Public Assessment Report

Decentralised Procedure

Omega 3-acid-ethyl esters 1000mg Soft Capsules

Omega-3-acid ethyl esters 90

Procedure No: UK/H/5252 and 5266-8/001/DC

UK Licence No: PL 00289/1756 and PL 00289/1778-80

Teva UK Limited
LAY SUMMARY

On 10 July 2013, the Medicines and Healthcare Products Regulatory Agency (MHRA) granted Marketing Authorisations to Teva UK Limited for the medicinal product Omega 3-acid-ethyl esters 1000mg Soft Capsules (PL 00289/1756 and 1778-80; UK/H/5252 and 5266-8/001/DC). This is a prescription-only medicine (POM).

Omega-3-acid ethyl esters 1000mg Soft Capsules contain highly purified omega-3 polyunsaturated fatty acids. Omega-3-acid ethyl esters 1000mg Soft Capsules belong to a group of so-called reducers of cholesterol and triglycerides.

Omega-3-acid ethyl esters 1000mg Soft Capsules 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.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Omega 3-acid-ethyl esters 1000mg Soft Capsules outweigh the risks and Marketing Authorisations were granted.
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</table>
Module 1
Information about the initial procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Omega-3-acid ethyl esters 1000mg Soft Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Omega-3-acid ethyl esters 90</td>
</tr>
<tr>
<td>Form</td>
<td>Soft capsule</td>
</tr>
<tr>
<td>Strength</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>
| MA Holder             | Teva UK Limited
|                       | Brampton Road, Hampden Park, Eastbourne, East Sussex BN22 9AG United Kingdom |
| Reference Member State (RMS) | UK                      |
| Concerned Member States (CMS) | UK/H/5252/001/DC: Italy |
|                       | UK/H/5266/001/DC: Italy                       |
|                       | UK/H/5267/001/DC: France and Italy            |
|                       | UK/H/5268/001/DC: France, Germany and Italy   |
| Procedure Number      | UK/H/5252/001/DC
|                       | UK/H/5266-8/001/DC                            |
| Timetable             | End of procedure (Day 180) – 28 June 2013     |
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 following text is the approved label text for Omega 3-acid-ethyl esters 1000mg Soft Capsules (PL 00289/1756; UK/H/5252/001/DC). The labelling text details for Omega 3-acid-ethyl esters 1000mg Soft Capsules (PL 00289/1778-80; UK/H/5266-8/001/DC) are consistent with this text, with the exception of the Marketing Authorisation number. No label mock-ups have been submitted for these Marketing Authorisations. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-up has been obtained.

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

1. **NAME OF THE MEDICINAL PRODUCT**

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

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   Teva UK Ltd

3. **EXPIRY DATE**

   EXP:

4. **BATCH NUMBER**

   Batch:

5. **OTHER**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER PACK CARTON

1. NAME OF THE MEDICINAL PRODUCT

Omega 3-acid-ethyl esters 1000mg Soft Capsules
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 principally 840 mg eicosapentaenoic acid (EPA) ethyl ester (460 mg) and docosahexaenoic acid (DHA) ethyl ester (380 mg).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, soft

20 capsules, soft
28 capsules, soft
30 capsules, soft
(3x10) capsules, soft
60 capsules, soft
90 capsules, soft
(9x10) capsules, soft
100 capsules, soft
120 capsules, soft

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Please read the package leaflet before use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Do not freeze. Store in the original container in order to protect from moisture.

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

Teva UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1756

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

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

IMMEDIATE PACKAGING / HDPE bottle

1. NAME OF THE MEDICINAL PRODUCT

Omega 3-acid-ethyl esters 1000mg Soft Capsules
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 principally 840 mg eicosapentanoic acid (EPA) ethyl ester (460 mg) and docosahexanoic acid (DHA) ethyl ester (380 mg).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, soft

Bottles:
- 20 capsules, soft
- 28 capsules, soft
- 30 capsules, soft
- 90 capsules, soft
- 98 capsules, soft
- 100 capsules, soft
Hospital pack: 280 (10x28) capsules, soft

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Please read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Store below 30°C. Do not freeze.
Store in the original container in order to protect from moisture.

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**

Teva UK Limited, Eastbourne, BN22 9AG

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 00289/1756

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Use as directed by the doctor

16. **INFORMATION IN BRAILLE**

Omega 3-acid-ethyl esters 1000mg Soft Capsules
1. **NAME OF THE MEDICINAL PRODUCT**

Omega 3-acid-ethyl esters 1000mg Soft Capsules
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 principally 840 mg eicosapentanoic acid (EPA) ethyl ester (460 mg) and docosahexaenoic acid (DHA) ethyl ester (380 mg).

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

Capsule, soft

Bottles:
- 20 capsules, soft
- 28 capsules, soft
- 30 capsules, soft
- 90 capsules, soft
- 98 capsules, soft
- 100 capsules, soft

Hospital pack: 280 (10x28) capsules, soft

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use
Please read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**
8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Do not freeze.
Store in the original container in order to protect from moisture.

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

Teva UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1756

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

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

1  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 1000mg Soft Capsules (PL 00289/1756 and 1778-80; UK/H/5252 and 5266-8/001/DC) could be approved.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Italy, France and Germany as Concerned Member States (CMS). These applications are duplicates of the Decentralised Procedure UK/H/2056/01/DC (CMS: Austria, Germany, Spain, France, Ireland, Italy, the Netherlands and Romania) which was approved in March 2012. The clinical dossier is identical to the one previously assessed and approved.

The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Omacor 1000mg, Weichkapsel (capsule, soft) authorised in Germany to Pronova BioPharma Norge AS, Norway on 11 September 1996. The corresponding reference product in the UK is Omacor 1000mg Capsules (PL 15905/0001), which was authorised 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 incoming 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 prescription-only medicine (POM) indicated for:
- Post-myocardial infarction
  Adjuvant treatment in 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 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 \( \beta \)-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 A\(_2\) production and a slight increase in bleeding time; there are not any 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 this application, comparing the applicant’s test product Omega-3-acid ethyl esters 1000mg Soft Gelatine Capsules and the reference product Omacor 1000 mg Capsule, Soft (Pronova Biocare AS, Norway). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
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 considers that the Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

The Marketing Authorisation Holder (MAH) has provided adequate justification for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 180) on 28 June 2013. After a subsequent national phase, licences were granted in the UK on 10 July 2013.

### II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Omega-3-acid ethyl esters 1000 mg Soft Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance (INN)</td>
<td>Omega-3-acid ethyl esters 90</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Other lipid-modifying agents, omega-3 triglycerides incl. other esters and acids (ATC code: C10AX06)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength</td>
<td>Soft capsule; 1000mg</td>
</tr>
<tr>
<td>Reference number for the Decentralised Procedure</td>
<td>UK/H/5252/001/DC  UK/H/5266-8/001/DC</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>UK/H/5252/001/DC: Italy</td>
</tr>
<tr>
<td></td>
<td>UK/H/5266/001/DC: Italy</td>
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<tr>
<td></td>
<td>UK/H/5267/001/DC: France and Italy</td>
</tr>
<tr>
<td></td>
<td>UK/H/5268/001/DC: France, Germany and Italy</td>
</tr>
<tr>
<td>Marketing Authorisation Numbers</td>
<td>PL 00289/1756</td>
</tr>
<tr>
<td></td>
<td>PL 00289/1778-80</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Teva UK Limited</td>
</tr>
<tr>
<td></td>
<td>Brampton Road, Hampden Park, Eastbourne, East Sussex BN22 9AG United Kingdom</td>
</tr>
</tbody>
</table>
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 is a combination of seven individual omega-3 acid ethyl esters, containing principally Eicosapentaenoic Acid Ethyl Ester (EPA-EE) at nominally 46% and Docosahexaenoic Acid Ethyl Ester (DHA-EE) at nominally 38%, the remaining 6% comprising the five ethyl esters of the following fatty acids: alpha-linolenic acid, moroctic acid, Eicosatetraenoic acid, Heneicosapentaenoic acid and Docosapentaeonoic acid.

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: (5Z,8Z,11Z,14Z,17Z)-Eicosa-5,8,11,14,17-pentaenoic acid ethyl ester
Non-proprietary names: Eicosapentaenoic acid ethyl ester, Timnodonic acid ethyl ester, ethyl-EPA
INN: Ethyl-eicosapent
Molecular formula: C_{22}H_{34}O_{2}
Molecular Mass: 330.55
Structure:

DHA-EE

Chemical Name: (4Z,7Z,10Z,13Z,16Z,19Z)-Docosa-4,7,10,13,16,19-hexaenoic acid ethyl ester
Non-proprietary names: Docosahexaenoic acid ethyl ester, cervonic acid ethyl ester, ethyl-DHA
INN: Doconexent ethyl
Molecular formula: C_{24}H_{36}O_{2}
Molecular Mass: 356.55
Structure:

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 Ingredient**

Other ingredients consist of the pharmaceutical excipients in the capsule core and shell, namely alpha-tocopherol, gelatin, glycerol, medium-chain triglycerides and liquid paraffin. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. 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, Omacer 1000mg, Capsule Soft (Pronova BioPharma Norge AS). Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro dissolution and impurity profiles have been provided for this product and the reference product. The in-vitro dissolution 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 either:

1. transparent polyvinylchloride/Aclar-aluminium blisters packed with the Patient Information Leaflet in cartons, in pack sizes of 20, 28, 30, 3x10, 60, 90, 9x10, 100 and 120 soft capsules.
2. high-density polyethylene (HDPE) containers with tamper evident HPDE screw caps packed with the Patient Information Leaflet in cartons, in pack sizes of 20, 28, 30, 90, 98 and 100 soft capsules and hospital packs of 280 (10x28) soft 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 (Directive 2002/72/EC, as amended) 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 2 years has been set, with the storage conditions “Store below 30°C. Do not freeze. Keep in the original package in order to protect from moisture”.

**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), Product 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. Data from the bioequivalence study detailed below was previously submitted in support of the application for Omega-3-acid ethyl esters 1000mg Soft Capsules (PL 00289/1415; UK/H/2056/01/DC).

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

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

Blood sampling was performed at specific time-points pre-dose to establish a baseline for blood concentrations of the two analytes eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA).

Subjects were fasted overnight for at least 10 hours prior to the scheduled time for breakfast. The subjects were administered 4 x 1000mg (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 EPA and DHA. A 4g dosage was used to ensure that analytes would be present at blood concentrations that were significantly different from background concentration. Subjects were randomly assigned to one of the three dosing sequences: ABB, BBA or BAB. Blood sampling was performed pre-dose and up to 72 hours post dose in each treatment period. 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>Analyte: Eicosapentaenoic Acid (EPA)</th>
<th>Mean (ng/mL)</th>
<th>Contrast Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arithmetic</td>
<td>Geometric</td>
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</tr>
<tr>
<td>Based on Baseline-adjusted Data</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AUC0-72 (µg·h/mL)</td>
<td>A 1461.47</td>
<td>39 1260.63</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B1 1547.06</td>
<td>36 1326.72</td>
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<tr>
<td></td>
<td>B2 1501.23</td>
<td>37 1326.72</td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>A 51.47</td>
<td>42 44.72</td>
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</tr>
<tr>
<td></td>
<td>B1 55.39</td>
<td>37 47.96</td>
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</tr>
<tr>
<td></td>
<td>B2 52.02</td>
<td>36 47.96</td>
<td></td>
</tr>
</tbody>
</table>

Cmax maximum plasma concentration
AUC0-72 area under the plasma concentration-time curve from time zero to 72 hours
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>Analyte: Docosahexaenoic Acid (DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
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<td>Based on Baseline-adjusted Data</td>
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<tr>
<td>AUC_{0-72} (μg·h/mL)</td>
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<tr>
<td>C_{max} (μg/mL)</td>
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- \(C_{max}\): maximum plasma concentration
- \(AUC_{0-72}\): area under the plasma concentration-time curve from time zero to 72 hours
- \(CV\): 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 Soft Gelatine Capsules is bioequivalent to the reference product Omacor 1000 mg soft capsules (Pronova Biocare AS, Norway) under fed conditions, as the 90% confidence interval for \(C_{max}\) and \(AUC_{0-72}\) 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).

An in-house study was conducted to compare the bioavailability of omega-3 fatty acids under fasted and fed states. The study demonstrated that (i) the fasted state is associated with a flat absorption curve for eicosapentaenoic acid and docosahexaenoic acid and that (ii) the bioavailability of eicosapentaenoic acid and docosahexaenoic acid are many-fold higher in the fed than fasted state. It is, therefore, considered that a bioequivalent study in the fed state is the more sensitive and thus more appropriate than a study performed in the fasted state.

**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.

**Summary of Product Characteristics (SmPC), 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 SmPC and in line with the current guidance. The labelling is in line with the 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.
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 1000mg Soft Capsules 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 Biocare 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

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