Direct Healthcare Professional Communication (DHPC)

31/07/2024

Omega-3-acid ethyl ester (Omipure), Dose-dependent increased risk of atrial fibrillation in patients with

established cardiovascular diseases or cardiovascular risk factors

Dear Healthcare Professional,

In agreement with Saudi Food and Drug Authority, AJA Pharmaceutical Industries Company. Ltd

would like to inform you of *Omega-3-acid ethyl ester Dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors treated with omega-3-acid ethyl ester compared to placebo.*

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 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.***

Further information on the safety concerns and the recommendations

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.

Omega-3 ethyl esters is indicated for:

- *The reduction of triglyceride levels (hypertriglyceridemia) when the response to diet and other non-pharmacological measures has proved inadequate.*

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 were assessed. These RCTs 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.[1], 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.[2] 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).*

[1] 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.

[2] 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.

- *A meta-analysis by Yan et al.[3], 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).*

Based on a review of this data, it was 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 (≥1/100 to <1/10).

AJA Pharmaceutical Industries Company. Ltd, in agreement with the SFDA, is updating

the product information of Omega-3-acid ethyl ester 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

[3] 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

Call for reporting

Please report any suspected adverse reactions associated with the use of *Omega-3-acid ethyl ester* in accordance with the national requirements via the national spontaneous reporting system.

To reports any side effect(s):

Saudi Arabia:

Saudi Food and Drug Authority (SFDA)

The National Pharmacovigilance Centre (NPC):

− SFDA Call Center: 19999

− E-mail: npc.drug@sfda.gov.sa

− Website: https://ade.sfda.gov.sa

In addition, suspected adverse reactions related to Aja pharma products may be reported to Aja pharma Pharmacovigilance department:

Email: PV@Ajapharma.com

Contact Person: Lama Alzaidi

Tel: +966-11-4148188 Ext 5726

Mobile +966550113712

Best Regards,

Lama Fahad Alzaidi

Qualified Person for Pharmacovigilance

AJA Pharmaceutical Industries Company. Ltd

Signature