LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by Sweden:

Product Name(s) in the Referring Member State	Megazza Strides, omega 3-acid-ethyl esters 1000mg Soft Capsules
Active substance(s)	omega-3 acid ethyl esters
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	Oral use
Applicant in the referring Member State	Strides Arcolab International Ltd

Background

Omega-3-acid-ethyl esters are an ethyl ester of polyunsaturated fatty acids with an eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) content of not less than 85% and an EPA to DHA ratio of 0.9 to 1.5. Medicinal products containing omega-3 acid-ethyl esters have been approved for oral use across the majority of the European union (EU) Member States for prevention after myocardial infarction and in the treatment of hypertriglyceridaemia (e.g. Omacor, FR/0105/001). No omega-3-acid-ethyl esters-containing medicinal products are currently authorised in Sweden, but a marketing authorisation application procedure was finalized in March 2018 for a generic medicinal product (with European Reference Product: Omacor), and is now awaiting national approval.

Issues to be considered

The original approval of Omacor was based on an open-label study GISSI study from 1999 (only study that is referred in the SmPC section 5.1). In this study, results for the primary endpoints of CV death/non-fatal MI and stroke were statistically significant, but only marginally so. In contrast, the majority of later studies have failed to show a beneficial effect. These included:

- Large meta-analyses from 2012 concluded that use of omega 3-fatty acids supplements is not associated with significant lower risk of cardiovascular outcomes[1,2,3].
- The most recent meta-analysis, published in January 2018 includes 10 studies involving

77917 individuals. The results are is in line with the previous meta-analyses and the authors conclude that use of omega 3-fatty acids is not associated with significant lower risk for fatal or non-fatal coronary heart disease or any major vascular events; see table 1. In particular, blinded studies have failed to show beneficial effects for any coronary heart disease; see table 2.[4]

Table 1. Associations of Omega-3 Fatty Acids with coronary heart disease and stroke (Meta-analysis by Aung et al. JAMA Cardiol 2018)

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

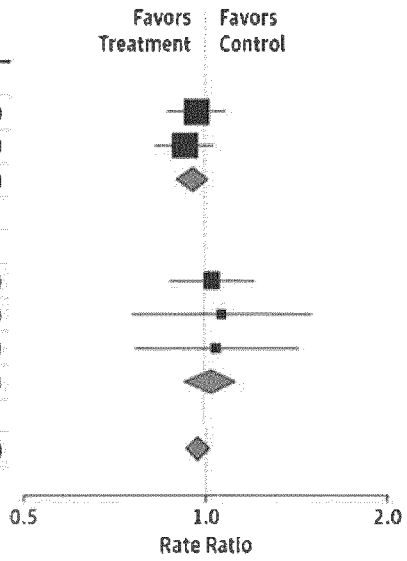
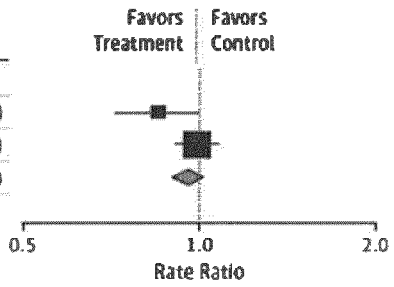


Table 2. Associations of Omega-3 Fatty Acids supplementation with any coronary heart disease, by Trial Design (Meta-analysis by Aung et al. JAMA Cardiol 2018

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
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



Since 2016, European Society of Cardiology and European Atherosclerosis Society finds in their Guidelines for prevention on cardiovascular disease[5] that the effect of omega 3-fatty acids supplement on all cause CAD and stroke mortality is questionable.This is also reflected in the Guidelines for the management of dyslipidaemia[6] which no longer recommend use of omega 3-fatty acids supplements for prevention of cardiovascular disease in people who have already experienced a cardiovascular event, in view of the recent evidence showing no benefit.

Cardiovascular disease is one of the most common diseases affecting the population. The target population of the claimed indication (prevention after myocardial infarction) is very wide. There is extensive research in this therapeutic area and several approved treatments have consistent data supporting efficacy in cardiovascular prevention.

Sweden considers that in recent clinical trials, no clinical benefit of omega 3-acid-ethyl esters-containing products has been demonstrated in prevention after myocardial infarction, and that these products lack of efficacy in this indication. In light of the above, Sweden is of the view that the above concerns should be thoroughly assessed at Union level as regards to their impact on the benefit-risk balance of omega-3-acid-ethyl esters-containing medicinal products for oral use in prevention after myocardial infarction.

Therefore, Sweden considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it gives its opinion under Article 31 of Directive 2001/83/EC as to whether the marketing authorisations of these products in prevention after myocardial infarction should be maintained, varied, suspended, or revoked.

References

1. Rizos EC, Ntzani EE, Bika E, Kostapanos MS,Elisaf MS. Association between omega-3 fatty acidsupplementation and risk of major cardiovascular disease events: a systematic review andmeta-analysis. JAMA. 2012;308(10):1024-1033.
2. Kotwall et al. Omega 3 Fatty Acids and Cardiovascular Outcomes Systematic Review 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 docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Arch Intern Med. 2012 May 14;172(9):686-694.
4. Aung et al. Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks Meta-analysis of 10 Trials Involving 77 917 Individuals. JAMA Cardiol. Published online January 31, 2018.
5. 2016 European Guidelines on cardiovascular disease prevention in clinical practice, European Heart Journal (2016)37, 2315-2381
6. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias European Heart Journal (2016) 37, 2999–3058).

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