Direct Healthcare Professional Communication (DHPC)

Date: 18th January 2024

Omega-3-acid ethyl ester medicines (Omacor/Teromeg 1000 mg capsules): 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 (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA), would like to inform you of the following:

Summary

Systematic reviews and meta-analyses of randomised 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 inform patients of the symptoms of atrial fibrillation and 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.

Data from these studies showed a dose-dependent increased risk of atrial fibrillation 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.

Summary of key safety data

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

[1] Pharmacovigilance Risk Assessment Committee

- A meta-analysis by Lombardi et al.[2], highlighted that omega-3 fatty acid supplementation was associated with an increased risk of incident atrial fibrillation 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 atrial fibrillation (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 fatty acid 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).

*CI = Confidence Interval; HR = Hazard Ratio; IRR = incidence rate ratio; P = Probability; RR = Relative Risk

The product information of omega-3- acid ethyl ester medicines will be updated to reflect the risk of atrial fibrillation and to include atrial fibrillation as a common adverse reaction (may affect up to 1 in 10 people).

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

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle ▼

You can report via:

- the Yellow Card website
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, timing onset, treatment dates, and product brand name.

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[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

Adverse events should also be reported to the Marketing Authorisation Holder for the medicinal product concerned via the company contact points outlined below.

Company contact point

If you wish to report an adverse event, have any questions, or if you require any further information, please contact the relevant Marketing Authorisation Holder for the product you are using.

Marketing Authorisation Holder	**To report an adverse event**	**To request further information**
BASF AS PL 15905/0001 Omacor 1000mg Soft Capsules	Pv.uk@viatris.com	Omega3@basf.com
STRIDES PHARMA UK LIMITED PL 13606/0223 Omega 3-acid-ethyl esters 1000mg soft capsules	drugsafety@strides.com	sadiq.basha@stridespharma.co.uk
MERCURY PHARMACEUTICALS LIMITED PL 12762/0473 Teromeg 1000mg capsules	medicalinformation@advanzpharma.com	medicalinformation@advanzpharma.com **CC:** drugsafety@advanzpharma.com
QUADRANT PHARMACEUTICALS LIMITED PLPI 20774/1308 Omacor 1000mg Soft Capsules	Louise.doyle@maxearn.co.uk Radoslaw.bandomir@maxearn.co.uk	Louise.doyle@maxearn.co.uk Radoslaw.bandomir@maxearn.co.uk
S AND M MEDICAL LIMITED PLPI 19488/1747 Omacor 1000mg Soft Capsules	RA@chemilines.com	RA@chemilines.com
GOWRIE LAXMICO LIMITED PLPI 18799/2282 Omacor 1000mg Soft Capsules	support@bnshealthcare.com	support@bnshealthcare.com
SUERTE PHARMA LIMITED PLPI 46420/0271 Omacor 1000mg Soft Capsules	Olujimi Shobande olujimi@nslgroup.co.uk Anuja Tirumalasetti anuja@suertepharma.co.uk	Olujimi Shobande olujimi@nslgroup.co.uk Anuja Tirumalasetti anuja@suertepharma.co.uk
S AND M MEDICAL LIMITED PLPI 19488/1704 Omacor 1000mg Soft Capsules	RA@chemilines.com	RA@chemilines.com
LEXON (UK) LIMITED PLPI 15184/1893 Omacor 1000mg Soft Capsules	yogesh.patel@lexonuk.com	yogesh.patel@lexonuk.com
MEDIWIN PPIP LTD PLPI 18980/0855 OMACOR 1000 MG SOFT CAPSULES	pharmacovigilance@mediwin.co.uk	pharmacovigilance@mediwin.co.uk