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IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA

An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Direct Healthcare Professional Communication

8th of November 2023

Omega-3-acid ethyl ester medicines: dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors

Dear Healthcare Professional,

Marketing authorisation holders of omega-3-acid ethyl ester medicines, in agreement with the European Medicines Agency and the Health Products Regulatory Authority, would like to inform you of the following:

Summary

Systematic reviews and meta-analyses of randomized controlled trials highlighted a dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors treated with omega-3-acid ethyl ester medicines compared to placebo.

- **The observed risk of atrial fibrillation was found to be highest with a dose of 4 g/day.**
- **Healthcare professionals should advise patients to seek medical attention if they develop symptoms of atrial fibrillation.**
- **If atrial fibrillation develops treatment with these medicines should be permanently discontinued.**

Background on the safety concern

Omega-3-acid ethyl esters 60 and 90 Ph.Eur. are ethyl esters of polyunsaturated fatty acids (PUFAs) with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as major components of the active ingredient.

Medicinal products containing omega-3 ethyl esters are indicated for the reduction of triglyceride levels (hypertriglyceridaemia) when the response to diet and other non-pharmacological measures has proved inadequate.

EMA's safety committee, PRAC[1], assessed data from several systematic reviews and meta-analyses of large randomised controlled trials (RCTs) that overall enrolled more than 80,000 patients mostly with cardiovascular diseases or cardiovascular risk factors and investigated omega-3 fatty acid treatment on cardiovascular outcomes compared with placebo.

[1] Pharmacovigilance Risk Assessment Committee

Data from these studies showed a dose-dependent increased risk of atrial fibrillation (AF) in patients with established cardiovascular diseases or cardiovascular risk factors who were treated with omega-3-acid ethyl ester medicines compared to those treated with placebo. The observed risk was found to be highest with a dose of 4 g/day.

The most relevant evidence concerning an increased risk of AF with omega-3 ethyl esters was provided from three meta-analyses including:

- A meta-analysis by Lombardi et al.[2], highlighted that omega-3 fatty acid supplementation was associated with an increased risk of incident AF as compared with placebo [IRR 1.37, 95% CI (1.22–1.54), P<0.001].

- A systematic review and meta-analysis by Gencer et al.[3] highlighted that omega-3 fatty acid supplements were associated with an increased risk of AF (HR 1.25, 95%CI 1.07–1.46, P=0.013). HR was greater in the trials testing >1g/day of omega-3 fatty acids (HR 1.49, 95%CI 1.04–2.15, P=0.042) as compared with those testing ≤1 g/day (HR 1.12, 95%CI 1.03–1.22, P=0.024, P for interaction<0.001).

- A meta-analysis by Yan et al.[4], evaluating the clinical value of omega-3 FA supplementation, highlighted that omega-3 fatty acid supplementation is associated with an increased risk of atrial fibrillation (RR 1.32 95%CI 1.11-1.58; P=0.002).

Based on a review of this data, EMA recommended that the product information of omega-3- acid ethyl ester medicines should be updated to reflect data regarding the risk of atrial fibrillation from these studies and also to include atrial fibrillation as an adverse reaction with a frequency of common.

Healthcare professionals should advise patients to seek medical attention in case of symptoms of atrial fibrillation such as light-headedness, asthenia, palpitations or shortness of breath. If atrial fibrillation develops, treatment should be permanently discontinued.

Call for reporting

Healthcare professionals are encouraged to report adverse events in patients taking omega-3- acid ethyl esters to Health Products Regulatory Authority.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: HPRA Pharmacovigilance. Website: www.hpra.ie

Company contact point

Marketing Authorisation Holder	**Product Licence number**	**Product Name**	**Email**	**Telephone**
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BASF AS	PA1099/001/001	Omacor 1000mg Soft Capsules	Omega3@basf.com	+47 22534850

Kind Regards,

Conor Booth

Conor Booth

Medical Affairs Manager

Signed on behalf of the Marketing Authorisation Holders listed above.

[2] Lombardi M, Carbone S, Del Buono MG, Chiabrando JG, Vescovo GM, Camilli M, Montone RA, Vergallo R, Abbate A, Biondi-Zoccai G, Dixon DL, Crea F. Omega-3 fatty acids supplementation and risk of atrial fibrillation: an updated meta-analysis of randomized controlled trials. Eur Heart J Cardiovasc Pharmacother. 2021 Jul 23;7(4):e69-e70. doi: 10.1093/ehjcvp/pvab008. PMID: 33910233; PMCID: PMC8302253.

[3] Gencer B, Djousse L, Al-Ramady OT, Cook NR, Manson JE, Albert CM. Effect of Long-Term Marine ω-3 Fatty Acids Supplementation on the Risk of Atrial Fibrillation in Randomized Controlled Trials of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. Circulation. 2021 Dec 21;144(25):1981-1990. doi: 10.1161/CIRCULATIONAHA.121.055654. Epub 2021 Oct 6. PMID: 34612056; PMCID: PMC9109217.

[4] J Yan, M Liu, D Yang, Y Zhang, F An, The most important safety risk of fish oil from the latest meta-analysis?, *European Journal of Preventive Cardiology*, Volume 29, Issue Supplement_1, May 2022, zwac056.186, https://doi.org/10.1093/eurjpc/zwac056.186