Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Medicines Safety Update

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## ACSOM membership announced

On 2 February 2010 Mark Butler, the Parliamentary Secretary for Health, announced the membership of the new Advisory Committee on the Safety of Medicines (ACSOM) for 2010–13. ACSOM replaces the Adverse Drug Reactions Advisory Committee (ADRAC) as the key advisory committee to the Therapeutic Goods Administration (TGA) on medicines safety.

The Committee will be chaired by Professor Emily Banks, a pharmacoepidemiologist and senior research fellow at the National Centre for Epidemiology and Population Health. Professor Banks has extensive experience in quantitative evaluation of the benefits and risks of medicines.

The Committee comprises medical experts, a pharmacist and a health consumer expert. The members are: Associate Professor Christopher Beer, Professor Nick Buckley, Associate Professor Danny Liew, Dr Kristine Macartney, Ms Alison Marcus, Dr Jane Robertson, Associate Professor Simone Strasser and Professor Duncan Topliss.

Once again the TGA thanks the past and outgoing ADRAC members for their contribution to the monitoring of medicines safety in Australia and looks forward to working with the members of ACSOM.

ACSOM recommendations will be published on the TGA website.

## Safety of fish oil and omega-3 fatty acids

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### Introduction

The anticoagulant properties of fish oil products and the consequent risk of bleeding tendency have led to safety concerns, in particular concerning the risk of postoperative bleeding. Anecdotally, it is understood that some surgeons and anaesthetists may delay procedures if their patients are taking fish oil and, while there is no specific clinical guideline to support this, there is some support in the medical literature. Thomas *et al* (2008) has reported epistaxis and easy bruising with the use of fish oils and suggested that these may potentiate the action of warfarin and present a risk to haemophiliacs.[1]

Fish oil contains the omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). There is good evidence indicating that DHA and EPA in the form of fish oil supplements have beneficial cardiovascular effects. This is presented in a comprehensive review undertaken by Colquhoun *et al* for the Australian National Heart Foundation (NHF), published in 2008.[2]

The most commonly proposed mechanism for the anticoagulant activity of fish oils relates to changes in the ratio of phospholipids in platelet membranes. *In vitro*, fish oils competitively inhibit cyclo-oxygenase which decreases synthesis of thromboxane $A_2$ from arachidonic acid (ARA) in platelets. The cyclo-oxygenase mediated generation of thromboxane $A_2$ from ARA in platelets plays an important role in blood coagulation. Consumption of fish-rich diets or fish oil supplements may reduce platelet aggregation through reduction of platelet ARA concentration and cyclo-oxygenase mediated generation of thromboxane $A_2$ from EPA.

DHA has the potential to influence platelet aggregation by competing with ARA for membrane incorporation in platelets and thereby reducing available ARA for thromboxane $A_2$ generation. Other mechanisms such as decreasing platelet growth and clotting factors are also postulated to play a role.[3,4]

There is some evidence for other benefits of fish oil. These include use for infant eye/brain development, inflammation, nutrition (in gastrointestinal disorders), mental health disorders, Alzheimer's disease and rheumatoid arthritis. While fish oil products are widely used, this suggests the potential for more extensive applications.[5]

### Summary of the literature

A literature search identified only three case reports presenting bleeding events or changes in laboratory results in patients taking fish oil and anticoagulant medication.[6–8] Evidence from several randomised placebo-controlled trials and reviews is presented below.

Leaf *et al* (1994) undertook a randomised controlled trial in 551 candidates for percutaneous intraluminal coronary angioplasty to investigate whether omega-3 fatty acids prevented restenosis. Subjects were randomised to receive high doses of EPA and DHA or placebo for 14 days before, and six months after, angioplasty. All patients also received 325 mg of aspirin for six months post angioplasty. While the intervention did not prevent restenosis, there was no statistically significant difference in bleeding time between groups.[9]

The safety of postoperative fish oil was evaluated by Heller *et al* (2002) in a randomised, double-blind, placebo-controlled trial of 44 patients administered high doses of omega-3 fatty acids in parenteral nutrition after major abdominal surgery. No significant between-group difference was seen in bleeding events.[10]

Commentary by Lichtenstein (2005) on clinical data concerning dietary supplements affecting antithrombotic therapy included the conclusion on safety from an evidence-based review on the effects of omega-3 fatty acids on cardiovascular disease, prepared for the US Agency for Healthcare Research and Quality in 2004. It was noted that while clinical bleeding was a theoretical concern, in the studies reviewed there was no difference in the overall number of bleeding events between supplement and control groups. It was concluded that adverse events related to consumption of fish oil appeared to be minor.[11]

Harris (2007) reviewed 19 clinical trials of candidates for vascular surgery or femoral artery puncture who were administered omega-3 fatty acids in addition to anticoagulant medications. In 14 of these trials, the fatty acids were administered one and 42 days prior to surgery, and in 5 studies, postoperatively, at doses varying from 1.4 to 21 g/day. It was concluded that clinically significant bleeding events were 'virtually non-existent'.[12]

The effects of prescription omega-3 acids (POM) and aspirin, alone and in combination, on platelet function in 10 healthy subjects were investigated by Larson *et al* (2008). This was an open-label four-week sequential therapy trial with each subject their own control. It was found that while platelet aggregation was not affected by POM alone, it was affected by aspirin and by aspirin with POM.[13]

Tavazzi *et al* (2008) published the results of a randomised, double-blind, placebo-controlled trial looking at the effect of n-3 polyunsaturated fatty acids (PUFA) in patients with chronic heart failure (New York Heart Association class II–IV). Participants were assigned to n-3 PUFA 1 g/day (n=3494) or placebo (n=3481). Analysis of those discontinuing the study due to adverse events was undertaken, and showed no significant difference between the treatment and placebo groups.[14]

Watson *et al* (2009) undertook a retrospective record review of 182 subjects treated with high-dose fish oil, aspirin and clopidogrel and 182 controls on aspirin and clopidogrel alone, with a mean follow-up period of 33 months. One major bleed was seen in the treatment group (a patient with rectal cancer requiring transfusion) and none in the control group (p=1.0). There were more minor bleeds in the control group compared to the treatment group but the difference was not statistically significant. It was concluded that high-dose fish oil is safe in combination with aspirin and clopidogrel, and does not increase the risk of bleeding compared with that seen with aspirin and clopidogrel alone.[15]

## Consumer use of fish oil and omega-3 fatty acids

Research shows that the popularity of complementary medicine (CM) use, and particularly fish oil, is worldwide and likely increasing.

The results from a Canadian National Population Health Survey undertaken in 2000–01 including 11,424 adults were published by Singh *et al*. These showed the prevalence of use of natural health products within the two days preceding was 9.3%, with fish oils the fourth most common product.[16]

An analysis of data by Elmer *et al*, collected as part of the Cardiovascular Health Study cohort study of risk factors for coronary heart disease (CHD) and stroke in adults 65 years and older, aimed to determine the prevalence of CM use concurrent with prescription and over-the-counter (OTC) medications and assess the risk for adverse interactions.[17] Fish or cod liver oil was the fourth most common CM, with 2.28% of study participants using it over the four periods. Its use was categorised as a possible or theoretical risk for bleeding adverse events, rather than a significant risk.

Ramsay *et al* published the results of a retrospective analysis of pharmaceutical care plans for patients starting warfarin, who attended an anticoagulation clinic in 2003, to ascertain their CM use.[18] Of the 631 plans analysed it was found that 170 (26.9%) patients were taking some form of CM. Approximately 60% of these were taking a CM that could interact with warfarin. Overall, more than 10% of the patients were taking fish or cod liver oil.

## Regulation

Currently in Australia, fish oil ingredients derived from whole body and liver of fish are permitted for use in complementary and some OTC (listed) medicines. There is also a recognised component name, 'omega-3 marine triglycerides'. There are no quantity restrictions for any of the ingredients or the components in the ingredients, and the use of these substances does not attract any advisory statements for labelling purposes.

Information from adverse event reports with omega-3 fatty acids and fish oil in the TGA adverse drug reaction database showed that to February 2010, there had been a total of 92 reports, dating back to 1987, with 11 of these describing

bleeding. These products were the sole suspect medication in only three (3.2%) cases. This finding is consistent with reports in international databases.

Notwithstanding the limitations of spontaneous adverse event reporting, these data suggest that there are relatively few reported bleeding-related adverse events with fish oil preparations, and that only a small proportion may be solely attributed to these products.

Health Canada permits a number of health claims for fish oil including the maintenance of good health, cardioprotection, assistance in reduction of serum triglycerides, and promotion of healthy mood balance. A June 2009 fish oil monograph indicates that no statements are required in relation to cautions, warnings, contraindications, and known adverse reactions.[19]

In 2004, the US Food and Drug Administration endorsed a qualified health claim indicating that, 'Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease'. It states that, 'Dietary supplements should not recommend or suggest in their labelling a daily intake exceeding 2 grams of EPA and DHA'.[20]

Included in the Australian NHF 2008 review were recommendations for consumption of combined DHA and EPA through use of omega-3 fatty acids or fish oil, or fish intake. These were for:

- all adult Australians to lower their risk of CHD
- women who are planning pregnancy, pregnant or breastfeeding
- children
- adult Australians with documented CHD
- Australians with lipid abnormalities.[2]

The NHF review did not consider fish oils to have a significant effect on haemostasis and did not include a cautionary statement.[2]

Similar recommendations have been made by the American Heart Association. These are qualified with statements to indicate that patients taking high dose omega-3 fatty acids should be under the care of a physician, and that high intake could cause bleeding in some people.[21]

In its information sheet on fats and oils, the British Heart Foundation supports intake of omega-3 fatty acids for cardioprotection. This indicates that patients taking warfarin and fish oil supplements concomitantly should consult with their medical practitioner because of the possibility of bleeding risk.[22]

## Summary

- Current evidence and recommendations for usage support fish oil for cardioprotection in patients with or without diagnosed CHD, decreasing triglycerides, and in women who are planning pregnancy, pregnant or breastfeeding, and children.
- There are multiple proposed additional uses for fish oil.
- It is likely that the use of fish oil will significantly increase.
- Regulatory agencies consider that fish oil and omega-3 fatty acid containing products are safe with some requiring warnings about the theoretical possibility of bleeding events and drug interactions in their product information.
- Evidence in relation to the safety concern about possible bleeding indicates that the theoretical possibility of increased bleeding tendency is not reflected functionally in results of human studies.

## Conclusion

Healthcare practitioners should ensure they are aware of all medications – including prescription, over-the-counter and complementary products – being taken by their patients. Despite the lack of evidence of a systematic safety concern, it would appear reasonable to be mindful of the theoretical risk of bleeding with fish oil when monitoring patients treated with fish oils and anticoagulants.

Bays (2007), in an article entitled 'Safety considerations with omega-3 fatty acid therapy', suggests:

- discontinuing high-dose fish oil consumption or supplementation during an acute bleeding illness, such as during and immediately after a haemorrhagic stroke, or in patients with or at high risk for haemorrhagic stroke
- discontinuing fish oil therapy 4–7 days before elective procedures with a high risk for bleeding complications, as often occurs with aspirin, warfarin, and clopidogrel, even though infusion of fish oils after major abdominal surgery through parenteral nutrition does not appear to result in clinically significant bleeding and has been suggested to be safe with specific regard to coagulation and platelet function
- considering the potential antithrombotic and cardiovascular benefits of restarting fish oil therapies postoperatively, given that thrombotic and cardiovascular events may occur following major surgery.[3]

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**WHAT TO REPORT? (You do not need to be certain, just suspicious!)**

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. The TGA particularly requests reports of:

- ALL suspected reactions to **new medicines**
- ALL suspected medicines interactions
- Suspected reactions causing
  - death
  - admission to hospital or prolongation of hospitalisation
  - increased investigations or treatment
  - birth defects

**For blue cards**

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ('blue card') which is available from the website: www.tga.gov.au/adr/bluecard.pdf or from the Office of Medicines Safety Monitoring, phone 1800 044 114.

Reports can also be submitted:

online on the TGA website www.tga.gov.au click on 'Report a problem' on the left
by fax 02 6232 8392
by email ADR.Reports@tga.gov.au

**For further information** from the Office of Medicines Safety Monitoring:

Phone 1800 044 114 Fax 02 6232 8392 Email ADR.Reports@tga.gov.au