

Direct Healthcare Professional Communication

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 <National Competent 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, PRAC¹, 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.

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].

¹ Pharmacovigilance Risk Assessment Committee

² Lombardi M, Carbone S, Del Buono MG, Chiabrando JG, Vescovo GM, Camilli M, Montone RA, Vergallo R, Abbate A, Biondi-Zoccali 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.

- 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 [NCA] <in accordance with the national spontaneous reporting system, including the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

[Note to NCAs: a table displaying the list of medicinal products nationally authorised could be included here in the final letter.]

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>

Communication plan for Direct Healthcare professional communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Omega-3-acid ethyl esters medicinal products for oral use
Marketing authorisation holder(s)	<p>It is strongly encouraged that a single consistent message is sent to healthcare professionals in each EU Member State.</p> <p>All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State. The single letter circulated in each Member State should cover all active substance-containing products authorised in that Member State.</p>
Safety concern and purpose of the communication	To inform healthcare professionals on the dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors treated with omega-3-acid ethyl esters medicinal products.
DHPC recipients	Healthcare professionals who may be involved in the management of patients treated with omega-3-acid ethyl esters medicinal products (e.g. cardiologists, geriatrics, endocrinologists, specialists in internal medicine, general practitioners, pharmacists and any other relevant target groups) to be agreed at national level.
Member States where the DHPC will be distributed	<p>All MSs where omega-3-acid ethyl esters are authorised.</p> <p>The decision to disseminate the DHPC at the national level is at the NCA's discretion.</p>
Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	06 October 2023
DHPC and communication plan (in English) agreed by CMDh	11 October 2023
Submission of translated DHPCs to the national competent authorities for review	CMDh position+ 7 calendar days (18 October 2023)
Agreement of translations by national competent authorities	CMDh position + 14 calendar days (25 October 2023)
Dissemination of DHPC	CMDh position + 28 calendar days (08 November 2023)