Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 1,000 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).

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

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

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 90 are 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 Fertility, 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 90 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 90 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.

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 30ºC. 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 and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA749/149/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 8th June 2012

10 DATE OF REVISION OF THE TEXT