

QIPP Detail Aid Support Document

Providing support for quality in prescribing

Omega-3 fatty acid compounds

KEY MESSAGES

- Omega-3 fatty acid compounds, Maxepa and Omacor, are licensed for hypertriglyceridaemia. Omacor is additionally licensed for secondary prevention in those who have had an MI. Use in other indications is unlicensed.
- NICE guidance recommends against prescribing omega-3 fatty acids for the primary prevention of coronary heart disease.
- Trials of omega-3 fatty acids added to optimal care to prevent CHD have not shown benefits on major cardiovascular endpoints.
- Fibrates should be used first line for raised triglycerides. High doses (4 capsules of Omacor) were required in trials to reduce triglycerides to a similar extent to fibrates in patients with type 2 diabetes. Doses below this resulted in a triglyceride reduction of approximately half this amount.
- Patients who have had an MI should be advised to consume two to four portions of oily fish per week.

WHAT IS THE PROBLEM?

- In 2010/11 the East Midlands spent nearly £800,000 on Omacor in primary care. There is little place for its use in optimal management of cardiovascular disease and this money could be better used for other interventions.

Apr 2010-Mar 2011	Total items	Total actual cost	Cost per item
Omacor	33469	£747,260.37	£22.33
Maxepa	2046	£45,412.92	£22.20
Overall		£792,673.29	

According to the PACT data, the average dose prescribed is Omacor 1.5 capsules/day and Maxepa 5.8 capsules per day. These doses are lower than licensed doses for hypertriglyceridaemia and are likely to be sub-optimal for reducing triglycerides. The Omacor dose suggests most use is post-MI for which the recommended dose is one capsule daily.

WHAT IS THE EVIDENCE?

- The omega-3 fatty acid compounds Omacor® and Maxepa® are licensed as adjunct to diet and/or statins for hypertriglyceridaemia. Omacor is additionally licensed as adjunctive therapy in secondary prevention in those who have had an MI. The products vary in the ratio of EPA/ DHA they contain. Unlicensed supplements are also available with varying amounts of fatty acids.

Omacor is not licensed for use with fibrates and the SPC states there is only limited information on their combined use.

- A Cochrane systematic review, search date 2004, included 48 randomised controlled trials (36,913 participants) and 41 cohort analyses. Pooled trial results did not show a reduction in the risk of total mortality or combined cardiovascular events in those taking omega 3 fatty acids. Trials varied in the doses used and trial design. More recent studies have not found a positive effect on mortality or major cardiovascular outcomes with omega-3 fatty acid compounds.

The Cochrane review assessed whether dietary or supplemental omega-3 fatty acids from oily fish or plant sources alter total mortality, cardiovascular events or cancers¹.

Restricting analysis to trials increasing the intake of fish-based omega-3 fatty acids, or those involving omega-3 fatty acid supplements, did not suggest significant effects on mortality or cardiovascular events in either group. Subgroup analysis by dietary advice or supplementation, baseline risk of CVD or omega-3 fatty acid dose suggested no clear effects of these factors on primary outcomes.

- NICE guidance recommends against prescribing omega-3 fatty acids for the primary prevention of coronary heart disease².
- NICE found evidence from only one trial that omega-3 fatty acids may be effective in secondary prevention if started within 3 months of an MI. This was a large open-label study which showed a reduction in all cause mortality. However patients were not receiving optimal cardiovascular preventative therapies and several important confounding factors (for example change in statin usage through the trial) were not adjusted for.

The NICE Clinical guideline on secondary prevention of MI³ states that:

One trial has shown a benefit of treatment with omega-3-acid ethyl esters in patients within 3 months of an MI. However, other secondary prevention treatment had not been optimised in this trial and the majority of patients had preserved left

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ventricular function. There is some uncertainty about how much additional benefit patients after acute MI optimally managed for secondary prevention, including those with left ventricular systolic dysfunction, will obtain from the addition of omega-3-acid ethyl esters treatment. There is also a paucity of evidence for the effectiveness of treating patients who have had an MI in the past, at least 3 months earlier.

The trial referred to was the GISSI-Prevenzione trial, a randomised open-label study of the independent and combined effects of omega-3 supplements and vitamin E on morbidity and mortality in over 11,000 patients with a recent MI⁴. In patients taking omega-3 supplements there was a relative risk reduction of 10% (95% CI 1-18%) in the primary combined efficacy endpoint of death, non-fatal MI and non-fatal stroke, compared to patients not taking omega-3 supplements. This translated to an absolute risk reduction of 1.3%. It is important to note that patients were asked to adhere to recommended preventative treatments- aspirin, beta-blockers, ACE inhibitors and statins but the use of statins increased from 4.7% at baseline to 45.5% at 42 months; the increase in statin use of the study period was not adjusted for as a confounding factor.

- *NICE clinical guidelines for type 2 diabetes concluded that omega-3 supplements could lower triglyceride levels, but overall the evidence showed minimal improvement in lipid profiles in people who had not had a MI. In addition, high doses (4 capsules of Omacor daily) were needed to show a reduction in triglycerides comparable to the reduction seen in trials with fenofibrate; doses lower than this resulted in triglyceride reductions of approximately half this amount.*

The guidelines assessed one Cochrane review and five RCTs and found that all trials found that treatment with omega-3 fatty acids significantly reduced triglycerides compared to placebo⁵.

The only other area where the Cochrane review identified significant changes was in LDL-C where omega-3 fatty acids were associated with a significant increase compared with placebo.

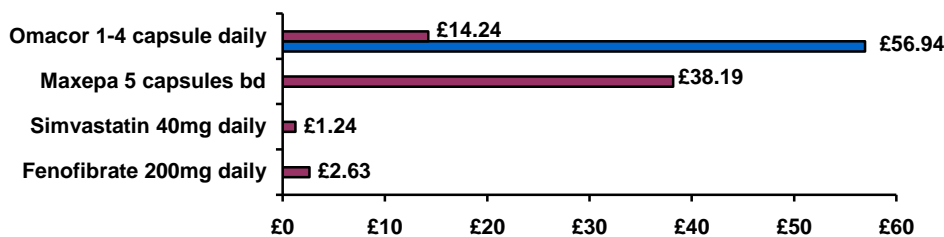
Trials with high doses of fish oil (>2g EPA, approximately equivalent to 4 capsules of Omacor) showed a significant increase in LDL-C of 0.51 mmol/l (0.18 to 0.84, p=0.003), this was non-significant for lower doses (<2g EPA, N=7).

Levels of triglycerides in the high-dose groups decreased by 1.11 mmol/l (-2.21 to -0.10, p=0.03), but in the low-dose group this was less at 0.54 mmol/l (-0.69 to -0.38, p<0.00001).

The Guideline Development Group (GDG) noted that appraising the evidence for fish oils as a homogeneous therapeutic concept is problematic, as the evidence included showed a variation in the fish oil dosage used. Clinical experience confirmed that large total doses of oils used to get an adequate dose of omega 3 fish oils in some preparations can cause adverse effects. From the evidence available omega 3 fish oil preparations could help lower triglyceride levels, but overall showed minimal improvement in lipid profiles in people who had not had a MI. The GDG agreed there were financial consequences in prescribing omega 3 supplements when the evidence showed no clear benefit. They concluded with the following recommendations:

- Do not prescribe fish oil preparations for the primary prevention of cardiovascular disease in people with Type 2 diabetes. This recommendation does not apply to people with hypertriglyceridaemia receiving advice from a healthcare professional with special expertise in blood lipid management.
- Consider a trial of highly concentrated licensed omega 3 fish oils for refractory hypertriglyceridaemia if lifestyle measures and fibrate therapy have failed.

WHAT ARE THE COSTS?



Costs for 28 days supply. Taken from Drug Tariff January 2012

Doses are a guide and do not imply therapeutic equivalence.

Simvastatin is not licensed for hypertriglyceridaemia alone, only for hypercholesterolaemia or mixed dyslipidaemia⁶.

The licensed dose of Omacor for secondary prevention of MI is one capsule daily. The dose for hypertriglyceridaemia is 2 capsules daily, increasing to 4 capsules daily if necessary.

References:

1. Hooper L, Harrison RA, Summerbell CD, et al. Omega 3 fatty acids for prevention and treatment of cardiovascular disease. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD003177.
2. NICE Clinical Guideline 67 Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease May 2008 (reissued March 2010) (available at <http://www.nice.org.uk/nicemedia/live/11982/40689/40689.pdf>)
3. NICE Clinical Guideline 48 MI: secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction May 2007 (available at <http://publications.nice.org.uk/mi-secondary-prevention-cg48>)
4. UKMi New Medicines on the Market Omacor 4/03/01 April 2003 (available at www.nelm.nhs.uk)
5. NICE Clinical Guideline 66 Type 2 diabetes May 2008 (available at <http://guidance.nice.org.uk/CG66>)
6. Zocor Summary of Product Characteristics, Merck Sharp & Dohme Ltd Date of revision of the text March 2011 (available at <http://www.medicines.org.uk/> accessed 26th January 2012)