Hertfordshire and West Essex Integrated Care System

NHS Hertfordshire and West Essex Integrated Care Board

HERTFORDSHIRE AND WEST ESSEX AREA PRESCRIBING COMMITTEE (HWE APC)
Omega-3-fatty acid compounds for secondary prevention of pancreatitis for the treatment of severe hypertriglyceridaemia

AMBER INITIATION:
Initiated by specialists in secondary and tertiary care with prescribing continued by GPs.

Name	What it is	Indication	Date decision last revised	Decision Status	Guidance
Omega-3 fatty acid compounds	Essential fatty acids	• Reduction of pancreatitis risk in severe hypertriglyceridaemia • *See separate decision document for adjunct to diet and statin in type IIb or III hypertriglyceridemia; adjunct to diet in type IV hypertriglyceridemia; adjunct in secondary prevention in those who have had a myocardial infarction (MI) in the preceding 3 months.*	December 2018 HMMC	Final	NHS England November 2017 (see separate guidance document)

Recommendation:

Omega-3 fatty acid compounds are recommended for restricted use as an option for secondary prevention of pancreatitis for the treatment of severe hypertriglyceridaemia if triglyceride (TG) levels are ≥10mmol/L despite addressing secondary causes, uptake of lifestyle changes and pharmacological therapy.

To be initiated in specialist lipid clinics only and continued in primary care (**AMBER INITIATION**).

For all other indications omega-3 fatty acid compounds are NOT RECOMMENDED FOR PRESCRIBING IN PRIMARY OR SECONDARY CARE (DOUBLE RED) (*refer to separate decision document*)

Background Information and Issues for Consideration

- Omega-3 fatty acid compounds are essential fatty acids which can be obtained from the diet. They are licensed for adjunct to diet and statin in type IIb or III hypertriglyceridemia; adjunct to diet in type IV hypertriglyceridemia; adjunct in secondary prevention in those who have had a myocardial infarction in the preceding 3 months.
- The NHS England publication: Items which should not routinely be prescribed in primary care cites various NICE guidance none of which recommends use of omega-3 fatty acid supplements (due to a lack of outcome data on benefits including cardiovascular). However, NICE do not appear to have specifically looked into the use of omega-3 fatty acids for this particular indication of preventing recurrent episodes of pancreatitis.
- Primary care prescribing of items which should not routinely be prescribed in primary care is being monitored by NHSE with an expected significant reduction in costs.
- Acute pancreatitis appears to be a well-established complication of hypertriglyceridemia and the risk of acute pancreatitis increases progressively as serum triglyceride levels increase
- There are no locally approved guidelines or guidelines from NICE and there do not appear to be any UK clinical guidelines on the treatment of hypertriglyceridaemia.
- There appear to be no UK clinical guidelines which recommended or even mention the use of omega-3 fatty acid supplements/fish oils in the prevention of pancreatitis.
- Treatments used to reduce triglyceride concentrations include lifestyle modification, statins, fibrates, omega-3 fatty acid compounds and nicotinic acid.

ASSESSMENT AGAINST THE ETHICAL FRAMEWORK

Evidence of Clinical Effectiveness

- Summary from London Medicines Information Service (Northwick Park) evidence evaluation was considered (full evaluation available in committee papers):
  - There is evidence that the omega-3 fatty acids can lower triglyceride levels in a dose-dependent fashion. A dose of 3-4 g/day of omega-3 fatty acid is needed to reduce hypertriglyceridemia by 20–50%. This would also lead to a mild increase (~5%) in HDL and an increase in LDL, due to conversion of VLDL to LDL. For comparison, fibrates and nicotinic acid used at licensed doses effectively lower triglyceride levels by 30–60% and also raise HDL levels.
  - Our systematic search of the published literature found no studies of any type whereby omega-3 fatty acids prevented symptoms or signs of pancreatitis from occurring.
  - There appears to be some differing opinion on drug treatment of hypertriglyceridemia to prevent pancreatitis and the triglyceride concentration at which treatment would be indicated.
- *Extract from PrescQIPP, Bulletin B210, October 2018, 2.0*: *Hypertriglyceridaemia (see references for link)*
  - A systematic review looking at the treatment of hypertriglyceridaemia with omega-3 fatty acids in 2005 looked at ten studies which reported long-chain omega-3 fatty acids to be effective in the treatment of hypertriglyceridaemia. The average decrease in triglycerides was 29% and total cholesterol 11.6%. The review stated that many of the RCTs had serious shortcomings including a short duration, no intention to treat analysis and lack of dietary control. The studies all looked at the secondary prevention of hypertriglyceridaemia.
  - Lifestyle modification advice should be given to all individuals with raised triglycerides. However, appropriate dietary management of hypertriglyceridemia differs between mild-to-moderate and severe hypertriglyceridemia.
  - The risk of acute pancreatitis increases when serum triglycerides are approximately 1000 mg/dL or greater (11.3 mmol/L) although some patients have developed acute pancreatitis at lower levels. Lifestyle modification alone is not sufficient treatment in patients with severe hypertriglyceridaemia. When levels are severely raised, the risk of acute pancreatitis outweighs the risk of MI. Fibrates are the first line treatment choice for patients with hypertriglyceridaemia. Niacin is also an option to reduce triglycerides however treatment is associated with significant side effects.[9]
  - For patients with significantly raised levels, two portions of fish per week would not provide the same level of triglyceride reduction as a daily dose of omega-3 fatty acids. Omega 3 fatty acids are very effective at reducing serum triglycerides although they are also subject to significant side effects which may limit their use. Licensed products should be reserved to treat those with severe hypertriglyceridaemia (10-20 mmol/litre) rather than as routine treatment.[9] It may be appropriate for the treatment of severe hypertriglyceridaemia to be managed by a specialist.

    Reference 9: Gelrud A, Whitcomb DC. Hypertriglyceridemia-induced acute pancreatitis. UpToDate website. Topic last updated 20/07/2015. Available at: https://www.uptodate.com/home
- Extract and evidence from notes of October 2018 North Central London Joint Formulary Committee: Omega-3 fatty acid ethyl esters (Omacor®, Mylan) for inherited hypertriglyceridaemia were considered (*see references for link).*
- Feedback from local specialist: There is no RCT evidence for omega-3 demonstrating a reduction in pancreatitis rates (similar to the other medical treatments such as statins, fibrates, diet life style advice etc.), just case reports, registry data etc. There is more RCT data on volanesorsen (see policy drivers for information on NICE TA in development (NHS England commissioning responsibility)). See the following from a 2018 paper (Pharmacological treatment options for severe hypertriglyceridemia and familial chylomicronemia syndrome - see references) where this is suggested about Omega-3 "These may need to be prescribed from hospital pharmacies on an orphan disease indication in countries where access to omega-3 preparations in primary care is limited. Their principal use is in heterozygous LPL deficiency (type V, type IV). Omega-3 preparations are commonly used to suppress hypertriglyceridemia in pregnancy where other compounds are contraindicated."
- SPC for Omacor states common side effects as gastrointestinal disorders (including abdominal distension, abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, eructation, gastro-oesophageal reflux disease, nausea or vomiting) which may limit use; There are no adequate data from the use of Omacor in pregnant women. Studies in animals have not shown reproductive toxicity. The potential risk for humans is unknown and therefore Omacor should not be used during pregnancy unless clearly necessary. Note manufacturers advise avoid statins and fibrates in pregnancy

Cost of treatment and Cost Effectiveness

Cost of Treatment

Product	Cost per 28 days (drug tariff)	Cost per year
Omacor (Eicosapentaenoic acid 460mg / Docosahexaenoic acid 380mg) capsules 1-4 capsules daily[#]	£14 - £57	£186 - £743*
Fenofibrate 200mg od	£4	£47
Atorvastatin 80mg od	£2	£26

* note there appear to be brands eg Omega 3 that if prescribed by brand would be lower cost (£78-£313/yr)
[#] it is expected that higher doses will be used for this indication and so costs likely to be at the higher range

Cost Effectiveness

- No cost-effectiveness information appears to be available on use of omega 3 compounds for reduction of pancreatitis risk in severe hypertriglyceridaemia
- A very old SMC evaluation from 2002 on Omacor for Treatment of hypertriglyceridaemia: Not recommended for use based on the lack of long-term data to indicate that reductions in triglyceride levels provide real benefit in terms of reducing cardiovascular events, on a lack of evidence of increased patient acceptability of the product, and lack of a

pharmacoeconomic case for the drug.

The needs of the population

- The needs of the population may be high as treatment options appear limited especially for patients when treatment with statins and fibrates are contra-indicated, not tolerated or ineffective.
- Although omega 3 fatty acid compounds may reduce triglyceride concentration there is a lack of outcome evidence that this reduces cardiovascular risk and risk of pancreatitis. However, extreme triglyceride levels are associated with pancreatitis and a high risk of morbidity and mortality independent of CVD.
- A NICE TA for a new treatment option is in development (volanesorsen for treating familial chylomicronaemia syndrome). The rare and specialist nature of this treatment and indication is recognised in this being for national commissioning by NHS England.

The needs of the community

- The needs of the community appear moderate as it appears that although a relatively small number of patients would require treatment, there is an associated cost pressure as this will be as an alternative or add on to current treatments and dose used is likely to be high.
- It is not possible from ePACT data to determine the number of patients prescribed omega-3 compounds for this indication
- From specialist estimates, patient numbers may be 5-20 which may cost £3k-£15k/year at highest dose (Hertfordshire)

Equity: No impact anticipated.

Policy Drivers

- NHS England publication: Items which should not routinely be prescribed in primary care: Guidance for CCGs includes omega-3 fatty acid compounds with the recommendations: Advise CCGs that prescribers in primary care should not initiate omega-3 Fatty Acids for any new patient; Advise CCGs to support prescribers in deprescribing omega-3 Fatty acids in all patients

The guidance states that 'No routine exceptions have been identified' to these recommendations.
CCG primary care prescribing of items which should not routinely be prescribed in primary care is being monitored by NHSE with an expected significant reduction in costs.

- NHS England, Medicines Policy Team, November 2018 email response summary:
  The guidance focuses on the routine prescribing of Omega-3 Fatty Acid Compounds in primary care it is based (on) NICE do not do recommendations. This specific indication (reduction of pancreatitis risk) was not considered as part of the development of the recommendations for the use of Omega-3 Fatty Acid Compounds. For the indication described it would be up to the CCG to consider the evidence of effectiveness for this indication and if they would like to include this in their local prescribing policies, however we would advise that any exceptions to the guidance do need to be based on robust clinical evidence.
- NICE Clinical Guidelines on Lipid Modification states the following for Omega-3 fatty acid compounds:
  - Omega-3 fatty acid compounds for preventing CVD: Do not offer omega-3 fatty acid compounds for the prevention of CVD to any of the following: people who are being treated for primary prevention, people who are being treated for secondary prevention, people with CKD, people with type 1 diabetes, people with type 2 diabetes.
  - Tell people that there is no evidence that omega-3 fatty acid compounds help to prevent CVD.
  - Combination therapy for preventing CVD: Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD.
- NICE Clinical Guidelines on Lipid Modification states the following for triglyceride concentration:
  - Refer for urgent specialist review if a person has a triglyceride concentration of more than 20 mmol/litre that is not a result of excess alcohol or poor glycaemic control.
  - In people with a triglyceride concentration between 10 and 20 mmol/litre: repeat the triglyceride measurement with a fasting test and review for potential secondary causes of hyperlipidaemia and seek specialist advice if the triglyceride concentration remains above 10 mmol/litre.
  - In people with a triglyceride concentration between 4.5 and 9.9 mmol/litre: be aware that the CVD risk may be underestimated by risk assessment tools and optimise the management of other CVD risk factors present and seek specialist advice if non-HDL cholesterol concentration is more than 7.5 mmol/ litre.

Note the guidelines do not make specific recommendations for the treatment of hypertriglyceridaemia. The Full Guideline states the following:

- The GDG discussed recommendations for people with raised triglycerides levels. The GDG noted that extreme triglyceride levels were associated with pancreatitis and a high risk of morbidity and mortality independent of CVD. Registry data confirms a 20-fold excess risk of pancreatitis occurs in patients with lipoprotein lipase deficiency. The GDG noted the Royal College of Pathologists' recommendation that triglycerides >20 mmol/litre were considered a laboratory result to be urgently reported to primary care. This value has been used extensively in international consensus statements. The GDG recommended that all patients with triglycerides >20 mmol/litre required urgent review by a lipid specialist if not caused by acute excess alcohol or poor glycaemic control. The GDG considered the management of patients with triglycerides between 10 and 20 mmol/litre. Many of these patients have secondary causes of hypertriglyceridaemia. Triglycerides are subject to large biological variation which is amplified in post-

prandial samples.

- NICE Guidelines on Familial Hypercholesterolaemia does not include recommendations for hypertriglyceridaemia. It does include that people with FH should not routinely be recommended to take omega-3 fatty acid supplements.
- PrescQIPP bulletin 47 on Omega-3 fatty acids includes:
  - 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.
  - Consider switching patients taking omega-3 fatty acid compounds for hypertriglyceridaemia to a fibrate or statin.
- PrescQIPP, Bulletin B210, October 2018, 2.0 (also see specific extract concerning hypertriglyceridaemia below)
  - Omega-3 fatty acids and other fish oils are not recommended for routine prescribing on the NHS as the evidence to support their efficacy is not strong enough and they are not considered to be cost-effective.
  - Patients already being prescribed these preparations should be reviewed and prescriptions stopped.
  - No new prescriptions for omega-3 fatty acids or other fish oils should be commenced.
  - Consider switching patients taking omega-3 fatty acid compounds for hypertriglyceridaemia to prevent myocardial infarction (MI) to evidence based treatment, in line with National Institute for Health and Care Excellence (NICE) clinical guideline 71 (CG71). For patients with severe hypertriglyceridaemia consider the risk of acute pancreatitis and ensure local treatment guidelines are available.
  - Use in patients with schizophrenia is unlicensed and should be reviewed in conjunction with a specialist with a view to stopping prescribing if no benefit has been achieved.
  - Patients wishing to take these products should be advised to increase their dietary intake or purchase them over the counter. Further advice is available at: https://www.bda.uk.com/foodfacts/omega3.pdf . Community pharmacists will be able to assist patients in obtaining a suitable preparation.
- Volanesorsen for treating familial chylomicronaemia syndrome (FCS) is a NICE TA in development with a publication date of April 2019 https://www.nice.org.uk/guidance/indevelopment/gid-hst10015 . The final scope states that the prevalence of FCS is estimated to be 1 to 2 per million people. This TA is for national commissioning by NHS England.
- North Central London Joint Formulary Committee, October 2018 (see references for link to full notes): Omega-3 fatty acids ethyl ester is approved for secondary prevention of pancreatitis for the treatment of inherited hypertriglyceridaemia (type 3 hyperlipidaemia, lipoprotein lipase deficiency or in presence of raised chylomicrons and VLDL), if TG levels are ≥10mmol/L despite addressing secondary causes, uptake of lifestyle changes and pharmacological therapy. To be initiated in lipid clinics only.
- WECCG – not recommended; Buckinghamshire Formulary - Non Formulary; Bedfordshire and Luton CCGs – not recommended; Cambridgeshire and Peterborough CCG - not recommended; Mid Essex CCG – not recommended

Note it is uncertain if omega 3 compounds have been considered for this specific indication.

Implementability: No issues identified, although this will need to be considered depending on recommendation made.

References

1. HMMC Recommendations, Omega-3 fatty acid compounds (not recommended; double red), Feb 2018 http://www.enhertsccg.nhs.uk/sites/default/files/content_files/Prescribing/Local_Decisions/Cardiovascular_system/Omega%203%20fatty%20acid%20compounds%20-%20NHSE%20items%20which%20should%20not%20routinely%20be%20prescribed.pdf
2. NHS England: Items which should not routinely be prescribed in primary care: Guidance for CCGs https://www.england.nhs.uk/publication/items-which-should-not-be-routinely-prescribed-in-primary-care-guidance-for-ccgs/
3. NICE Clinical guideline [CG181], Cardiovascular disease: risk assessment and reduction, including lipid modification https://www.nice.org.uk/guidance/cg181
4. NICE Clinical guideline [CG71, Familial hypercholesterolaemia: identification and management, last updated Nov 2017 https://www.nice.org.uk/guidance/cg71
5. PrescQIPP Bulletin 47, Oct 2013: Omega-3 fatty acids https://www.prescqipp.info/component/jdownloads/send/85-omega-3-fatty-acids/787-bulletin-47-omega-3-fatty-acids
6. SPC Omacor https://www.medicines.org.uk/emc/product/1706
7. SMC Omega-3-acid ethyl esters (Omacor®) for Treatment of hypertriglyceridaemia, November 2002 https://www.scottishmedicines.org.uk/medicines-advice/omega-3-acid-ethyl-esters-omacor-fullsubmission-1602/
8. Chaudhry R, Viljoen A, Wierzbicki AS, Pharmacological treatment options for severe hypertriglyceridemia and familial chylomicronemia syndrome. Expert Rev Clin Pharmacol. 2018 Jun;11(6):589-598 https://www.ncbi.nlm.nih.gov/pubmed/29842811
9. Extract from notes of October 2018 NCLJFC: Omega-3 fatty acid ethyl esters (Omacor®, Mylan) for inherited hypertriglyceridaemia 8.4 (Applicant: RFL) https://www.ncl-mon.nhs.uk/wp-content/uploads/2017/07/1810_NCL_JFC_Minutes_October2018.pdf
10. PrescQIPP, Bulletin B210, Omega-3 fatty acid compounds and other fish oils, October 2018, 2.0 https://www.prescqipp.info/our-resources/bulletins/bulletin-210-omega-3-fatty-acid-compounds-and-other-fish-oils/

Version	2.0 Harmonisation of Hertfordshire Medicines Management Committee (HMMC) guidance and West Essex Medicines Optimisation Programme Board (WEMOPB) guidance updates include: • Rebadging with HWE ICB and removal of ENHCCG and HVCCG headers.
Developed by	ENHCCH and HCCCG PMOT
Approved by	HMMC
Date approved/updated	December 2018
Review date:	The recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.
Superseded version	1.0