LOVASTATIN- lovastatin tablet
DIRECT RX

LOVASTATIN 20mg

DESCRIPTION

Lovastatin is a cholesterol lowering agent isolated from a strain of Aspergillus terreus. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding ß-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

Lovastatin is [1S-[1 α(R*),3 α,7ß,8ß(2S*,4S*), 8aß]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. The empirical formula of lovastatin is C24H3605 and its molecular weight is 404.55. Its structural formula is:

[Chemical Structure]

Lovastatin is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile.

Lovastatin Tablets USP are supplied as 10 mg, 20 mg and 40 mg tablets for oral administration. In addition to the active ingredient lovastatin, each tablet contains the following inactive ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose and corn starch. Butylated hydroxyanisole (BHA) is added as a preservative. In addition the 10 mg tablets also contain red iron oxide and yellow iron oxide; the 20 mg tablets also contain FD&C blue No. 2; and the 40 mg tablets also contain D&C yellow No. 10 and FD&C blue No. 2.

CLINICAL PHARMACOLOGY I

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological and clinical studies have established that high LDL-C and low high-density lipoprotein cholesterol (HDL-C) are both associated with coronary heart disease. However, the risk of developing coronary heart disease is continuous and graded over the range of cholesterol levels and many coronary events do occur in patients with total cholesterol (total-C) and LDL-C in the lower end of this range.

Lovastatin has been shown to reduce elevated LDL-C concentrations. LDL is formed from very low-density lipoprotein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of lovastatin may involve both reduction of VLDL-C concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. Apolipoprotein B also falls during treatment with lovastatin.

Lovastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol.

Pharmacokinetics

Lovastatin is a lactone which is readily hydrolyzed in vivo to the corresponding ß-hydroxyacid, a strong inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the ß-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of lovastatin.

Following an oral dose of 14C-labeled lovastatin in man, 10% of the dose was excreted in urine and

83% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (lovastatin plus 14C-metabolites) peaked at 2 hours and declined rapidly to about 10% of peak by 24 hours postdose. Absorption of lovastatin, estimated relative to an intravenous reference dose, in each of four animal species tested, averaged about 30% of an oral dose. In animal studies, after oral dosing, lovastatin had high selectivity for the liver, where it achieved substantially higher concentrations than in non-target tissues. Lovastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of lovastatin, the availability of drug to the general circulation is low and variable. In a single dose study in four hypercholesterolemic patients, it was estimated that less than 5% of an oral dose of lovastatin reaches the general circulation as active inhibitors. Following administration of lovastatin tablets the coefficient of variation, based on between-subject variability, was approximately 40% for the area under the curve (AUC) of total inhibitory activity in the general circulation.

Both lovastatin and its ß-hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Animal studies demonstrated that lovastatin crosses the blood-brain and placental barriers.

The major active metabolites present in human plasma are the ß-hydroxyacid of lovastatin, its 6'-hydroxy derivative, and two additional metabolites. Peak plasma concentrations of both active and total inhibitors were attained within 2 to 4 hours of dose administration. While the recommended therapeutic dose range is 10 mg/day to 80 mg/day, linearity of inhibitory activity in the general circulation was established by a single dose study employing lovastatin tablet dosages from 60 mg to as high as 120 mg. With a once-a- day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady state between the second and third days of therapy and were about 1.5 times those following a single dose. When lovastatin was given under fasting conditions, plasma concentrations of total inhibitors were on average about two-thirds those found when lovastatin was administered immediately after a standard test meal.

In a study of patients with severe renal insufficiency (creatinine clearance 10 mL/min to 30 mL/min), the plasma concentrations of total inhibitors after a single dose of lovastatin were approximately two-fold higher than those in healthy volunteers.

In a study including 16 elderly patients between 70 to 78 years of age who received lovastatin 80 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18 to 30 years of age (see PRECAUTIONS, Geriatric Use).

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for lovastatin and lovastatin acid is presumably due, in part, to inhibition of CYP3A4.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Strong inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see WARNINGS, Myopathy/Rhabdomyolysisand PRECAUTIONS, Drug Interactions).

Lovastatin is a substrate for cytochrome P450 isoform 3A4 (CYP3A4) (see PRECAUTIONS, Drug Interactions). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study1, 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 80 mg lovastatin on the third day. This regimen of grapefruit juice resulted in a mean increase in the serum concentration of lovastatin and its ß-hydroxyacid metabolite (as measured by the area under the concentration-time curve) of 15-fold and 5-fold, respectively [as measured using a chemical assay - high performance liquid chromatography]. In a second study, 15 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 40 mg lovastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean

increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using an enzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.34-fold and 1.36-fold, respectively, and of lovastatin and its ß-hydroxyacid metabolite [measured using a chemical assay - liquid chromatography/tandem mass spectrometry - different from that used in the first1 study] of 1.94-fold and 1.57-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied.

Table 1: The Effect of Other Drugs on Lovastatin Exposure When Both Were Co-Administered

*
Results based on a chemical assay.
†
Lovastatin acid refers to the β-hydroxyacid of lovastatin.
‡
The mean total AUC of lovastatin without itraconazole phase could not be determined accurately. Results could be representative of strong CYP3A4 inhibitors such as ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone.
§
Estimated minimum change.
¶
The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied.
#
Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose lovastatin and 30 and 90 minutes following single dose lovastatin on Day 3.
Þ
Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and lovastatin was administered in the evening on Day 3.
ß
Cyclosporine-treated patients with psoriasis or post kidney or heart transplant patients with stable graft function, transplanted at least 9 months prior to study.
à
ND = Analyte not determined.
è
Lactone converted to acid by hydrolysis prior to analysis. Figure represents total unmetabolized acid and lactone.

Number of Subjects

Dosing of Co-Administered Drug or Grapefruit Juice

Dosing of Lovastatin

AUC Ratio* (with/without co-administered drug)

No Effect = 1.00

Lovastatin

Lovastatin Acid†

Gemfibrozil

11

600 mg BID for 3 days

40 mg

0.96
2.80
Itraconazole‡
12
200 mg QD for 4 days
40 mg on Day 4
>36§
22
10
100 mg QD for 4 days
40 mg on Day 4
>14.8§
15.4
Grapefruit Juice¶ (high dose)
10
200 mL of double-strength TID#
80 mg single dose
15.3
5.0
Grapefruit Juice¶ (low dose)
16
8 oz (about 250 mL) of single-strengthÞ for 4 days
40 mg single dose
1.94
1.57
Cyclosporine
16
Not describedß
10 mg QD for 10 days
5- to 8-fold
NDà
Number of Subjects
Dosing of Co-Administered Drug or Grapefruit Juice
Dosing of Lovastatin
AUC Ratio* (with/without co-administered drug)
No Effect = 1.00
Total Lovastatin Acidè

Diltiazem

10

120 mg BID for 14 days

20 mg

3.57è

1Kantola, T, et al., Clin Pharmacol Ther 1998; 63(4):397-402.

CLINICAL PHARMACOLOGY II

Clinical Studies in Adults

Lovastatin has been shown to reduce total-C and LDL-C in heterozygous familial and non-familial forms of primary hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4 to 6 weeks. The response was maintained during continuation of therapy. Single daily doses given in the evening were more effective than the same dose given in the morning, perhaps because cholesterol is synthesized mainly at night.

In multicenter, double-blind studies in patients with familial or non-familial hypercholesterolemia, lovastatin, administered in doses ranging from 10 mg q.p.m. to 40 mg b.i.d., was compared to placebo. Lovastatin significantly decreased plasma total-C, LDL-C, total-C/HDL-C ratio and LDL-C/HDL-C ratio. In addition, lovastatin produced increases of variable magnitude in HDL-C, and modestly decreased VLDL-C and plasma TG (see Tables 2 through 4 for dose response results).

The results of a study in patients with primary hypercholesterolemia are presented in Table 2.

Table 2: Lovastatin vs. Placebo (Mean Percent Change from Baseline After 6 Weeks)

DOSAGE

N

TOTAL-C

LDL-C

HDL-C

LDL-C/
HDL-C

TOTAL-C
/HDL-C

TG

Placebo

33

-2

-1

-1

0

+1

+9

Lovastatin
10 mg q.p.m.
33
-16
-21
+5
-24
-19
-10
20 mg q.p.m.
33
-19
-27
+6
-30
-23
+9
10 mg b.i.d.
32
-19
-28
+8
-33
-25
-7
40 mg q.p.m.
33
-22
-31
+5
-33
-25
-8
20 mg b.i.d.
36
-24
-32

+2

-32

-24

-6

Lovastatin was compared to cholestyramine in a randomized open parallel study. The study was performed with patients with hypercholesterolemia who were at high risk of myocardial infarction. Summary results are presented in Table 3.

Table 3: Lovastatin vs. Cholestyramine (Percent Change from Baseline After 12 Weeks)

TREATMENT

N

TOTAL-C
(mean)

LDL-C
(mean)

HDL-C
(mean)

LDL-C
/HDL-C
(mean)

TOTAL-C/HDL-C
(mean)

VLDL-C
(median)

TG
(mean)

Lovastatin

20 mg b.i.d.

85

-27

-32

+9

-36

-31

-34

-21

40 mg b.i.d.

88

-34

-42

+8

-44

-37

-31

-27

Cholestyramine

12 g b.i.d.

88

-17

-23

+8

-27

-21

+2

+11

Lovastatin was studied in controlled trials in hypercholesterolemic patients with well-controlled non-insulin dependent diabetes mellitus with normal renal function. The effect of lovastatin on lipids and lipoproteins and the safety profile of lovastatin were similar to that demonstrated in studies in nondiabetics. Lovastatin had no clinically important effect on glycemic control or on the dose requirement of oral hypoglycemic agents.

Expanded Clinical Evaluation of Lovastatin [EXCEL] Study

Lovastatin was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240 mg/dL to 300 mg/dL [6.2 mmol/L to 7.6 mmol/L], LDL-C >160 mg/dL [4.1 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. All changes in the lipid measurements (Table 4) in lovastatin treated patients were dose-related and significantly different from placebo ($p<0.001$). These results were sustained throughout the study.

Table 4: Lovastatin vs. Placebo (Percent Change from Baseline-Average Values Between Weeks 12 and 48)

*

Patients enrolled

DOSAGE

N*

TOTAL-C
(mean)

LDL-C
(mean)

HDL-C
(mean)

LDL-C/
HDL-C
(mean)

TOTAL-C/HDL-C

(mean)

TG
(median)

Placebo

1663

+0.7

+0.4

+2.0

+0.2

+0.6

+4

Lovastatin

20 mg q.p.m.

1642

-17

-24

+6.6

-27

-21

-10

40 mg q.p.m.

1645

-22

-30

+7.2

-34

-26

-14

20 mg b.i.d.

1646

-24

-34

+8.6

-38

-29

-16

40 mg b.i.d.

1649

-29

-40

+9.5

-44

-34

-19

CLINICAL PHARMACOLOGY III

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a double-blind, randomized, placebo-controlled, primary prevention study, demonstrated that treatment with lovastatin decreased the rate of acute major coronary events (composite endpoint of myocardial infarction, unstable angina, and sudden cardiac death) compared with placebo during a median of 5.1 years of follow-up. Participants were middle-aged and elderly men (ages 45 to 73) and women (ages 55 to 73) without symptomatic cardiovascular disease with average to moderately elevated total-C and LDL-C, below average HDL-C, and who were at high risk based on elevated total-C/HDL-C. In addition to age, 63% of the participants had at least one other risk factor (baseline HDL-C <35 mg/dL, hypertension, family history, smoking and diabetes).

AFCAPS/TexCAPS enrolled 6,605 participants (5,608 men, 997 women) based on the following lipid entry criteria: total-C range of 180 mg/dL to 264 mg/dL, LDL-C range of 130 mg/dL to 190 mg/dL, HDL-C of <45 mg/dL for men and <47 mg/dL for women, and TG of <400 mg/dL. Participants were treated with standard care, including diet, and either lovastatin 20 mg to 40 mg daily (n=3,304) or placebo (n=3,301). Approximately 50% of the participants treated with lovastatin were titrated to 40 mg daily when their LDL-C remained >110 mg/dL at the 20 mg starting dose.

Lovastatin reduced the risk of a first acute major coronary event, the primary efficacy endpoint, by 37% (lovastatin 3.5%, placebo 5.5%; p<0.001; Figure 1). A first acute major coronary event was defined as myocardial infarction (54 participants on lovastatin, 94 on placebo) or unstable angina (54 vs. 80) or sudden cardiac death (8 vs. 9). Furthermore, among the secondary endpoints, lovastatin reduced the risk of unstable angina by 32% (1.8% vs. 2.6%; p=0.023), of myocardial infarction by 40% (1.7% vs. 2.9%; p=0.002), and of undergoing coronary revascularization procedures (e.g., coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 33% (3.2% vs. 4.8%; p=0.001). Trends in risk reduction associated with treatment with lovastatin were consistent across men and women, smokers and non-smokers, hypertensives and non-hypertensives, and older and younger participants. Participants with >2 risk factors had risk reductions (RR) in both acute major coronary events (RR 43%) and coronary revascularization procedures (RR 37%). Because there were too few events among those participants with age as their only risk factor in this study, the effect of lovastatin on outcomes could not be adequately assessed in this subgroup.

[Figure 1]

Figure 1: Acute Major Coronary Events (Primary Endpoint)

Atherosclerosis

In the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT), the effect of therapy with lovastatin on coronary atherosclerosis was assessed by coronary angiography in hyperlipidemic patients. In the randomized, double-blind, controlled clinical trial, patients were treated with conventional measures (usually diet and 325 mg of aspirin every other day) and either lovastatin 20 mg to 80 mg daily or placebo. Angiograms were evaluated at baseline and at two years by computerized

quantitative coronary angiography (QCA). Lovastatin significantly slowed the progression of lesions as measured by the mean change per-patient in minimum lumen diameter (the primary endpoint) and percent diameter stenosis, and decreased the proportions of patients categorized with disease progression (33% vs. 50%) and with new lesions (16% vs. 32%).

In a similarly designed trial, the Monitored Atherosclerosis Regression Study (MARS), patients were treated with diet and either lovastatin 80 mg daily or placebo. No statistically significant difference between lovastatin and placebo was seen for the primary endpoint (mean change per patient in percent diameter stenosis of all lesions), or for most secondary QCA endpoints. Visual assessment by angiographers who formed a consensus opinion of overall angiographic change (Global Change Score) was also a secondary endpoint. By this endpoint, significant slowing of disease was seen, with regression in 23% of patients treated with lovastatin compared to 11% of placebo patients.

In the Familial Atherosclerosis Treatment Study (FATS), either lovastatin or niacin in combination with a bile acid sequestrant for 2.5 years in hyperlipidemic subjects significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions by QCA compared to diet and, in some cases, low-dose resin.

The effect of lovastatin on the progression of atherosclerosis in the coronary arteries has been corroborated by similar findings in another vasculature. In the Asymptomatic Carotid Artery Progression Study (ACAPS), the effect of therapy with lovastatin on carotid atherosclerosis was assessed by B-mode ultrasonography in hyperlipidemic patients with early carotid lesions and without known coronary heart disease at baseline. In this double-blind, controlled clinical trial, 919 patients were randomized in a 2 x 2 factorial design to placebo, lovastatin 10 mg to 40 mg daily and/or warfarin. Ultrasonograms of the carotid walls were used to determine the change per patient from baseline to three years in mean maximum intimal-medial thickness (IMT) of 12 measured segments. There was a significant regression of carotid lesions in patients receiving lovastatin alone compared to those receiving placebo alone ($p=0.001$). The predictive value of changes in IMT for stroke has not yet been established. In the lovastatin group there was a significant reduction in the number of patients with major cardiovascular events relative to the placebo group (5 vs. 14) and a significant reduction in all-cause mortality (1 vs. 8).

Eye

There was a high prevalence of baseline lenticular opacities in the patient population included in the early clinical trials with lovastatin. During these trials the appearance of new opacities was noted in both the lovastatin and placebo groups. There was no clinically significant change in visual acuity in the patients who had new opacities reported nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity.

A three-year, double-blind, placebo-controlled study in hypercholesterolemic patients to assess the effect of lovastatin on the human lens demonstrated that there were no clinically or statistically significant differences between the lovastatin and placebo groups in the incidence, type or progression of lenticular opacities. There are no controlled clinical data assessing the lens available for treatment beyond three years.

Clinical Studies in Adolescent Patients

Efficacy of Lovastatin in Adolescent Boys with Heterozygous Familial Hypercholesterolemia

In a double-blind, placebo-controlled study, 132 boys 10 to 17 years of age (mean age 12.7 yrs) with heterozygous familial hypercholesterolemia (heFH) were randomized to lovastatin (n=67) or placebo (n=65) for 48 weeks. Inclusion in the study required a baseline LDL-C level between 189 mg/dL and 500 mg/dL and at least one parent with an LDL-C level > 189 mg/dL. The mean baseline LDL-C value was 253.1 mg/dL (range: 171 mg/dL to 379 mg/dL) in the lovastatin group compared to 248.2 mg/dL (range: 158.5 mg/dL to 413.5 mg/dL) in the placebo group. The dosage of lovastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter.

Lovastatin significantly decreased plasma levels of total-C, LDL-C and apolipoprotein B (see Table 5).

Table 5: Lipid-lowering Effects of Lovastatin in Adolescent Boys with Heterozygous Familial Hypercholesterolemia (Mean Percent Change from Baseline at Week 48 in Intention-to-Treat Population)

*
data presented as median percent changes

DOSAGE

N

TOTAL-C

LDL-C

HDL-C

TG*

Apolipoprotein B

Placebo

61

-1.1

-1.4

-2.2

-1.4

-4.4

Lovastatin

64

-19.3

-24.2

+1.1

-1.9

-21

The mean achieved LDL-C value was 190.9 mg/dL (range: 108 mg/dL to 336 mg/dL) in the lovastatin group compared to 244.8 mg/dL (range: 135 mg/dL to 404 mg/dL) in the placebo group.

Efficacy of Lovastatin in Post-Menarchal Girls with Heterozygous Familial Hypercholesterolemia

In a double-blind, placebo-controlled study, 54 girls 10 to 17 years of age who were at least 1 year post-menarche with heFH were randomized to lovastatin (n=35) or placebo (n=19) for 24 weeks. Inclusion in the study required a baseline LDL-C level of 160 mg/dL to 400 mg/dL and a parental history of familial hypercholesterolemia. The mean baseline LDL-C value was 218.3 mg/dL (range: 136.3 mg/dL to 363.7 mg/dL) in the lovastatin group compared to 198.8 mg/dL (range: 151.1 mg/dL to 283.1 mg/dL) in the placebo group. The dosage of lovastatin (once daily in the evening) was 20 mg for the first 4 weeks, and 40 mg thereafter.

Lovastatin significantly decreased plasma levels of total-C, LDL-C, and apolipoprotein B (see Table 6).

Table 6: Lipid-lowering Effects of Lovastatin in Post-Menarchal Girls with Heterozygous Familial Hypercholesterolemia (Mean Percent Change from Baseline at Week 24 in Intention-to-Treat

Population)

*

data presented as median percent changes

DOSAGE

N

TOTAL-C

LDL-C

HDL-C

TG*

Apolipoprotein B

Placebo

18

+3.6

+2.5

+4.8

-3.0

+6.4

Lovastatin

35

-22.4

-29.2

+2.4

-22.7

-24.4

The mean achieved LDL-C value was 154.5 mg/dL (range: 82 mg/dL to 286 mg/dL) in the lovastatin group compared to 203.5 mg/dL (range: 135 mg/dL to 304 mg/dL) in the placebo group.

The safety and efficacy of doses above 40 mg daily have not been studied in children. The long-term efficacy of lovastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

INDICATIONS AND USAGE

Therapy with lovastatin tablets USP should be a component of multiple risk factor intervention in those individuals with dyslipidemia at risk for atherosclerotic vascular disease. Lovastatin tablets USP should be used in addition to a diet restricted in saturated fat and cholesterol as part of a treatment strategy to lower total-C and LDL-C to target levels when the response to diet and other nonpharmacological measures alone has been inadequate to reduce risk.

Primary Prevention of Coronary Heart Disease

In individuals without symptomatic cardiovascular disease, average to moderately elevated total-C and LDL-C, and below average HDL-C, lovastatin tablets USP are indicated to reduce the risk of:

- Myocardial infarction

- Unstable angina

- Coronary revascularization procedures

(See CLINICAL PHARMACOLOGY, Clinical Studies)

Coronary Heart Disease

Lovastatin tablets USP are indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total-C and LDL-C to target levels.

Hypercholesterolemia

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lovastatin tablets USP are indicated as an adjunct to diet for the reduction of elevated total-C and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb2), when the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.

2Classification of Hyperlipoproteinemias

Lipid Elevations

Type

Lipoproteins Elevated

Major

Minor

I

chylomicrons

TG

↑→C

IIa

LDL

C

–

IIb

LDL, VLDL

C

TG

III (rare)

IDL

C/TG

–

IV

VLDL

TG

↑→C

V (rare)

chylomicrons, VLDL

TG

↑→C

IDL = intermediate-density lipoprotein.

Adolescent Patients with Heterozygous Familial Hypercholesterolemia

Lovastatin tablets USP are indicated as an adjunct to diet to reduce total-C, LDL-C and apolipoprotein B levels in adolescent boys and girls who are at least one year post-menarche, 10 to 17 years of age, with heFH if after an adequate trial of diet therapy the following findings are present:

1. LDL-C remains >189 mg/dL or

2. LDL-C remains >160 mg/dL and:

•there is a positive family history of premature cardiovascular disease or

•

two or more other CVD risk factors are present in the adolescent patients
General Recommendations

Prior to initiating therapy with lovastatin tablets USP, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = total-C - [0.2 x (TG) + HDL-C]

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, lovastatin tablets USP are not indicated.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

CHD, coronary heart disease
Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category

LDL Goal
(mg/dL)

LDL Level at Which to Initiate Therapeutic Lifestyle Changes
(mg/dL)

LDL Level at Which to Consider Drug Therapy
(mg/dL)

CHD*or CHD risk equivalents
(10-year risk >20%)

<100

≥100

≥130
(100-129: drug optional)†

2+ Risk factors
(10-year risk ≤20%)

<130

≥130

10-year risk 10-20%: ≥130
10-year risk <10%: ≥160

0-1 Risk factor

<160

≥160

≥190
(160-189: LDL-lowering drug optional)

After the LDL-C goal has been achieved, if the TG is still >200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is >130 mg/dL (see NCEP Guidelines above).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy.

Although lovastatin tablets USP may be useful to reduce elevated LDL-C levels in patients with combined hypercholesterolemia and hypertriglyceridemia where hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL or IDL (i.e., hyperlipoproteinemia types I, III, IV, or V).2

2 Classification of Hyperlipoproteinemias

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category

Total-C (mg/dL)

LDL-C (mg/dL)

Acceptable

<170

<110

Borderline

170 to 199

110 to 129

High

≥200

≥130

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Concomitant administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and cobicistat-containing products) (see WARNINGS, Myopathy/Rhabdomyolysis).

Pregnancy and Lactation

(See PRECAUTIONS, Pregnancy and Nursing Mothers).

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as lovastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, lovastatin is contraindicated during pregnancy and in nursing mothers. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy).

WARNINGS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

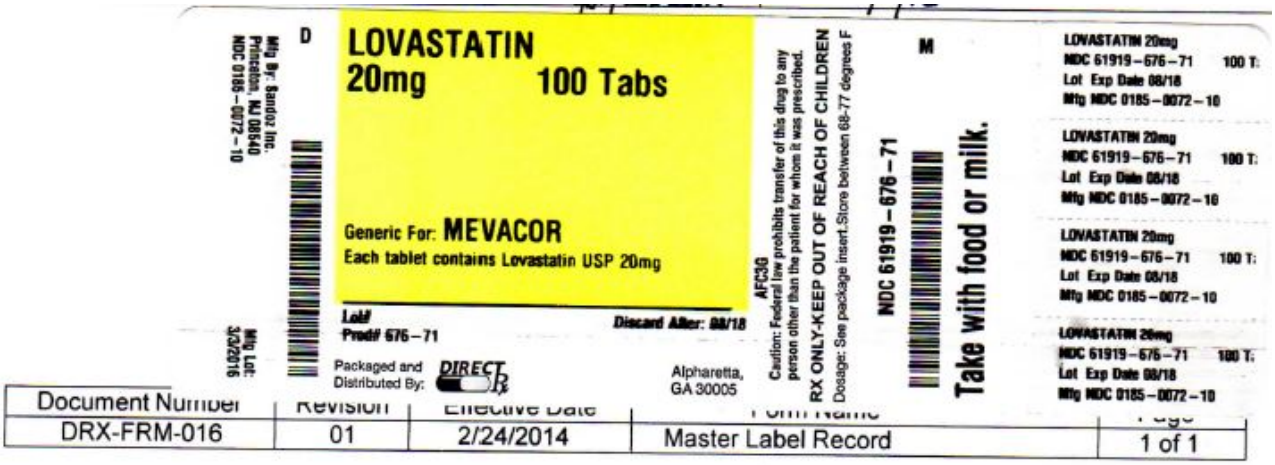
Concomitant administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and cobicistat-containing products) (see WARNINGS, Myopathy/Rhabdomyolysis).

Pregnancy and Lactation

(See PRECAUTIONS, Pregnancy and Nursing Mothers).

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as lovastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, lovastatin is contraindicated during pregnancy and in nursing mothers. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy).

PACKAGE LABEL DISPLAY PANEL.



LOVASTATIN

lovastatin tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-676(NDC:0185-0072)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LOVASTATIN (UNII: 9LHU78OQFD) (LOVASTATIN - UNII:9LHU78OQFD)	LOVASTATIN	20 mg

Inactive Ingredients	
Ingredient Name	**Strength**
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics			
Color	blue	**Score**	no score
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	E;72
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**

1	NDC:61919-676-71	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/03/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075636	03/03/2016	

Labeler - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	repack(61919-676)

Revised: 1/2020 DIRECT RX