Annex II

Scientific conclusions

Scientific conclusions

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.

Omega-3 acid ethyl esters are an ethyl esters 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.

Overall summary of the scientific evaluation

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

[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

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[4]), the results from the GISSI-P study could also not 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 effect 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 they include 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 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[5] and Macchia[6]) 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)[7] 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

[4] 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.

[5] 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.

[6] 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.

[7] 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

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.[8], 2005; Brouwer et al.[9] 2006, Raitt et al.[10], 2005; Weisman et al.[11], 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. 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.

Re-examination procedure

[8] Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, Cox B, Zhang H, Schoenfeld D; Fatty Acid Antiarrhythmia Trial Investigators. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circulation. 2005 Nov 1;112(18):2762-8.

[9] Brouwer IA, Zock PL, Camm AJ, Böcker D, Hauer RN, Wever EF, Dullemeijer C, Ronden JE, Katan MB, Lubinski A, Buschler H, Schouten EG; SOFA Study Group. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. JAMA. 2006 Jun 14;295(22):2613-9.

[10] Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, McClelland J, Cook J, MacMurdy K, Swenson R, Connor SL, Gerhard G, Kraemer DF, Oseran D, Marchant C, Calhoun D, Shnider R, McAnulty J. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. JAMA. 2005 Jun 15;293(23):2884-91.

[11] Weisman D, Beinart R, Erez A, Koren-Morag N, Goldenberg I, Eldar M, Glikson M, Luria D. Effect of supplemented intake of omega-3 fatty acids on arrhythmias in patients with ICD: fish oil therapy may reduce ventricular arrhythmia. J Interv Card Electrophysiol. 2017 Sep;49(3):255-261

Following the adoption of the CHMP opinion in December 2018, a re-examination request was received from the MAHs involved in the procedure, BASF AS (representing Mylan Hrvatska D.O.O, BGP Products Ltd, Ferrer-Galenica S.A and Strides Arcolab International Limited) 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.).

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[12], VITAL by Manson et al. 2019[13], REDUCE-IT by Bhatt et al. 2019[14]) 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 factors, patients in the REDUCE-IT trial suffered also from 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.

[12] Louise Bowman, Marion Mafham, William Stevens, Richard Haynes, Theingi Aung, Fang Chen, Georgina Buck, Rory Collins, and Jane Armitage, The ASCEND Study Collaborative Group. ASCEND: A Study of Cardiovascular Events iN Diabetes: Characteristics of a randomized trial of aspirin and of omega-3 fatty acid supplementation in 15,480 people with diabetes. https://doi.org/10.1016/j.ahj.2017.12.006.

[13] JoAnn E. Manson, Nancy R. Cook, I-Min Lee, William Christen, Shari S. Bassuk, Samia Mora, Heike Gibson, Christine M. Albert, David Gordon, Trisha Copeland, Denise D'Agostino, Georgina Friedenberg, Claire Ridge, Vadim Bubes, Edward L. Giovannucci, Walter C. Willett, and Julie E. Buring, for the VITAL Research Group. Marine n−3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. DOI: 10.1056/NEJMoa1811403

[14] Deepak L. Bhatt, P. Gabriel Steg, Michael Miller, Eliot A. Brinton, Terry A. Jacobson, Steven B. Ketchum, Ralph T. Doyle, Jr., Rebecca A. Juliano, Lixia Jiao, Craig Granowitz, Jean-Claude Tardif, and Christie M. Ballantyne, for the REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. DOI: 10.1056/NEJMoa1812792

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.

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.

Upon request from the MAHs, a second SAG CVS meeting was convened on 19 March 2019. The opinion of the Group was split: 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. The 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.

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.

Grounds for CHMP opinion

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.

CHMP opinion

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.