117(3):340-6.

GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999 Aug 7;354(9177):447-5

Heydari B, Abdullah S, Pottala JV, Shah R, Abbasi S, Mandry D, et al. Effect of Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction: The OMEGA-REMODEL Randomized Clinical Trial. Circulation. 2016 Aug 2;134(5):378-91

Johansen O, Brekke M, Seljeflot I, Abdelnoor M, Arnesen H. N-3 fatty acids do not prevent restenosis after coronary angioplasty: results from the CART study. Coronary Angioplasty Restenosis Trial. Journal of the American College of Cardiology 1999 May;33(6):1619-26.

Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. Omega 3 Fatty acids and cardiovascular outcomes: systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2012 Nov;5(6):808-18.

Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med. 2010 Nov 18;363(21):2015-26.

Kwak SM, Myung SK, Lee YJ, Seo HG; Korean Meta-analysis Study Group. Efficacy of omega-3 fatty acid supplements (Eicosapentaenoic Acid and Docosahexanoic Acid) in the secondary prevention of cardiovascular disease. Arch Intern Med. 2012 May 14;172(9):686-94.

Macchia A, Romero M, D'Ettorre A, Tognoni G, Mariani J. Exploratory 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. 2013;8(5):e62772.

Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L. 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. Am J Clin Nutr. 2001 Jul;74(1):50-6.

Poole CD, Halcox JP, Jenkins-Jones S, Carr ES, Schifflers MG, Ray KK, et al. Omega-3 Fatty acids and mortality outcome in patients with and without type 2 diabetes after myocardial infarction: a retrospective, matched-cohort study. Clin Ther. 2013 Jan;35(1):40-51.

Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a Randomized, Placebo-Controlled Trial to Test the Effect on Highly Purified Omega-3 Fatty Acids on Top of Modern Guideline-Adjusted Therapy After Myocardial Infarction. Circulation. 2010 Nov 23;122(21):2152-9.

Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA. 2012 Sep 12;308(10):1024-33.

Siscovick DS, Barringer TA, Fretts AM, Wu JH, Lichtenstein AH, Costello RB,et al.Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart association. Circulation. 2017 Apr 11;135(15):e867-e884.

Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, 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 Oct 4;372(9645):1223-30.

Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y,et al.ffects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomized open-label, blinded endpoint analysis.Lancet. 2007 Mar 31;369(9567):1090-8. Erratum in: Lancet. 2007 Jul 21;370(9583):220.