Public Assessment Report

Decentralised Procedure

Omega 3-acid-ethyl esters 1000mg Soft Capsules

(omega-3-acid ethyl esters 90)

Procedure No: UK/H/5391/001/DC

UK Licence No: PL 28176/0145

Strides Arcolab International Limited
LAY SUMMARY

Omega-3 acid ethyl esters 1000mg Soft Capsules
(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 1000mg Soft Capsules (PL 28176/0145; UK/H/5391/001/DC). It explains how Omega-3-acid ethyl esters 1000mg Soft Capsules 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 1000mg Soft Capsules.

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

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

What are Omega-3-acid ethyl esters 1000mg Capsules and what are they used for?
Omega-3-acid ethyl esters 1000mg Capsules contain highly purified omega-3 polyunsaturated fatty acids. Omega-3-acid ethyl esters 1000mg 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 1000mg Capsules are a ‘generic’ medicine. This means that Omega-3-acid ethyl esters 1000mg Capsules are similar to a reference medicine already authorised in the European Union (EU) called Omacor 1000mg Soft Capsules (Pronova BioPharma Norge AS, Norway).

How do Omega-3-acid ethyl esters 1000mg 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 are Omega-3-acid ethyl esters 1000mg Capsules used?
Omega-3-acid ethyl esters 1000 mg Capsules can only be obtained on prescription. This medicine should be taken exactly as advised by the doctor.

Omega-3-acid ethyl esters 1000mg are soft capsules taken by mouth; the capsules are swallowed with a drink of water. The capsules are taken at meal times to help reduce gastro-intestinal side-effects.

The recommended dose after a heart attack is one capsule a day.

The recommended dose for high blood triglyceride levels (high levels of fat in the blood or hypertriglyceridaemia) is two capsules a day. 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 1000mg Capsules are used, please see the Summaries of Product Characteristics available on the MHRA website.

What benefits of Omega-3-acid ethyl esters 1000mg Capsules have been show in studies?
As Omega-3-acid ethyl esters 1000mg Capsules is a generic medicine, studies in patients have been
Omega-3-acid ethyl esters 1000mg Capsules, Soft

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 (Strides Arcolab International Limited) has provided data from the published literature on Omega-3-acid ethyl esters.

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

For the full list of restrictions, see the package leaflet available on the MHRA website.

Why is Omega-3-acid ethyl esters 1000mg Capsules approved?
It was concluded that, in accordance with EU requirements, Omega-3-acid ethyl esters 1000mg 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 1000mg Capsules?
A Risk Management Plan has been developed to ensure that Omega-3-acid ethyl esters 1000mg Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Omega-3-acid ethyl esters 1000mg Capsules approved, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Omega-3-acid ethyl esters 1000mg Capsules.
Spain, Italy and the UK agreed to grant a Marketing Authorisation for Omega-3-acid ethyl esters 1000mg Soft Capsules on 19 June 2014. A Marketing Authorisation was granted in the UK on 15 July 2014.

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

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

This summary was last updated in September 2017.
SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Omega 3-acid-ethyl esters 1000mg Capsules, Soft (PL 28176/0145; UK/H/5391/001/DC) could be approved.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Spain and Italy as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Omacor 1000mg Soft 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 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 ingredient, 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 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 these applications, comparing the applicant’s test product Omega-3-acid ethyl esters Capsules 1g (soft gelatin), and the reference product Omacor 1000 mg Soft Capsules (Abbott Healthcare Products Limited, UK).

The Applicant states that the study was conducted in accordance with the study protocol and all other pertinent requirements of the Ethical guidelines for biomedical research on human participants, ICMR (2006), ICH (Step 5) ‘Guidance on Good Clinical Practice’, Schedule Y (amended version, 2005) of CDSCO, ‘Good Laboratory Practice’, ‘Good Clinical Practices for Clinical Research in India’ Guidelines, Good clinical laboratory practice (GCLP), Declaration of Helsinki (Seoul 2008) and EMEA Guideline on the investigation of bioequivalence.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.
Following an Article 31 referral regarding the clinical research organisation that conducted the bioequivalence study, additional in vitro disintegration data was provided to demonstrate comparable bioavailability to the reference product (see Annex 2).

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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 19 June 2014. After a subsequent national phase, a licence was granted in the UK on 15 July 2014.

II QUALITY ASPECTS

II.1 Introduction
Omega 3-acid-ethyl esters 1000mg soft capsules are soft, oblong, transparent gelatin capsules containing pale yellow coloured oily liquid imprinted with '740'. Each capsule contains 1000 mg Omega-3-Acid Ethyl Esters 90, comprising principally 840 mg ethylesters of eicosapentaenoic acid (EPA) (465 mg) and docosahexaenoic acid (DHA) (375 mg).

Other ingredients consist of the pharmaceutical excipients in the capsule core and shell, namely alpha-tocopherol, gelatin, glycerol, purified water, medium-chain triglycerides and Isopropyl alcohol and Opacode white printing ink (consisting of shellac glaze, titanium dioxide, purified water, n-butyl alcohol, lecithin (soya) and simeticone). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is packaged in white opaque high-density polyethylene (HDPE) containers with white opaque HDPE screw closures with induction sealing. The bottles are supplied with the Patient Information Leaflet in cartons, in pack sizes of 20, 28, 100 and 120 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.

II.2 Drug substance
Compendial Name: Omega-3 acid ethyl esters 90 (Ph. Eur.)
Chemical name: Omega-3-Acid Ethyl Esters 90 is predominantly composed of the ethyl esters eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids.
Appearance: Light yellow liquid.
Solubility Practically insoluble in water, very soluble in acetone, in ethanol (96%), in heptane and in methanol.

EPA ethyl ester
Chemical name: Ethyl(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenoate
Molecular formula: C_{22}H_{34}O_{2}
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 auxiliary 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.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to produce a safe, stable, capsule formulation bioequivalent to, and containing qualitatively and quantitatively the same active substance, as the reference product, Omacor 1000 mg Soft Capsules (Pronova BioPharma Norge AS). Suitable pharmaceutical development data have been provided for the application.
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. All the excipients comply with their respective European Pharmacopoeia monographs, with the exception of Opacode white printing in which 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 supplier of gelatin have provided a Certificate of Suitability from the European Directorate for the Quality of Medicines and Healthcare (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.

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 that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

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 24 months for the unopened product, and 120 days for the opened product has been set, with the storage conditions ‘Store below 30°C.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current versions of the SmPC and PIL are available on the MHRA website.

The approved labelling is shown below:
Each capsule contains 1000 mg of Omega-3 Acid Ethyl Esters 90, comprising principally 840 mg ethyl esters of eicosapentaenoic acid (EPA) (465 mg) and docosahexaenoic acid (DHA) (375 mg).

Lecithin (soya). See leaflet for further information. Read the package leaflet before use. Keep out of the sight and reach of children.

Store below 30°C. Keep the container in the outer carton in order to protect from the light. Shelf life after first opening of HDPE container is 120 days.

Each medicinal product subject to medical prescription. Use as directed by the Physician.
III NON-Clinical ASPECTS

III.1 Introduction

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.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.
III.3 Pharmacokinetics
No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology
No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is 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.

III.6 Discussion of the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV. CLINICAL ASPECTS

IV.1 Introduction
No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of levonorgestrel. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
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 this application.

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

An open-label, balanced, randomised, two-treatment, three-period, three-sequence, single dose, crossover partial –replicate, reference-scaled bioequivalence study comparing the applicant’s test product Omega-3-acid ethyl esters 1g Capsules (soft gelatin) and the reference product Omacor 1000 mg Soft Capsules (Abbott Healthcare Products Limited, UK) in healthy adult male 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 capsules (4 x 1000 mg) as a single dose of either the test (Treatment T) or the reference (Treatment R) 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).

Subjects were randomly assigned to one of the possible sequences of test product (T) and reference product (R) (either TRR or RTR or RRT) in consecutive order.

Blood sampling was performed pre-dose and up to 24 hours post dose in each treatment period. The washout period between the treatment arms was 7 days. Pharmacokinetic parameters were measured for EPA and DHA from plasma and statistically analysed.

A summary of the pharmacokinetic results of the bioequivalence study is presented below:
Statistical Results of Test Product-T versus Reference Product-R for Ester EPA

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Mean</th>
<th>T/R Ratio %</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product (T)</td>
<td>Reference Product (R)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>480.457</td>
<td>479.5159</td>
<td>100.20%</td>
</tr>
<tr>
<td>$\text{AUC}_{0,t}$ (ng.hr/mL)</td>
<td>944.5342</td>
<td>977.1069</td>
<td>96.67%</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ maximum analyte concentration over the sampling period
$\text{AUC}_{0,t}$ area under the analyte concentration versus time curve from time zero to t hours
CV coefficient of variation

Ratios and 90% confidence intervals calculated from ln-transformed data

Statistical Results of Reference Product ISCV for Ester EPA

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Intra Subject CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>58.9%</td>
</tr>
<tr>
<td>$\text{AUC}_{0,t}$ (ng.hr/mL)</td>
<td>44.0%</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ maximum analyte concentration over the sampling period
$\text{AUC}_{0,t}$ area under the analyte concentration versus time curve from time zero to t hours
ISCV Intra subject coefficient of variation
CV coefficient of variation

Statistical Results of Test Product-T versus Reference Product-R for Ester DHA

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Mean</th>
<th>T/R Ratio %</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product (T)</td>
<td>Reference Product (R)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>1122.8957</td>
<td>1282.9986</td>
<td>87.52%</td>
</tr>
<tr>
<td>$\text{AUC}_{0,t}$ (ng.hr/mL)</td>
<td>2410.6863</td>
<td>2688.4558</td>
<td>89.67%</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ maximum analyte concentration over the sampling period
$\text{AUC}_{0,t}$ area under the analyte concentration versus time curve from time zero to t hours
Ratios and 90% CI calculated from ln-transformed data

Statistical Results of Reference Product ISCV for Ester DHA

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Intra Subject CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>51.4%</td>
</tr>
<tr>
<td>$\text{AUC}_{0,t}$ (ng.hr/mL)</td>
<td>39.5%</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ maximum analyte concentration over the sampling period
$\text{AUC}_{0,t}$ area under the analyte concentration versus time curve from time zero to t hours
ISCV Intra subject coefficient of variation
CV coefficient of variation

Conclusion

The Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80% to 125% for $C_{\text{max}}$ and AUC values.

The intra-subject coefficient of variation for the reference product for $C_{\text{max}}$ of both analytes was high, therefore, as defined in the protocol wider criteria for $C_{\text{max}}$ would apply. This was relevant only to $C_{\text{max}}$. 


for DHA for which the lower limit was below 80% (but within the pre-defined 69.84% to 143.19% range). For all other parameters the 90% CI of the ratios were within the standard 80%–125% range.

Overall, taking into account the limitations of studying bioequivalence for an endogenous substance with high variability the data support the claim that the applicant’s test product Omega-3-acid ethyl esters 1g Capsules (soft gelatin) is bioequivalent to the reference product Omacor 1000 mg Soft Capsules (Abbott Healthcare Products Limited, UK) under fed conditions.

Following an Article 31 referral regarding the clinical research organisation that conducted the bioequivalence study, additional in vitro disintegration data was provided to demonstrate comparable bioavailability to the reference product (see Annex 2).

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical 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 this type of application. The reference product is established and the application is supported by the demonstration of bioequivalence with the reference product. Efficacy is reviewed in the clinical overview.

IV.5 Clinical Safety
No new safety data were submitted and none are required for this type of application 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.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
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.

An acceptable Risk Management Plan has been provided. Routine risk minimisation is provided through the Summary of Product Characteristics and the Patient Information Leaflet and this is sufficient.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risk:</td>
<td><strong>Increase in bleeding time</strong></td>
<td>Currently available data does not support the need for additional risk minimization activities.</td>
</tr>
<tr>
<td></td>
<td>Strides proposed SmPC for omega 3-acid-ethyl esters includes following information on this safety concern:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Section 4.4:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use of this medication does not eliminate the need for the surveillance usually required for patients of this type.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Make allowance for the increased bleeding time in patients at high risk of haemorrhage (because of severe trauma, surgery, etc).</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Section 4.5:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Omega-3-acid ethyl esters 90 have been given in conjunction with warfarin without haemorrhagic complications. However, the</td>
<td></td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Important identified risk:** Elevated hepatic enzymes

Strides proposed SmPC for omega 3-acid-ethyl esters includes following information on this safety concern:

**Section 4.4:**

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)

**Section 4.8:**

Hepatobiliary disorders:

Rare: hepatic disorders

Investigations:

Very rare: Moderate elevation of transaminases has been reported in patients with hypertriglyceridaemia.

Currently available data does not support the need for additional risk minimization activities.

**Missing information:** Use of Omega-

Strides proposed SmPC for omega 3-acid-ethyl esters includes following information on this safety concern:

Currently available data does not support the need for additional risk
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
</table>
| **3-acid ethyl esters during lactation**                                     | **Section 4.6:**  
There are no data on the excretion of Omega-3-acid ethyl esters 90 in animal and human milk.  
Omega-3-acid ethyl esters 90 should not be used during lactation                                                                                                                   | minimization activities.                                                                                                                                     |
| **Missing information:** Use of Omega-3-acid ethyl esters in children         | **Section 4.2:**  
There is no information regarding the use of Omega 3-acid-ethyl esters Strides 1000mg soft capsules in children.  
**Section 4.4:**  
In the absence of efficacy and safety data, use of this medication in children is not recommended.                                                                               | Currently available data does not support the need for additional risk minimization activities.                                                              |
| **Missing information:** Use of Omega-3-acid ethyl esters in patients with     | Strides proposed SmPC for omega 3-acid-ethyl esters includes following information on this safety concern:  
**Section 4.2:**  
There is no information regarding the use of Omega 3-acid-ethyl esters Strides 1000mg soft capsules in patients with                                                                 | currently available data does not support the need for additional risk minimization activities.                                                              |
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>hepatic impairment</td>
<td>Omega 3-acid-ethyl esters Strides 1000mg soft capsules in patients with hepatic impairment.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Section 4.4:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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).</td>
<td></td>
</tr>
<tr>
<td>Missing information:</td>
<td>Strides proposed SmPC for omega 3-acid-ethyl esters includes following information on this safety concern:</td>
<td>Currently available data does not support the need for additional risk minimization activities.</td>
</tr>
<tr>
<td>Use of Omega-3-acid-ethyl esters in patients with renal impairment</td>
<td>Section 4.2:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>There is only limited information regarding the use in patients with renal impairment.</td>
<td></td>
</tr>
<tr>
<td>Missing information:</td>
<td>Strides proposed SmPC for omega 3-acid-ethyl esters includes following information on this safety concern:</td>
<td>Currently available data does not support the need for additional risk minimization activities.</td>
</tr>
<tr>
<td>Use of Omega-3-acid-ethyl esters in elderly patients over 70 years of age</td>
<td>Section 4.2:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>There is no information regarding the use of Omega 3-acid-ethyl esters Strides 1000mg soft capsules in elderly patients over 70 years</td>
<td></td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Missing information: Use of Omega-3-acid-ethyl esters during pregnancy | Strides proposed SmPC for omega 3-acid-ethyl esters includes following information on this safety concern:  
**Section 4.6:**  
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 90 should not be used during pregnancy unless clearly necessary. | Currently available data does not support the need for additional risk minimization activities. |
| Missing information: Concomitant use with fibrates | Strides proposed SmPC for omega 3-acid-ethyl esters includes following information on this safety concern:  
**Section 4.4:**  
There is no experience regarding hypertriglyceridaemia in combination with fibrates. | Currently available data does not support the need for additional risk minimization activities. |

**IV.7 Discussion of the clinical aspects**  
The grant of a Marketing Authorisation is recommended.

**V. USER CONSULTATION**  
The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflets are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that they contain.
VI OVERALL CONCLUSION AND 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.
Annex 1- Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval / non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>To remove the BE Study and replace with in vitro data.</td>
<td>PL 28176/0145 - 0018</td>
<td>None</td>
<td>06/04/17</td>
<td>22/08/17</td>
<td>Approval</td>
<td>Y (Annex 2)</td>
</tr>
</tbody>
</table>
ANNEX 2

Our Reference: PL 28176/0145 - 0018
Product: Omega 3-acid-ethyl esters 1000mg Soft Capsules
Marketing Authorisation Holder: Strides Arcolab International Limited
Active Ingredient(s): Omega-3 acid ethyl esters 90
Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Complex

Reason:
This type II variation is being submitted as an outcome to an Article 31 referral regarding the clinical research organisation that conducted the bioequivalence study used to initially support this article 10.1 generic application.

It is proposed to submit additional in vitro disintegration data to demonstrate comparable bioavailability to the reference product.

Supporting Evidence:
The results of an in-vitro disintegration study conducted across the physiological pH range have been presented for batches of the test and reference products.

Data has also been provided demonstrating that the test and reference products have comparable chemical and physical properties.

The Clinical Overview and Quality Overall Summary have both been updated with information related to the biowaiver instead of the bioequivalence study.

Evaluation:
The biowaiver is considered acceptable as fast and comparable disintegration of the capsules has been demonstrated over the whole physiological range. As stated in Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party EMA/618604/2008 Rev. 13 ‘Since the liquid oily active substance of the capsules filled with omega-3 fatty acid EEs will be directly available for absorption after rupture and disintegration and a different formulation effect cannot be expected from the allowed preservative, in vivo BE study could be waived’.

Conclusion:
The proposal to provide additional in vitro data is justified and the variation is considered approvable.

Decision:
Approved on 22 August 2017.