Lovaza, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each one gram capsule of Lovaza (omega-3 acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).

The structural formula of EPA ethyl ester is:

\[
\text{C}_{22}\text{H}_{36}\text{O}_{2}
\]

And the molecular weight of EPA ethyl ester is 330.51.

The structural formula of DHA ethyl ester is:

\[
\text{C}_{24}\text{H}_{36}\text{O}_{2}
\]

And the molecular weight of DHA ethyl ester is 356.55.

Lovaza capsules also contain the following inactive ingredients: 4 mg \(\alpha\)-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).

CLINICAL PHARMACOLOGY

Mechanism of Action:
The mechanism of action of Lovaza is not completely understood. Potential mechanisms of action include inhibition of acyl CoA,12- diacylglycerol acyltransferase, increased mitochondrial and peroxisomal \(\beta\)-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. Lovaza may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

Pharmacokinetic and Bioavailability Studies:
In healthy volunteers and in patients with hypertriglyceridemia (HTG), EPA and DHA were absorbed when administered as ethyl esters. Omega-3 acids administered as ethyl esters (Lovaza) induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with Lovaza was independent of age (<49 years vs. >49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Lovaza in children are not available.

Drug Interactions:

Cytchrome P450-Dependent Monoxygenase Activities:
The effect of a mixture of fatty acids (3:1 EPA:DHA) and their FAA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 \(\mu\)M concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 \(\mu\)M concentration, the FAA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Since the free forms of the EPA and DHA are undetectable in the circulation (<1 \(\mu\)M), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism EPA/DHA combinations are not expected in humans.

CLINICAL STUDIES

High Triglycerides: Add-on to HMG-CoA reductase inhibitor therapy

The effects of Lovaza 4 g per day as add-on therapy to treatment with simvastatin were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 255 adult patients (122 on Lovaza and 133 on placebo) with persistent high triglycerides (200 - 499 mg/dL) despite simvastatin therapy (Table 1). Patients were treated with open-label simvastatin 40 mg per day for 8 weeks prior to randomization to control their LDL-C to no greater than 10% above NCEP ATP III goal and remained on this dose throughout the study. Following the 8 weeks of open-label treatment with simvastatin, patients were randomized to either Lovaza 4 g per day or placebo for an additional 8 weeks with simvastatin co-therapy. The median baseline triglyceride and LDL-C levels in these patients were 268 mg/dL and 89 mg/dL, respectively. Median baseline non-HDL-C and LDL-C levels were 138 mg/dL and 45 mg/dL, respectively.

The changes in the major lipoprotein lipid parameters for the Lovaza plus simvastatin and the placebo plus simvastatin groups are shown in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LOVADA + Simvastatin</th>
<th>Placebo + Simvastatin</th>
<th>Difference</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL-C</td>
<td>137</td>
<td>123</td>
<td>-9.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>TG</td>
<td>268</td>
<td>182</td>
<td>-29.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>TC</td>
<td>184</td>
<td>172</td>
<td>-4.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>52</td>
<td>37</td>
<td>-27.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apo-B</td>
<td>86</td>
<td>80</td>
<td>-6.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>52</td>
<td>44</td>
<td>-8.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 1: Response to the Addition of LOVADA 4 g per day to On-going Simvastatin 40 mg per day Therapy in Patients with High Triglycerides (200 to 499 mg/dL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LOVADA N=122</th>
<th>Placebo N=132</th>
<th>Difference</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL % Chg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL % Chg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For some patients, increases in alanine aminotransferase (ALT) levels without a concurrent rise in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Lovaza therapy.

In some patients, Lovaza increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Lovaza therapy.

INDICATIONS AND USAGE

Very High Triglycerides

Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (>500 mg/dL) triglyceride levels.

Usage Considerations:
In individuals with hypertriglyceridemia (HTG), excess body weight and excess alcohol intake may be important contributing factors and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributing to hyperlipidemia (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent, if medically indicated, may obviate the need for specific drug therapy for HTG.

The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet (See PRECAUTIONS).

CONTRAINDICATIONS

Lovaza is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

PRECAUTIONS

General:

Initial Therapy: Laboratory studies should be performed to ascertain that the patient’s TG levels are consistently abnormal before instituting Lovaza therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient’s TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG-lowering drug therapy.

Continued Therapy: Laboratory studies should be performed periodically to measure the patient’s TG levels during Lovaza therapy. Lovaza therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.

Information for Patients:

Lovaza should be used with caution in patients with known sensitivity or allergy to fish. Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.

Laboratory Tests:
In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent rise in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Lovaza therapy.

Table 2: Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (>500 mg/dL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LOVADA N=42</th>
<th>Placebo N=42</th>
<th>Difference</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>816</td>
<td>788</td>
<td>+6.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>271</td>
<td>292</td>
<td>-3.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>172</td>
<td>170</td>
<td>+0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>22</td>
<td>24</td>
<td>+9.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>89</td>
<td>108</td>
<td>+48.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 2: Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (>500 mg/dL)
LOVAZA™
(omega-3-acid ethyl esters) Capsules

Drug Interactions:
Anticoagulants: Some studies with omega-3-acids demonstrated prolongation of
bleeding time. The prolongation of bleeding time reported in these studies has not
exceeded normal limits and did not produce clinically significant bleeding episodes.
Clinical studies have not been done to thoroughly examine the effect of Lovaza and
concomitant anticoagulants. Patients receiving treatment with both Lovaza and
anticoagulants should be monitored periodically.

HMG-CoA reductase inhibitors: In a 14-day study of 24 healthy adult subjects, daily
coadministration of simvastatin 80 mg with Lovaza 4 g did not affect the extent (AUC)
or rate (C) of exposure to simvastatin or the major active metabolite, beta-hydroxy
simvastatin at steady state.

Cytochrome P450-Dependent Monoxygenase Activities: Omega-3-fatty acid
containing products have been shown to increase hepatic concentrations of cytochrome
P450 and activities of certain P450 enzymes in rats. The potential of Lovaza to induce
P450 activities in humans has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral
gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females
for 89 weeks without an increased incidence of tumors (up to 5 times human systemic
exposures following an oral dose of 4 g/day based on a body surface area comparison).
Standard lifetime carcinogenicity bioassays were not conducted in mice.
Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic
activation in the bacterial mutagenesis ( Ames) test with Salmonella typhimurium and
Escherichia coli or in the chromosomal aberration assay in Chinese hamster V79 lung cells
or human lymphocytes. Omega-3-acid ethyl esters were negative in the in vivo mouse
micronucleus assay.
In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were
treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and
throughout mating, gestation and lactation. No adverse effect on fertility was observed at
2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day
based on a body surface area comparison). In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks
prior to mating and continuing throughout gestation and lactation, no adverse effects were
observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).

Pregnancy Category C:
There are no adequate and well-controlled studies in pregnant women. It is unknown
whether Lovaza can cause fetal harm when administered to a pregnant woman or
can affect reproductive capacity. Lovaza should be used during pregnancy only if the
potential benefit justifies the potential risk to the fetus.
Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant
rats when given in doses resulting in exposures 7 times the recommended human dose of
4 g/day based on a body surface area comparison.

In a rabbit study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated
for 10 weeks prior to mating and females were treated for 2 weeks prior to and
throughout mating, gestation and lactation. No adverse effect on fertility was observed at
2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day
based on a body surface area comparison).

In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation
day 6 through 15, no adverse effects were observed (14 times human systemic exposure
following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation
day 6 through 15, no adverse effects were observed (14 times human systemic exposure
following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks
prior to mating and continuing throughout gestation and lactation, no adverse effects were
observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).

Adverse Events:

Body System

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>LOVAZA (N = 226)</th>
<th>Placebo* (N = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body systems</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Subjects with at least 1 adverse event</td>
<td>80 35.4</td>
<td>63 27.6</td>
</tr>
<tr>
<td>Body as a whole</td>
<td>5 2.2</td>
<td>3 1.3</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 2.2</td>
<td>4 1.8</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>6 2.7</td>
<td>11 4.9</td>
</tr>
<tr>
<td>Infection</td>
<td>4 1.8</td>
<td>3 1.3</td>
</tr>
<tr>
<td>Pain</td>
<td>3 1.3</td>
<td>1 0.4</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4 1.8</td>
<td>3 1.3</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>3 1.3</td>
<td>2 0.9</td>
</tr>
<tr>
<td>Digestive</td>
<td>6 2.7</td>
<td>4 1.8</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4 1.8</td>
<td>3 1.3</td>
</tr>
<tr>
<td>Eruption</td>
<td>3 1.3</td>
<td>2 0.9</td>
</tr>
<tr>
<td>Skin</td>
<td>3 1.3</td>
<td>2 0.9</td>
</tr>
<tr>
<td>Rash</td>
<td>4 1.8</td>
<td>3 1.3</td>
</tr>
<tr>
<td>Special senses</td>
<td>3 1.3</td>
<td>2 0.9</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>4 1.8</td>
<td>3 1.3</td>
</tr>
</tbody>
</table>

In a rabbit study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated
for 10 weeks prior to mating and females were treated for 2 weeks prior to and
throughout mating, gestation and lactation. No adverse effect on fertility was observed at
2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day
based on a body surface area comparison).

In a rabbit study with oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks
prior to mating and continuing throughout gestation and lactation, no adverse effects were
observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).

In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation
day 6 through 15, no adverse effects were observed (14 times human systemic exposure
following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation
day 14 through lactation day 21, no adverse effects were seen at 2000 mg/kg/day (5 times
the human systemic exposure following an oral dose of 4 g/day based on body surface area comparison). However, decreased liver births (20% reduction) and decreased
survival to postnatal day 4 were observed in a dose-ranging study using higher doses of 3000 mg/kg/day (7 times the human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).

In pregnant rats given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation
day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day
(2 times human systemic exposure following an oral dose of 4 g/day based on a body
surface area comparison). However, at higher doses, evidence of maternal toxicity was
observed (4 times human systemic exposure following an oral dose of 4 g/day based on body
surface area comparison).