Public Assessment Report

Decentralised Procedure

Omega-3-acid ethyl esters 1000mg Soft Capsules

(Eicosapentaenoic Acid Ethyl Ester, Docosahexaenoic Acid Ethyl Ester)

UK/H/2056/001/DC

UK licence no: PL 00289/1415

Teva UK Limited
LAY SUMMARY

On 7th March 2012, the Reference Member State (RMS) and the Concerned Member States (CMSs) agreed to grant Marketing Authorisation to TEVA UK Limited for the medicinal product Omega 3-acid-ethyl esters 1000mg Soft Capsules. The marketing authorisation was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 3rd April 2012. This medicine is only available on prescription from your doctor.

Omega 3-acid-ethyl esters 1000mg Soft Capsules contains 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 treatment after a heart attack

• to treat certain forms of increased triglycerides (fats) in the blood after changes to the diet have not worked.

Based on the data submitted by Teva UK Limited, Omega 3-acid-ethyl esters 1000mg Soft Capsules were considered to be a generic version of the UK reference product, Omacor 1000mg, Capsule, Soft (PL 15905/0001, Pronova BioPharma Norge AS, Norway).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Omega 3-acid-ethyl esters 1000mg Soft Capsules outweigh the risks, hence Marketing Authorisation has been granted.
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## Module 1

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<th>Omega 3-acid-ethyl esters 1000mg Soft Capsules</th>
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Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each soft capsule contains 1,000mg 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).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, soft.
Oblong, transparent, elastic soft gelatin capsule containing clear, light-yellow oil.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
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.

4.2 Posology and method of administration
Post-myocardial infarction
One capsule daily.

Hypertriglyceridaemia
Initial treatment two capsules daily. If adequate response is not obtained, the dose may be increased to four capsules daily.

The capsules may be taken with food to avoid gastrointestinal disturbances.

There is no information regarding the use of omega-3-acid ethyl esters 90 in children and adolescents, in elderly patients over 70 years of age, or in patients with hepatic impairment (see section 4.4), and only limited information regarding the use in patients with renal impairment.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
Warnings
Because of the moderate increase in bleeding time (with the high dosage, i.e. 4 capsules), patients receiving anticoagulant therapy must be monitored and the dosage of anticoagulant adjusted if necessary (see section 4.5). Use of this medicinal product does not eliminate the need for the surveillance usually required for patients of this type.

Make allowance for the increased bleeding time in patients at high risk of haemorrhage (because of severe trauma, surgery, etc.).

In the absence of efficacy and safety data, use of this medication in children and adolescents is not recommended.
Omega-3-acid ethyl esters is not indicated in exogenous hypertriglyceridaemia (type 1 hyperchylomicronaemia). There is only limited experience in secondary endogenous hypertriglyceridaemia (especially uncontrolled diabetes).

There is no experience regarding hypertriglyceridaemia in combination with fibrates.

Special precaution
Regular monitoring of hepatic function (ASAT and ALAT) is required in patients with hepatic impairment (in particular with the high dosage, i.e. 4 capsules).

4.5 Interaction with other medicinal products and other forms of interaction
Oral anticoagulants: see section 4.4.

Omega-3-acid ethyl esters 90 have been given in conjunction with warfarin without haemorrhagic complications. However, the prothrombin time must be checked when omega-3-acid ethyl esters 90 are combined with warfarin or when treatment with omega-3-acid ethyl esters 90 is stopped.

4.6 Pregnancy and lactation
Pregnancy
There are no adequate data from the use of omega-3-acid ethyl esters 90 in pregnant women.

Studies in animals have not shown reproductive toxicity. The potential risk for humans is unknown and therefore Omega 3-acid-ethyl esters should not be used during pregnancy unless clearly necessary.

Lactation
There are no data on the excretion of omega-3-acid ethyl esters 90 in animal and human milk. Omega 3-acid-ethyl esters should not be used during lactation.

4.7 Effects on ability to drive and use machines
Not relevant.

4.8 Undesirable effects
The frequencies of adverse reactions are ranked according to the following: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (≥1/10,000), not known (cannot be estimated from the available data).

Infection and infestations
Uncommon: gastroenteritis

Immune system disorders
Uncommon: hypersensitivity

Metabolism and nutrition disorders
Rare: hyperglycaemia

Nervous system disorders
Uncommon: dizziness, dysgeusia
Rare: headache

Vascular disorders
Very rare: hypotension

Respiratory thoracic and mediastinal disorders
Very rare: nasal dryness

Gastrointestinal disorders
Common: dyspepsia, nausea
Uncommon: abdominal pain, gastrointestinal disorders, gastritis, abdominal pain upper
Rare: gastrointestinal pain
Very rare: lower gastrointestinal haemorrhage

Hepatobiliary disorders
Rare: hepatic disorders

Skin and subcutaneous tissue disorders
Rare: acne, rash pruritic
Very rare: urticaria

General disorders and administration site conditions
Rare: ill-defined disorders

Investigations
Very rare: white blood count increased, blood lactate dehydrogenase increased
Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

4.9 Overdose
There are no special recommendations. Administer symptomatic treatment.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Other lipid-modifying agents, omega-3 triglycerides incl. other esters and acids, ATC code: C10AX06.

The omega-3 series polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential fatty acids.

Omega-3-acid ethyl esters 90 is active on the plasma lipids by lowering triglyceride levels as a result of a fall in VLDL (very low density lipoprotein), and the substance is also active on haemostasis and blood pressure.

Omega-3-acid ethyl esters 90 reduce the synthesis of triglycerides in the liver because EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis and they inhibit esterification of other fatty acids.

The increase in peroxisomes of β-oxidation of fatty acids in the liver also contributes to the fall in triglycerides, by reducing the quantity of free fatty acids available for their synthesis. The inhibition of this synthesis lowers VLDL.

Omega-3-acid ethyl esters 90 increase LDL-cholesterol in some patients with hypertriglyceridaemia. A rise in HDL-cholesterol is only small, significantly smaller than seen after administration of fibrates, and not consistent.

The long-term lipid-lowering effect (after more than one year) is not known. Otherwise there is no strong evidence that lowering triglycerides reduces the risk of ischaemic heart disease.

During treatment with omega-3-acid ethyl esters 90, there is a fall in thromboxane A2 production and a slight increase in bleeding time. No significant effect has been observed on the other coagulation factors.

11324 patients, with recent MI (<3 months) and receiving a recommended preventative treatment associated with a Mediterranean diet, were randomised in the GISSI-Prevenzione study in order to receive omega-3-acid ethyl esters 90 (n=2836), vitamin E (n=2830), omega-3-acid ethyl esters 90 + vitamin E (n=2830) or no treatment (n=2828). GISSI-P was a multicentre, randomised, open-label study performed in Italy.

The results observed over 3.5 years, with omega-3-acid ethyl esters 90 1g/day, have shown a significant reduction of a combined endpoint including all-cause death, non-fatal MI and non-fatal stroke (decrease in relative risk of 15% [2-26] p=0.0226 in patients taking omega-3-acid ethyl esters 90 alone compared to control, and of 10% [1-18] p=0.0482 in patients taking omega-3-acid ethyl esters 90 with or without vitamin E). A reduction of the second pre-specified endpoint criteria including cardiovascular deaths, non-fatal MI and non-fatal stroke has been shown (decrease in relative risk of 20% [5-32] p=0.0082 in patients taking omega-3-acid ethyl esters 90 alone compared to control, decrease in relative risk of 11% [1-20] p= 0.0526 in patients taking omega-3-acid ethyl esters 90 with or without vitamin E). The secondary analysis for each component of the primary endpoints has shown
a significant reduction of all-cause deaths and cardiovascular deaths, but no reduction of non-fatal cardiovascular events or fatal and non-fatal strokes.

5.2 Pharmacokinetic properties
During and after absorption, there are three main pathways for the metabolism of the omega-3 fatty acids:
- the fatty acids are first transported to the liver where they are incorporated into various categories of lipoproteins and then channelled to the peripheral lipid stores;
- the cell membrane phospholipids are replaced by lipoprotein phospholipids and the fatty acids can then act as precursors for various eicosanoids;
- the majority is oxidised to meet energy requirements.

The concentration of omega-3 fatty acids, EPA and DHA, in the plasma phospholipids corresponds to the EPA and DHA incorporated into the cell membranes.

Animal pharmacokinetic studies have shown that there is a complete hydrolysis of the ethyl ester accompanied by satisfactory absorption and incorporation of EPA and DHA into the plasma phospholipids and cholesterol esters.

5.3 Preclinical safety data
No safety issues have been identified relevant to human use at the recommended daily intake.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule core
Alpha-tocopherol

Capsule shell
Gelatin
Glycerol
Medium-chain triglycerides
Paraffin, liquid

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store below 30°C. Do not freeze. Keep in the original package in order to protect from moisture.

6.5 Nature and contents of container
Transparent PVC/Aclar® – Aluminium blisters, available in packs of 20, 28, 30, 3x10, 60, 90, 9x10, 100 and 120 capsules.

HDPE containers with tamper evident HDPE screw cap, available in packs of 20, 28, 30, 90, 98, 100 and hospital packs of 280 (10x28) capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1415

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/04/2012
DATE OF REVISION OF THE TEXT
03/04/2012
Module 3

OMEGA 3-ACID-ETHYL ESTERS 1000 mg SOFT CAPSULES

PACKAGE LEAFLET INFORMATION FOR THE USER

Read all of this leaflet carefully before you start taking this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:
1. What Omega 3-acid-ethyl esters 1000 mg Soft Capsules are and what they are used for
2. Before you take Omega 3-acid-ethyl esters 1000 mg Soft Capsules
3. How to take Omega 3-acid-ethyl esters 1000 mg Soft Capsules
4. Possible side effects
5. How to store Omega 3-acid-ethyl esters 1000 mg Soft Capsules
6. Further information

1. WHAT OMEGA 3-ACID-ETHYL ESTERS 1000 mg SOFT CAPSULES ARE AND WHAT THEY ARE USED FOR

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

Omega 2-acid-ethyl esters 1000 mg Soft Capsules are used:
• together with other medicines for treatment after a heart attack
• to treat certain forms of increased triglycerides (fats) in the blood after changes to the diet have not worked.

2. BEFORE YOU TAKE OMEGA 3-ACID-ETHYL ESTERS 1000 mg SOFT CAPSULES

Do not take Omega 3-acid-ethyl esters 1000 mg Soft Capsules
• if you are allergic (hypersensitive) to the main ingredient or any of the other ingredients of Omega 3-acid-ethyl esters 1000 mg Soft Capsules (see Section 6: Further Information).

If any of the above applies to you, do not take this medicine, and talk to your doctor.

Take special care with Omega 3-acid-ethyl esters 1000 mg Soft Capsules
• if you are due to have or have had surgery recently
• if you have had a trauma recently
• if you have a kidney problem
• if you have diabetes which is not controlled
• if you have problems with your liver. Your doctor will monitor any effects Omega 3-acid-ethyl esters 1000 mg Soft Capsules may have on your liver with blood tests.

If any of the above applies to you, talk to your doctor or pharmacist before taking this medicine.

Using other medicines
If you are using a medicine to stop blood clotting in your arteries, such as warfarin, you may need extra blood tests and your usual dose of your blood thinning medicine may have to be changed.

Please tell your doctor or pharmacist if you are using or have recently used other medicines including medicines obtained without prescription.

Taking Omega 3-acid-ethyl esters 1000 mg Soft Capsules with food or drink

You may take the capsules at meal times. This is to help lower the chances of side effects that affect the area in and around the stomach (the gastro-intestinal area).

Use in elderly

Use Omega 3-acid-ethyl esters 1000 mg Soft Capsules with care if you are over 70 years.

Use in children and teenagers
Children and teenagers should not take this medicine.

Pregnancy and breast-feeding

You should not take this medicine if you are pregnant or breast-feeding, unless your doctor decides it is absolutely necessary. Ask your doctor or pharmacist for advice before using any medicine.

Driving and using machines

This medicine is not likely to affect you being able to drive or use any tools or machines.

3. HOW TO TAKE OMEGA 3-ACID-ETHYL ESTERS 1000 mg SOFT CAPSULES

Always take Omega 3-acid-ethyl esters 1000 mg Soft Capsules exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Swallow the capsules with a drink of water.
You may take the capsules at meal times to help reduce gastro-intestinal side effects.
Your doctor will decide how long you should take this medicine.

Dose after a heart attack

The usual dose is one capsule a day.
Dose to treat high blood triglyceride levels (high levels of fat in the blood or hypertriglyceridaemia)
The usual dose is 2 capsules a day, as recommended by a doctor. If the medicine is not working well enough at this dose, your doctor may increase this to 4 capsules a day.
If you take more of Omega 3-acid-ethyl esters 1000 mg Soft Capsules than you should
If you accidentally take more of this medicine than you should, do not worry, as this is unlikely to need special treatment.
If you forget to take Omega 3-acid-ethyl esters 1000 mg Soft Capsules
If you miss a dose, take it when you remember unless it is almost time for your next dose, in which case take the next dose as usual. Do not take a double dose (twice the dose recommended by your doctor) to make up for a forgotten dose.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 POSSIBLE SIDE EFFECTS
Like all medicines, Omega 3-acid-ethyl esters 1000 mg Soft Capsules can cause side effects, although not everybody gets them. The following are side effects that may happen with this medicine:
Common side effects (occur in 1 to 10 users in 100):
• stomach problems and indigestion (dyspepsia)
• feeling sick (nausea).
Uncommon side effects (occur in 1 to 10 users in 1,000):
• abdominal and stomach pain
• allergic reactions
• dizziness
• problems with taste
• diarrhoea
• being sick (vomiting).
Rare side effects (occur in 1 to 10 users in 10,000):
• headache
• acne
• itchy rash (pruritus)
• high blood sugar levels
• liver problems.
Very rare side effects (occur in less than 1 in 10,000 users):
• blood in your stools
• low blood pressure
• dry nose
• raised red skin rash (hives or urticaria)
• changes in the results of certain blood tests.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 HOW TO STORE OMEGA 3-ACID-ETHYL ESTERS 1000 mg SOFT CAPSULES
• Keep out of the reach and sight of children.
• Do not use Omega 3-acid-ethyl esters 1000 mg Soft Capsules after the expiry date which is printed on the carton, bottle blister. The expiry date refers to the last day of the month.
• Store Omega 3-acid-ethyl esters 1000 mg Soft Capsules below 30°C. Do not freeze. Store in the original container in order to protect from moisture.
• Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION
What Omega 3-acid-ethyl esters 1000 mg Soft Capsules contains
The active substances are omega-3-acid ethyl esters. Each soft capsule contains 1,000 mg of omega-3-acid ethyl esters 50 comprising principally 840 mg of eicosapentaenoic acid (EPA) ethyl ester (460 mg) and docosahexaenoic acid (DHA) ethyl ester (380 mg) (these substances are called omega-3 polyunsaturated fatty acids) including as antioxidant 4 mg of the inactive ingredient d-alpha-tocopherol.
• The soft capsule shell is made up of gelatin, glycerol and traces of medium-chain triglycerides and paraffin liquid.

What Omega 3-acid-ethyl esters 1000 mg Soft Capsules looks like and contents of the pack
Omega 3-acid-ethyl esters 1000 mg Soft Capsules are transparent soft gelatin capsules containing pale yellow oil. Omega 3-acid-ethyl esters 1000 mg Soft Capsules is available in the following pack sizes:
- Transperant PVC/Aclar® -
- Aluminium blisters, available in packs of 20, 28, 30, 90, 9 x 10, 100 and 120 capsules.
- HDPE containers with tamper evident HDPE screw cap, available in packs of 20, 28, 30, 90, 98, 100 and hospital packs of 280 (10 x 28) capsules.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: TEVA UK Limited, Brampton Road, Hampton Park, Eastbourne, BN22 9AG.
This leaflet was last revised in March 2012
PL 00289/1415
Each soft capsule contains 1000 mg of omega-3 acid ethyl esters 90 comprising principally 640 mg eicosapentaenoic acid (EPA) ethyl ester (460 mg) and docosahexaenoic acid (DHA) ethyl ester (380 mg). **DOSAGE:** Read the package leaflet before use. Use as directed by the doctor. **KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.** Store below 30°C. Do not freeze. Store in the original container in order to protect from moisture.
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Omega 3-acid-ethyl esters 1000mg Soft Capsules in the treatment of post-myocardial infarction and hypertriglyceridaemia could be approved.

This application is for Omega 3-acid-ethyl esters 1000mg Soft Capsules submitted under Article 10.1 of Directive 2001/83/EC as amended. The application refers to the UK product, Omacor 1000mg, Capsule, Soft (PL 15905/0001), authorised to Pronova BioPharma Norge AS, Norway on 15 July 1999, through a Change of Ownership procedure from 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.

With the UK as the RMS in this Decentralised Procedure (UK/H/2056/001/DC), TEVA UK Limited applied for the Marketing Authorisation for Omega 3-acid-ethyl esters 1000mg Soft Capsules in Austria, Germany, Spain, France, Ireland, Italy, The Netherlands and Romania.

Omega 3-acid-ethyl esters 1000mg Soft Capsules are indicated for the following:

- **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** - as a supplement to diet in endogenous hypertriglyceridaemia 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 omega-3 series polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential fatty acids.

Omega-3-acid ethyl esters 90 is active on the plasma lipids by lowering triglyceride levels as a result of a fall in VLDL (very low density lipoprotein). Omega-3-acid ethyl esters 90 reduce the synthesis of triglycerides in the liver because EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis and they inhibit esterification of other fatty acids.

The increase in peroxisomes of β-oxidation of fatty acids in the liver also contributes to the fall in triglycerides, by reducing the quantity of free fatty acids available for their synthesis. The inhibition of this synthesis lowers VLDL.
Omega-3-acid ethyl esters 90 increase LDL-cholesterol in some patients with hypertriglyceridaemia. A rise in HDL-cholesterol is only small, significantly smaller than seen after administration of fibrates, and not consistent.

The long-term lipid-lowering effect (after more than one year) is not known. Otherwise there is no strong evidence that lowering triglycerides reduces the risk of ischaemic heart disease.

During treatment with omega-3-acid ethyl esters 90, there is a fall in thromboxane A2 production although the clinical relevance of this is not known. No significant effect has been observed on the other coagulation factors.

No new non-clinical and clinical studies were conducted, which is acceptable given that the application was based on being generic medicinal product of originator product that have been licensed for over 10 years. A bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly 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.

A suitable justification has been provided for non-submission of a Risk Management Plan. As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

All Member States agreed to grant a licence for the above product at the end of procedure (Day 210 – 7th March 2012). After a subsequent national phase, the UK granted a licence for this product on 3rd April 2012 (PL 00289/1415).
II. ABOUT THE PRODUCT

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<tr>
<td></td>
<td>Eicosapentaenoic Acid Ethyl Ester (at nominally 46%)</td>
</tr>
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<td></td>
<td>Docosahexaenoic Acid Ethyl Ester (at nominally 38%)</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, BN22 9AG</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: omega-3 acid ethyl esters 90

Nomenclature:

Compendial name: Omega-3-acid ethyl esters 90

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 6-16% comprising the five ethyl esters of the following fatty acids: alpha-linolenic acid, moroctic acid, Eicosatetraenoic acid, Heneicosapentaenoic acid and Docosapentaenoic acid.

Description: A visually clear, colourless to yellow, freeflowing 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-EE

Chemical Name: (5Z,8Z11Z,14Z,17Z)-Eicosa-5,8,11,14,17-Pentaenoic Acid Ethyl Ester

CAS number: 86227-47-6

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 weight: 330.55 g/mol

Structure:

![EPA-EE Structure](image1)

DHA-EE

Chemical Name: (4Z,7Z,10Z,13Z,16Z,19Z)-Docosa-4,7,10,13,16,19-Hexaenoic Acid Ethyl Ester

CAS Number: 81926-94-5

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 weight: 356.55 g/mol

Structure:

![DHA-EE Structure](image2)
The active substance, omega-3-acid ethyl esters 90, is the subject of a European Pharmacopeia (Ph. Eur) 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 specifications 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-TSE relevant animal species. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of genetically modified origin.

Appropriate specifications have been 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 specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been applied.

**DRUG PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients Alpha-tocopherol making up the capsule core. The capsule shell is consisting of gelatin, glycerol, medium-chain triglycerides and paraffin liquid.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. The only excipient used that contains material of animal origin is gelatin. Satisfactory documentation has been provided by the gelatin suppliers stating that the gelatin they provide complies with the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

**Pharmaceutical Development**

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a stable, immediate-release capsule formulation bioequivalent to, and containing qualitatively and quantitatively the same active substance as, the reference product, Omacor 1000mg, Capsule, Soft (Pronova BioPharma Norge AS).
Comparative dissolution and impurity data were provided for batches of the test product and appropriate reference product. The dissolution and impurity profiles were satisfactory.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process.

**Finished Product Specification**
Finished product specifications are provided for release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container-Closure System**
The finished product is packed in Transparent polyvinylchloride (PVC)/Aclar® – Aluminium blisters, available in packs of 20, 28, 30, 3x10, 60, 90, 9x10, 100 and 120 capsules.

Or

High-density polyethylene (HDPE) bottles with tamper evident HDPE screw cap, available in packs of 20, 28, 30, 90, 98, 100 and hospital packs of 280 (10x28) capsules.

Not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years with a storage conditions of ‘Store below 30°C’, ‘Do not Freeze’ and ‘Keep in the original package in order to protect from moisture’ are set. These are satisfactory.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC. 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 it contains.
The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

**Marketing Authorisation Application (MAA) Forms**
The MAA form is pharmaceutically satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
There are no objections to the approval of Omega 3-acid-ethyl esters 1000mg Soft Capsules from a pharmaceutical point of view.

**III.2 NON-CLINICAL ASPECTS**
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 90 is widely used and well-known active substance, the applicant has not provided additional studies in support of their application. Overview based on literature review is, thus, appropriate.

No new non-preclinical data have been supplied with this application and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of Omega 3-acid-ethyl esters 1000mg Soft Capsules from a non-clinical point of view.

**III.3 CLINICAL ASPECTS**

**Clinical Pharmacology**
The application is supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Omega 3-acid-ethyl esters 1000mg Soft Capsules, to that of the reference product, Omacor 1000 mg soft capsules (Pronova Biocare AS, Norway). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products.

This was an open-label, randomised, three-period, three-sequence, two-treatment, single-dose, partial replicate, crossover bioequivalence study conducted in healthy adult human subjects under fed conditions. Subjects were randomly assigned to one of the three dosing sequences: ABB, BBA or BAB.

Blood samples were collected at specified time-points pre-dose to establish a baseline for blood concentrations of the two analytes (eicosapentaenoic and docosahexaenoic acid ethyl
esters). Subjects were fasted overnight for 10hrs and were then given a high-fat, high calorie breakfast 30mins prior to administration of study medication. The standardised meals were limited in EPA and DHA content. A 4g dosage was used to ensure that analytes would be present at blood concentrations that were significantly different from background concentrations. A satisfactory washout period of 14 days was maintained between the dosing days in each group.

Blood was collected prior to administration of drug and at specified time points up to 72.0 hours after drug administration. Plasma levels of EPA and DHA were quantified by a validated LC-MS/MS method.

The primary pharmacokinetic parameters for the study were $C_{\text{max}}$ and $AUC_{0-t}$.

Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) of the ratio of the test and reference products fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed $C_{\text{max}}$ and $AUC_{0-t}$ for EPA and DHA.

**Results:**

An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

**Safety** - There were no deaths or serious or significant adverse events. The safety issues reported were similar in the test and reference product arms of the study and are consistent with information in section 4.8 of the SmPC of the reference product and with information available in Martindale: “the most common adverse effects of omega-3 fatty acid preparations are gastrointestinal disturbances, particularly at high doses. Increases in hepatic transaminases have been reported”.

The summary of the results of the bioequivalence study are tabulated below:

**Summary pharmacokinetic data for EPA and DHA for a randomised, open-label, 3-period, 3-sequence, 2-treatment, single-dose, partial replicate crossover study; healthy subjects, dosed fed; t=72 hours; washout period: 14 days**

<table>
<thead>
<tr>
<th>Analyte: Eicosapentaenoic Acid (EPA)</th>
<th>Parameter</th>
<th>TRT</th>
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<tr>
<td></td>
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<td>Arithmetic (CV%)</td>
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<td>Based on Baseline-adjusted Data</td>
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<tr>
<td>$AUC_{0-t}$ (µg·h/mL)</td>
<td>A</td>
<td>1461.47</td>
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<td></td>
<td>B1</td>
<td>1547.06</td>
<td>36</td>
<td>1326.72</td>
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<tr>
<td></td>
<td>B2</td>
<td>1501.23</td>
<td>37</td>
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<tr>
<td>$C_{\text{max}}$ (µg/mg)</td>
<td>A</td>
<td>51.47</td>
<td>42</td>
<td>44.72</td>
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<tr>
<td></td>
<td>B2</td>
<td>52.02</td>
<td>36</td>
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$A$ vs. $B$ 95.02 81.09 - 111.34 93.24 84.15 - 103.30
Discussion on Bioequivalence

The results of the bioequivalence study show that Omega 3-acid-ethyl esters 1000mg Soft Capsules and Omacor 1000 mg soft capsules (Pronova Biocare AS, Norway) are bioequivalent, under fed conditions, as the confidence intervals for Cₘₐₓ and AUC₀₋ₜ for EPA and DHA fall within the acceptance criteria ranges of 80.00-125.00% in line with current guidelines.

An in-house study was conducted to compare the bioavailabilities 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 bioavailabilities of eicosapentaenoic acid and docosahexaenoic acid are many-fold higher in the fed than the fasted state. It is, therefore, considered that a bioequivalence study in the fed state is the more sensitive and thus more appropriate than a study performed in the fasted state.

Clinical efficacy

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

Clinical safety

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of omega-3-acid ethyl esters 90 is well-known.

CLINICAL OVERVIEW

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product and is acceptable.
Patient Information Leaflet
The final PIL text is in line with the approved SmPC and is satisfactory.

Labelling
The labelling text is satisfactory.

CONCLUSIONS
Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, 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 and none are required for applications of this type.

CLINICAL
Bioequivalence have been demonstrated between the applicant’s Omega-3-acid ethyl esters 1000 mg Soft Gelatine Capsules and the reference product, (Omacor® 1000 mg soft capsules).

No new or unexpected safety concerns arise from this application.

The SmPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with omega-3-acid ethyl esters 90 is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
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<th>Scope</th>
<th>Outcome</th>
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