Public Assessment Report

Decentralised Procedure

Omega 3-acid-ethyl esters 1000 mg Capsules, Soft
(omega-3-acid ethyl esters 90)

Procedure No: UK/H/5143, 5303 and 5350/001/DC

UK Licence No: PL 40120/0001-0003

EPAX AS
LAY SUMMARY

Omega-3-acid ethyl esters 1000 mg Capsules, Soft
(Omega-3-acid ethyl esters 90, 1000 mg, soft capsule)

This is a summary of the Public Assessment Report (PAR) for Omega-3-acid ethyl esters 1000 mg Capsules, Soft (PL 40120/0001-0003; UK/H/5143, 5303 and 5350/001/DC). It explains how Omega-3-acid ethyl esters 1000 mg Capsules, Soft were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Omega-3-acid ethyl esters 1000 mg Capsules, Soft.

For practical information about using Omega-3-acid ethyl esters 1000 mg Capsules, Soft patients should read the package leaflet or contact their doctor or pharmacist.

Omega-3-acid ethyl esters 1000 mg Capsules, Soft may be referred to as Omega-3-acid ethyl esters 1000 mg Capsules in this report.

What are Omega-3-acid ethyl esters 1000 mg and what are they used for?
Omega-3-acid ethyl esters 1000 mg contain highly purified omega-3 polyunsaturated fatty acids. Omega-3-acid ethyl esters 1000 mg are used:
• together with other medicines for the treatment after a heart attack;
• to treat certain forms of increased triglycerides (fats) in the blood after changes to the diet have not worked.

Omega-3-acid ethyl esters 1000 mg Capsules are a ‘generic’ medicine. This means that Omega-3-acid ethyl esters 1000 mg Capsules are similar to a reference medicine already authorised in the European Union (EU) called Omacor 1000mg Capsules (Pronova BioPharma Norge AS, Norway).

How are Omega-3-acid ethyl esters 1000 mg Capsules used?
Omega-3-acid ethyl esters 1000 mg are taken by mouth; the capsules are swallowed with a drink of water. The recommended dose after a heart attack is one capsule a day. The recommended dose for high blood triglyceride is two capsules a day, as recommended by a doctor. If the medicine is not working well enough at this dose, the doctor may increase this to four capsules a day. For further information on how Omega-3-acid ethyl esters 1000 mg Capsules are used, please see the Summaries of Product Characteristics available on the MHRA website.

Omega-3-acid ethyl esters 1000 mg Capsules can be obtained without a prescription, available only from pharmacies under the supervision of a pharmacist.

How do Omega-3-acid ethyl esters 1000 mg Capsules work?
The active, omega-3-acid ethyl esters 90, consists principally of the omega-3 series polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid, which are essential fatty acids. Eicosapentaenoic acid and docosahexaenoic acid reduce the production of cholesterol and triglycerides in the body. Omega-3-acid ethyl esters 1000 mg Capsules belong to a group of so-called reducers of cholesterol and triglycerides.

How have Omega-3-acid ethyl esters 1000 mg Capsules been studied?
As Omega-3-acid ethyl esters 1000 mg Capsules are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Omacor 1000mg Capsules (Pronova BioPharma Norge AS, Norway). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
In addition, the company (EPAX AS) has provided data from the published literature on Omega-3-acid ethyl esters.

**What are the benefits and risks of Omega-3-acid ethyl esters 1000 mg Capsules?**
Because Omega-3-acid ethyl esters 1000 mg Capsules are generic medicines and are bioequivalent to the reference medicine, their benefits and risks are taken as being the same as those of the reference medicine.

**Why is Omega-3-acid ethyl esters 1000 mg Capsules approved?**
It was concluded that, in accordance with EU requirements, Omega-3-acid ethyl esters 1000 mg Capsules have been shown to have comparable quality and to be bioequivalent to Omacor 1000mg Capsules (Pronova BioPharma Norge AS, Norway). Therefore, the view was that, as for Omacor 1000mg Capsules (Pronova BioPharma Norge AS, Norway), the benefits of these capsules outweighs the identified risks.

**What measures are being taken to ensure the safe and effective use of Omega-3-acid ethyl esters 1000 mg Capsules?**
A Risk Management Plan has been developed to ensure that Omega-3-acid ethyl esters 1000 mg Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Omega-3-acid ethyl esters 1000 mg Capsules approved, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Omega-3-acid ethyl esters 1000 mg Capsules.**
Marketing Authorisations were granted in the UK on 27 November 2013.

The full PAR for Omega-3-acid ethyl esters 1000 mg Capsules follows this summary.

For more information about treatment with Omega-3-acid ethyl esters 1000 mg Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2014.
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Module 1
Information about the initial procedure

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<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
</tr>
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<td><strong>Active Substance</strong></td>
<td>Omega-3-acid ethyl esters 90</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Soft capsule</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>1000 mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>EPAX AS</td>
</tr>
<tr>
<td></td>
<td>Munkedamsveien 35</td>
</tr>
<tr>
<td></td>
<td>0250 Oslo</td>
</tr>
<tr>
<td></td>
<td>Norway</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>UK/H/5143/001/DC: Austria, Belgium, Germany, Greece, Spain, France and Ireland</td>
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<tr>
<td></td>
<td>UK/H/5303/001/DC: Germany, Spain and France</td>
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<tr>
<td></td>
<td>UK/H/5350/001/DC: Germany, Greece, Spain, France, Italy, Norway and Romania</td>
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<td><strong>Procedure Numbers</strong></td>
<td>UK/H/5143/001/DC</td>
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<td>UK/H/5350/001/DC</td>
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<td><strong>Timetable</strong></td>
<td>End of procedure (Day 210) – 04 November 2013</td>
</tr>
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Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

The Marketing Authorisation Holder has submitted the text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON/BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Omega-3-acid ethyl esters 1000 mg Capsules, soft
Omega-3-acid ethyl esters 90

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each soft capsule contains 1000 mg of omega-3-acid ethyl esters 90, comprising 840 mg eicosapentaenoic acid (EPA) ethyl ester (460 mg) and docosahexaenoic acid (DHA) ethyl ester (380 mg).

3. LIST OF EXCIPIENTS

Capsule core: alpha-tocopherol in sunflower oil
Capsule shell: gelatin, glycerol, purified water, medium-chain triglycerides, lecithin (soya)

4. PHARMACEUTICAL FORM AND CONTENTS

Soft Capsules

1 x 28 capsules
1 x 100 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
9. SPECIAL STORAGE CONDITIONS

This product should be used within 100 days of opening the bottle.
Store below 25°C. Do not freeze.
Keep the bottle in the outer carton in order to protect from the light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Epax AS
Munkedamveien 35
0250, Oslo
Norway

12. MARKETING AUTHORISATION NUMBER(S)

PL 40120/0001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Omega-3-acid ethyl esters 1000 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON/BOTTLE

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Omega-3-acid ethyl esters 1000 mg Capsules, soft
Omega-3-acid ethyl esters 90

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EXP

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11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Epax AS
Munkedalaveien 35, 0250, Oslo
Norway

12. MARKETING AUTHORISATION NUMBER(S)

PL 40120/0002

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Omega-3-acid ethyl esters 1000 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON/BOTTLE

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Omega-3-acid ethyl esters 1000 mg Capsules, soft

Omega-3-acid ethyl esters 90

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7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP

9. SPECIAL STORAGE CONDITIONS

This product should be used within 100 days of opening the bottle. Store below 25°C. Do not freeze. Keep the bottle in the outer carton in order to protect from the light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATIONS HOLDER

Epax AS
Munkedamveien 35, 0250, Oslo
Norway

12. MARKETING AUTHORIZATION NUMBER(S)

PL 40120/0003

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Omega-3-acid ethyl esters 1000 mg
Module 5
Scientific discussion during the initial procedure

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Omega 3-acid-ethyl esters 1000 mg Capsules, Soft (PL 40120/0001-0003; UK/H/5143, 5303 and 5350/001/DC) could be approved.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Belgium, Germany, Greece, Spain, France and Ireland (with UK/H/5143/01/DC), Germany, Spain and France (with UK/H/5303/01/DC) and Germany, Greece, Spain, France, Italy, Norway and Romania (with UK/H/5350/01/DC) as Concerned Member States (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Omacor 1000 mg Capsules (PL 15905/0001), which was authorised in the UK to Pronova BioPharma Norge AS, Norway on 15 July 1999, through a Change of Ownership procedure from Pharmacia Laboratories Limited (PL 00022/0178). The initial UK licence, PL 00022/0178, was authorised to Pharmacia Laboratories Limited on 23 July 1996 through an ongoing Mutual Recognition Procedure. The reference product has been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

The product is a pharmacy (P) medicine indicated for:

- **Post-myocardial infarction**
  Adjuvant treatment after secondary prevention after myocardial infarction, in addition to other standard therapy (e.g. statins, anti-platelet medicinal products, beta-blockers, ACE inhibitors).

- **Hypertriglyceridaemia**
  Endogenous hypertriglyceridaemia as a supplement to diet when dietary measures alone are insufficient to produce an adequate response:
  - type IV in monotherapy,
  - type IIb/III in combination with statins, when control of triglycerides is insufficient.

The active, omega-3-acid ethyl esters 90, consists principally of the ethyl esters of the omega-3 series polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid, which are essential fatty acids that lower blood triglyceride concentration by inhibiting esterification of other fatty acids and by promoting an increase in β-oxidation of fatty acids in the liver. There may be an associated increase in blood low density lipoprotein (LDL)-cholesterol in some patients with hypertriglyceridaemia. The long-term lipid-lowering effect (after more than one year of exposure) is not known. Eicosapentaenoic acid and docosahexaenoic acid also affect haemostasis: there is a fall in thromboxane A2 production and a slight increase in bleeding time: there are no known significant effects on other coagulation factors. Benefit has been described in subjects who have recently sustained a myocardial infarction.

One single-dose, bioequivalence study was submitted to support these applications, comparing the applicant’s test product Omega-3-acid ethyl esters 1000 mg Capsules, Soft and the reference product Omacor 1000 mg Capsules, Soft (Pronova BioPharma Norge AS, Norway). The Applicant states that the study was conducted in accordance with Good Clinical Practice, as established by the International Conference on Harmonization (ICH), the basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 312), and the principles enunciated in the World Medical Association Declaration of Helsinki (Seoul, October 2008).

The Applicant received ethical approval from the Ethics Review Board of Optimum Clinical Research Inc., Canada on 2nd May 2012.
With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 04 November 2013. After a subsequent national phase, licences were granted in the UK on 27 November 2013.

II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Omega-3-acid ethyl esters 1000 mg Capsules, Soft |
| Name(s) of the active substance (INN) | Omega-3-acid ethyl esters 90 |
| Pharmacotherapeutic classification (ATC code) | Other cholesterol and triglycerides reducers (ATC code: C10AX06) |
| Pharmaceutical form and strength | Soft capsule; 1000 mg |
| Reference number(s) for the Decentralised Procedure | UK/H/5143/001/DC  
UK/H/5303/001/DC  
UK/H/5350/001/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | UK/H/5143/001/DC: Austria, Belgium, Germany, Greece, Spain, France and Ireland  
UK/H/5303/001/DC: Germany, Spain and France  
UK/H/5350/001/DC: Germany, Greece, Spain, France, Italy, Norway and Romania |
| Marketing Authorisation Numbers | PL 40120/0001-0003 |
| Name and address of the authorisation holder | EPAX AS  
Munkedamsveien 35  
0250 Oslo  
Norway |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Compendial Name: Omega-3 acid ethyl esters 90 (Ph. Eur.)
Chemical name: Omega-3 Acid Ethyl Esters 90 compromises of ethyl esters of alpha-linolenic acid (C18:3 n-3), moroctic acid (C18:4 n-3), eicosatetraenoic acid (C20:4 n-3), timnodonic (eicosapentaenoic) acid (C20:5 n-3 EPA), heneicosapentaenoic acid (C21:5 n-3), clupanodonic acid (C22:5, n-3) and cervonic (docosahexaenoic) acid (C22:6 n-3, DHA). The main components are eicosapentaenoic acid ethyl ester (EPA-EE) and docosahexaenoic acid ethyl ester (DHA-EE).

Appearance: A visually clear, colourless to yellow, free flowing liquid at ambient temperature with no rancid odour.

Solubility (EPA-EE and DHA-EE) - Very soluble in organic solvents, practically insoluble in water (pH 3 to 7).

EPA
Chemical name: Ethyl(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenoate
Non-proprietary names: Eicosapentaenoic acid ethyl ester, Timnodonic acid ethyl ester
INN: Ethyl-eicosapent
Molecular formula: C22H34O2
Molecular Mass: 330.51

DHA-EE
Chemical name: Ethyl(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoate
Non-proprietary names: Docosahexaenoic acid ethyl ester, cervonic acid ethyl ester
INN: Doconexent ethyl
Molecular formula: C24H36O2
Molecular Mass: 356.55

The active substance, omega-3-acid ethyl esters 90, is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. The substance is derived from an animal source and an appropriate declaration is provided confirming that the fish oil is from non-Transmissible Spongiform Encephalopathy (TSE) relevant animal species. Confirmation has been provided that the raw materials, intermediates and auxillary agents used in synthesis of the active are not of genetically modified origin. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

### MEDICINAL PRODUCT

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients in the capsule core and shell, namely alpha-tocopherol in sunflower oil, gelatin, glycerol, purified water, medium-chain triglycerides and lecithin (soya). Appropriate justification for the inclusion of each excipient has been provided.

Purified water, gelatin and glycerol comply with their respective European Pharmacopoeia monographs. Alpha-tocopherol in sunflower oil is controlled to a suitable in-house specification. Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specification.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that it is manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to produce a safe, stable, immediate-release capsule formulation bioequivalent to, and containing qualitatively and quantitatively the same active substance, as the reference product, Omacor 1000 mg, Capsule Soft (Pronova BioPharma Norge AS). Suitable pharmaceutical development data have been provided for these applications.

Comparative in-vitro disintegration and impurity profiles have been provided for this product and the reference product. The in-vitro disintegration and impurity profiles were satisfactory.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full-scale production-scale batches and has shown satisfactory results.

**Control of Finished Product**

The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**

The finished product is packaged in high-density polyethylene (HDPE) containers with snap-on caps and integrated seals both made from polyethylene (PE). The bottles are supplied with the Patient Information Leaflet in cartons, in pack sizes of 28 and 100 capsules.
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Regulation (EU) No. 10/2011) concerning materials in contact with foodstuff.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months for the unopened product, and 100 days for the opened product has been set, with the storage conditions ‘Store below 25°C. Do not freeze.’

**Bioequivalence/Bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section III.3, Clinical Aspects.

**Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labelling text are satisfactory from a pharmaceutical perspective. The Marketing Authorisation Holder (MAH) has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

**Marketing Authorisation Application (MAA) Forms**
The MAA forms are satisfactory from a pharmaceutical perspective.

**Expert Report (Quality Overall Summary)**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of Marketing Authorisations is recommended.

**III.2 NON-CLINICAL ASPECTS**
The pharmacodynamic, pharmacokinetic and toxicological properties of omega-3-acid ethyl esters 90 (mainly eicosapentaenoic and docosahexaenoic acid ethyl esters) are well-known. As omega-3-acid ethyl esters are widely used, well-known active substances, the applicant has submitted no new non-clinical data and none are required. Overview based on literature review is, thus appropriate.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed product.
The grant of Marketing Authorisations is recommended.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
The clinical pharmacology of omega-3-acid ethyl esters 90 (mainly eicosapentaenoic and docosahexaenoic acid ethyl esters) is well-known. No new pharmacodynamic or pharmacokinetic data was required for these applications.

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study.

An open-label, single-dose, randomized, four-period, two-sequence, two-treatment, replicate, crossover study comparing the applicant’s test product Omega-3-acid ethyl esters 1000 mg Capsules, Soft and the reference product Omacor 1000 mg soft capsules (Pronova BioPharma Norge AS, Norway) in healthy adult male and female subjects under fed conditions.

Subjects were fasted overnight for at least 10 hours prior to the scheduled time for breakfast. The subjects were administered 4 x 1000 mg (4 g) of either the test (Treatment A) or the reference (Treatment B) product with 240 mL of water, 30 minutes after the start of a high fat, high calorie breakfast limited in eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA).

Consumption of foods high in omega-3 was restricted from two days prior to Period 1 check-in until the completion of the entire study. Subjects were randomly assigned to one of the two dosing sequences: ABAB or BABA. A 4g dosage was used to ensure that analytes would be present at blood concentrations that were significantly different from background concentration.

Blood sampling was performed pre-dose and up to 72 hours post dose in each treatment period. Blood sampling was performed at specific time-points pre-dose to establish a baseline for blood concentrations of the two analytes EPA and DHA. The washout period between the treatment arms was 14 days. Pharmacokinetic parameters were measured for EPA and DHA from plasma and statistically analysed.

Summary of the pharmacokinetic results of the bioequivalence study are presented below:
**Summary pharmacokinetic parameters (means, ratios and confidence intervals [CI]) for EPA**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TRT</th>
<th>Arithmetic</th>
<th>(CV%)</th>
<th>Geometric</th>
<th>Contrast</th>
<th>Ratio (90% CI)</th>
<th>Intra-Sub CV(%)</th>
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<tbody>
<tr>
<td>AUC&lt;sub&gt;0-72&lt;/sub&gt;</td>
<td>A&lt;sub&gt;1&lt;/sub&gt;</td>
<td>1305.75</td>
<td>(33)</td>
<td>1164.74</td>
<td>A vs. B</td>
<td>94.66</td>
<td>89.15 - 100.51</td>
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<td></td>
<td>A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1197.67</td>
<td>(35)</td>
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<td>B&lt;sub&gt;1&lt;/sub&gt;</td>
<td>1309.41</td>
<td>(35)</td>
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<td></td>
<td>B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1284.33</td>
<td>(28)</td>
<td></td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>A&lt;sub&gt;1&lt;/sub&gt;</td>
<td>45.07</td>
<td>(34)</td>
<td>40.91</td>
<td>A vs. B</td>
<td>100.20</td>
<td>94.32 - 106.44</td>
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<td></td>
<td>A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>42.87</td>
<td>(42)</td>
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<td></td>
<td>B&lt;sub&gt;1&lt;/sub&gt;</td>
<td>43.50</td>
<td>(35)</td>
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<td>B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>42.86</td>
<td>(31)</td>
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</tbody>
</table>

- C<sub>max</sub> maximum analyte concentration over the sampling period
- AUC<sub>0-72</sub> area under the analyte concentration versus time curve from time zero to 72 hours, as calculated by the linear trapezoidal method
- CV coefficient of variation
- Ratios and 90% CI calculated from ln-transformed data

**Summary pharmacokinetic parameters (means, ratios and confidence intervals [CI]) for DHA**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TRT</th>
<th>Arithmetic</th>
<th>(CV%)</th>
<th>Geometric</th>
<th>Contrast</th>
<th>Ratio (90% CI)</th>
<th>Intra-Sub CV(%)</th>
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<tbody>
<tr>
<td>AUC&lt;sub&gt;0-72&lt;/sub&gt;</td>
<td>A&lt;sub&gt;1&lt;/sub&gt;</td>
<td>678.39</td>
<td>(47)</td>
<td>624.35</td>
<td>A vs. B</td>
<td>91.18</td>
<td>85.18 - 97.61</td>
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<td></td>
<td>A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>703.51</td>
<td>(40)</td>
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<tr>
<td></td>
<td>B&lt;sub&gt;1&lt;/sub&gt;</td>
<td>726.66</td>
<td>(35)</td>
<td>684.73</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>743.73</td>
<td>(40)</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>A&lt;sub&gt;1&lt;/sub&gt;</td>
<td>28.86</td>
<td>(54)</td>
<td>24.84</td>
<td>A vs. B</td>
<td>103.89</td>
<td>96.90 - 111.38</td>
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<tr>
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<td>A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>27.78</td>
<td>(59)</td>
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<tr>
<td></td>
<td>B&lt;sub&gt;1&lt;/sub&gt;</td>
<td>26.49</td>
<td>(53)</td>
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</tr>
<tr>
<td></td>
<td>B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>25.50</td>
<td>(37)</td>
<td></td>
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</tr>
</tbody>
</table>

- C<sub>max</sub> maximum analyte concentration over the sampling period
- AUC<sub>0-72</sub> area under the analyte concentration versus time curve from time zero to 72 hours, as calculated by the linear trapezoidal method
- CV coefficient of variation
- Ratios and 90% CI calculated from ln-transformed data

**Conclusion**
The data support the claim that the applicant’s test product Omega-3-acid ethyl esters 1000 mg Capsules, Soft is bioequivalent to the reference product Omacor 1000 mg soft capsules (Pronova BioPharma Norge AS, Norway) under fed conditions, as the 90% confidence interval for C<sub>max</sub> and AUC<sub>0-72</sub> for EPA and DHA lie within the acceptance criteria limits of 80.00 % to 125.00%, in line with current guidelines (CPMP/EWP/QWP/1401/98 Rev 1/Corr The Note for Guidance on the Investigation of Bioequivalence).

**Efficacy**
The efficacy of omega-3-acid ethyl esters 90 is well-established from its extensive use in clinical practice. No new efficacy data have been submitted and none are required for applications of this type. The reference product is established and the applications are supported by the demonstration of bioequivalence with the reference product. Efficacy is reviewed in the clinical overview.

**Safety**
No new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence study. Safety is reviewed in the clinical overview. The safety profile of omega-3-acid ethyl esters 90 is well-known.
Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable from a clinical perspective. The SmPCs are consistent with that for the innovator product. The PIL is consistent with the details in the SmPCs and in line with current guidance. The labelling is in line with current guidance.

Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Applicant provided a Pharmacovigilance System Master File Summary (version 1.0, September 2012) stating that they have at their service a Qualified Person for Pharmacovigilance (QPPV) responsible for Pharmacovigilance who is suitably trained and aware of the responsibilities outlined in the current applicable European Union (EU) legislation. The QPPV has the necessary means for collection and notification of any adverse drug reaction occurring either in the Community or in a third country, and the means to fulfil all other requirements of current European Pharmacovigilance legislation.

An acceptable Risk Management Plan has been provided.

Conclusion
The grant of Marketing Authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The important quality characteristics of Omega 3-acid-ethyl esters 1000 mg Capsules, Soft are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of omega-3-acid ethyl esters 90 are well-known, no additional data were required.

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
No new data were submitted and none are required for these applications.

Bioequivalence has been demonstrated between the applicant’s product and the reference product Omacor 1000 mg Soft Capsules (Pronova BioPharma Norge AS, Norway).

SAFETY
No new data were submitted and none are required for applications of this type. As the safety profile of omega-3-acid ethyl esters 90 is well known, no additional safety data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.
BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with omega-3-acid ethyl esters 90 is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be positive.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
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