LIPOSTAT®

Pravastatin Sodium

TABLETS

Lipostat tablets for oral administration providing 10 mg, 20 mg, 40 mg, or 80 mg pravastatin sodium. Inactive ingredients: microcrystalline cellulose, lactose, magnesium oxide, magnesium stearate, povidone, and croscarmellose sodium.

INDICATIONS AND USAGE

Therapy with **LIPOSTAT** should be considered a component of multiple risk factor intervention in those individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia.

LIPOSTAT should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures alone has been inadequate(see Guidelines below).

Prevention of Coronary Heart Disease: In hypercholesterolemic patients without clinically evident coronary heart disease, **LIPOSTAT** is indicated as an adjunct to diet to reduce the risk of fatal and non-fatal myocardial infarction, need for myocardial revascularization procedures, and to improve survival by reducing cardiovascular deaths.

Coronary Artery Disease: In patients with a history of either a myocardial infarction or unstable angina pectoris, LIPOSTAT is indicated to reduce the risk for total mortality, CHD death, recurrent coronary event (including myocardial infarction), need for myocardial revascularization procedures, and need for hospitalization.

Cerebrovascular Disease: In patients with a history of coronary artery disease [i.e., either a myocardial infarction or unstable angina pectoris], **LIPOSTAT** is indicated to reduce the risk of stroke or transient ischemic attacks (TIAs).

Atherosclerotic Disease Progression and Clinical Cardiovascular Events:

In hypercholesterolemic patients with atherosclerotic cardiovascular disease, **LIPOSTAT** is indicated as an adjunct to diet to slow the progressive course of atherosclerosis and reduce the incidence of clinical cardiovascular events.

Cardiac and Renal Transplantation: In patients receiving immunosuppressive therapy following solid organ transplantation, **LIPOSTAT** is indicated to improve survival in cardiac transplant patients and to reduce the risk of acute rejection in kidney transplant patients.

Hyperlipidemia & Dyslipidemia: LIPOSTAT is indicated for the reduction of elevated total-cholesterol, LDL-cholesterol, apolipoprotein B and triglyceride levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia.

In Children and Adolescent Patients (8-18 years of age): LIPOSTAT is indicated as an adjunct to diet and lifestyle modification for the treatment of heterozygous familial hypercholesterolemia.

Prior to initiating therapy with **LIPOSTAT**, secondary causes for hypercholesterolemia (e.g., obesity, 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 triglycerides (TG) less than 400 mg/dL, LDL-C can be estimated using the following equation:

LDL-C = Total-C - HDL-C - 1/5 TG

For TG levels >400 mg/dL, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. Periodic lipid determinations should be performed and dosage adjusted according to the patient's response to therapy.

The National Cholesterol Education Program's Treatment Guidelines are summarized below:

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[a] or CHD risk equivalents (10-year risk > 20%)	< 100	≥ 100	≥ 130 (100-129: drug optional)[b]
2+ Risk factors (10-year risk ≤ 20%)	< 130	≥ 130	10-year risk 10%-20%: ≥ 130 10-year risk < 10%: ≥ 160[c]
0 -1 Risk factor[c]	< 160	≥ 160	≥ 190 (160-189: LDL-lowering drug optional)

a CHD, coronary heart disease

b 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.

c Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

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.

ATP III Classification of LDL, Total and HDL Cholesterol (mg/ dL)

LDL Cholesterol	
< 100	Optimal
100 - 129	Near optimal/ above optimal
130 - 159	Borderline high
160 - 189	High
190 or more	Very high
Total Cholesterol	
< 200	Desirable
200 - 239	Borderline high
240 or more	High
HDL Cholesterol	
< 40	Low
> 60	High

From: NATIONAL INSTITUTE OF HEALTH (USA)
Third Report of the National Cholesterol Education Program (NCEP)
Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) May 2001.

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 - 199	110 - 129
High	>199	> 129

As with other lipid-lowering therapy, LIPOSTAT is not indicated when hypercholesterolemia is due to hyperalphalipoproteinemia (elevated HDL-C).

DOSAGE AND ADMINISTRATION

Prior to initiating LIPOSTAT, the patient should be placed on a standard cholesterol-lowering diet which should be continued during treatment.

For adults and adolescents (14 years and older), the recommended starting dose is 40 mg once daily. For adults, if 40 mg does not achieve desired cholesterol levels, 80 mg once daily may be considered. Once daily administration in the evening appears to be marginally more effective than once daily administration in the morning. **LIPOSTAT** may be taken without regard to meals.

The recommended dosage in children (8-13 years of age) is 20 mg once a day.

For patients with renal or hepatic impairment, a lower starting dose should be considered.

Since the maximal effect of a given dose is seen within four weeks, periodic lipid determinations should be performed at this time and dosage adjusted according to the patient's response to therapy and established treatment guidelines. The recommended dosage range is 10 to 80 mg administered once a day. **LIPOSTAT** may be given in divided doses.

In patients taking cyclosporine, with or without other immunosuppressive drugs, concomitantly with pravastatin, therapy should be initiated with 10-20 mg per day and titration to higher doses should be performed with caution. Most patients treated with this combination received a maximum pravastatin dose of 20 mg/day.

CONCOMITANT THERAPY

Some patients may require combination therapy with one or more lipid-lowering agents. Pharmacokinetic interaction studies with pravastatin administered concurrently with nicotinic acid, probucol, and gemfibrozil (see PRECAUTIONS, Skeletal Muscle) did not demonstrate any statistically significant alterations in the bioavailability of pravastatin.

The lipid-lowering effects of **LIPOSTAT** on total and LDL cholesterol are enhanced when combined with a bile acid-binding resin. When administering a bile acid-binding resin (e.g., cholestyramine, colestipol) and pravastatin, **LIPOSTAT** should be given either one hour or more before or at least four hours following the resin.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication, active liver disease or unexplained persistent elevations of serum transaminases.

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to a pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. Women of childbearing potential **LIPOSTAT** should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient again apprised of the potential hazard to the fetus.

PRECAUTIONS

General

HMG-CoA reductase inhibitors have been associated with biochemical abnormalities of liver function. As with other lipid-lowering agents, including nonabsorbable bile acid-binding resins, increases in liver enzymes to less than three times the upper limit of normal have occurred during therapy with pravastatin. The significance of these changes, which usually appear during the first few months of treatment initiation, is not known. In the majority of patients treated with pravastatin in clinical trials, these increased values declined to pretreatment levels despite continuation of therapy at the same dose.

Marked persistent increases (greater than three times the upper limit of normal) in serum transaminases were seen in 6 out 1136 (0.5%) patients treated with pravastatin in clinical trials. These elevations were not associated with clinical signs and symptoms of liver disease and usually declined to pretreatment levels upon discontinuation of therapy. Only two patients had persistent abnormalities possibly attributable to therapy.

As with other lipid-lowering agents, liver function tests should be performed periodically.

Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) equal or exceed three times the upper limit of normal and persist, therapy should be discontinued.

Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion.

Skeletal Muscle. Myalgia, myopathy, and rhabdomyolysis have been reported with the use of HMG-CoA reductase inhibitors. Uncomplicated myalgia has rarely been reported in pravastatin-treated patients with an incidence similar to placebo. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine kinase (CK) values to greater than 10 times the upper limit of normal, was reported to be possibly due to pravastatin in <0.1% of patients in clinical trials. Rhabdomyolysis with renal dysfunction,

secondary to myoglobinuria has also very rarely been reported with pravastatin. However, myopathy should be considered in any patients with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness. Pravastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is suspected or diagnosed.

The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either fibrates, cyclosporine, erythromycin or niacin. The use of fibrates alone is occasionally associated with myopathy. In a limited size clinical trial of combined therapy with pravastatin (40 mg/day) and gemfibrozil (1200 mg/day) myopathy was not reported, although a trend towards CK elevations and musculoskeletal symptoms was seen. The combined use of pravastatin and fibrates should generally be avoided.

Myopathy has not been observed in clinical trials involving a total of 100 post-transplant patients (76 cardiac and 24 renal) treated concurrently for up to 2 years with pravastatin (10-40 mg) and cyclosporine, some of whom also received other immunosuppressants. Further, in clinical trials involving small numbers of patients treated with pravastatin, together with niacin, there were no reports of myopathy.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported, that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Drug Interactions

Antipyrine - Clearance of antipyrine by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) that are metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol - When pravastatin was administered one hour before or four hours after cholestyramine or one hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect of pravastatin. Concomitant administration resulted in an

approximately 40 to 50% decrease in the mean AUC of pravastatin (see Concomitant Therapy, DOSAGE AND ADMINISTRATION).

Cyclosporine - Some investigators have measured cyclosporine plasma levels in patients on pravastatin (up to 20 mg), and to date, these results indicate no clinically meaningful elevations in cyclosporine levels. In one single-dose study, pravastatin plasma levels were found to be increased in cardiac transplant patients receiving cyclosporine.

Gemfibrozil – In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax and T_{max} for the pravastatin metabolite SQ31, 906. Combination therapy with pravastatin and gemfibrozil is generally not recommended. (See PRECAUTIONS: General: Skeletal Muscle.)

Warfarin - Bioavailability parameters at steady state for pravastatin were not altered following concomitant administration with warfarin. Pravastatin did not alter the plasma protein-binding of warfarin. Chronic dosing of the two drugs did not produce any changes in the anticoagulant action of warfarin (i.e., no increase was seen in mean prothrombin time after six days of concomitant therapy) with 40 mg pravastatin daily.

Other Drugs - Unlike most other HMG-CoA reductase inhibitors, pravastatin is not significantly metabolized by cytochrome P450 3A4. Plasma levels of pravastatin in vivo were not elevated when cytochrome P450 3A4 was inhibited by agents such as itraconazole, diltiazem or verapamil.

In interaction studies with aspirin, antacids (one hour prior to LIPOSTAT), cimetidine, gemfibrozil, nicotinic acid or probucol, no statistically significant differences in bioavailability of pravastatin were seen when **LIPOSTAT** was administered.

During clinical trial, no noticeable drug interactions were reported when LIPOSTAT was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 22-month oral study in mice, with pravastatin doses of 10 to 100 mg/kg daily did not demonstrate any carcinogenic potential. In a 2-year study in mice fed pravastatin at doses of 250 and

500 mg/kg/day (approximately 155 times the maximum human mg/kg dose), there was a statistically significant increase in the incidence of hepatocellular carcinomas in males and females at both doses. At these doses, lung adenomas in females were also significantly increased. In a 2-year oral study in rats, a statistically significant increase in the incidence of hepatocellular carcinomas was observed in male rats given 100 mg/kg daily (approximately 60 times the maximum human mg/kg dose) of pravastatin. This change was not seen in male rats given 40 mg/kg daily (25 times the maximum human mg/kg dose) or less, or in female rats at any dose level.

In six genetic toxicology studies performed with pravastatin, there was no evidence of mutagenic potential at the chromosomal or gene level.

In a study in rats, with daily doses as high as 500 mg/kg (approximately 310 times the maximum human mg/kg dose), pravastatin did not produce any adverse effects on fertility or general reproductive performance.

Pregnancy

See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Although pravastatin was not teratogenic in rats at doses as high as 1000 mg/kg daily nor in rabbits at doses of up to 50 mg/kg daily, LIPOSTAT should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking LIPOSTAT, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers

A negligible amount of pravastatin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, if the mother is being treated with **LIPOSTAT**, nursing should be discontinued.

Pediatric Use

Safety and efficacy in children and adolescents from 8-18 years of age has been established in an adequate and well-controlled study. There are insufficient clinical data to recommend use in children less than 8 years old

Geriatric Use

Among 6,593 patients who received pravastatin in two placebo-controlled secondary prevention trials (CARE and LIPID), no overall differences in efficacy or safety were observed between older patients (65 years or older, n=2,439) and younger patients.

ADVERSE CLINICAL EVENTS

LIPOSTAT is generally well tolerated. Adverse events, both clinical and laboratory, are usually mild and transient. In all clinical studies (controlled and uncontrolled), approximately 2% of patients were discontinued from treatment due to adverse experiences attributable to LIPOSTAT.

The safety and tolerability of pravastatin at a dose of 80 mg in two controlled trials, with a mean exposure of 8.6 months was similar to that of pravastatin at lower doses.

Short Term Trials

All adverse clinical events (regardless of attribution) reported in greater than 2% of patients in placebo-controlled studies of up to four months duration are presented in the following table:

ADVERSE CLINICAL EVENTS REPORTED IN PRAVASTATIN-TREATED PATIENTS
PERCENTAGE OF TOTAL POPULATION TREATED

	LIPOSTAT (N = 900) %	Placebo (N = 411) %
Gastrointestinal		
Nausea/Vomiting	7.3	7.1
Diarrhea	6.2	5.6
Constipation	6.0	7.1
Abdominal Pain	5.4	6.9
Flatulence	3.3	3.6
Musculoskeletal		
Musculoskeletal Pain (Localized)	10.0	9.0
Myalgia	2.7	1.0
Respiratory		
Common Cold	7.0	6.3
Rhinitis	4.0	4.1
Nervous System		
Headache	6.2	3.9
Dizziness	3.3	3.2
General		
Fatigue	3.8	3.4
Chest Pain (noncardiac)	3.7	1.9
Dermatologic		
Rash	4.0 *	1.1
Cardiovascular		
Chest Pain	4.0	3.4

* Statistically significantly different from placebo.

Long Term Morbidity and Mortality Trials

In seven randomized double blind placebo-controlled trials involving over 21,400 patients treated with pravastatin (N=10,764) or placebo (N=10,719), the safety and tolerability in the pravastatin group was comparable to that of the placebo group. Over 19,000 patients were followed for a median of 4.8-5.9 years, while the remaining patients were followed for two years or more. Collectively, these seven trials represent 47,613 patient-years of exposure to pravastatin. Adverse drug experiences of probable, possible or uncertain relationship to therapy, occurring in at least 1% of patients treated with pravastatin in seven long-term morbidity/mortality trials are shown in the table below:

INCIDENCE OF ADVERSE DRUG EXPERIENCES REPORTED IN PRAVASTATIN AND PLACEBO TREATED PATIENTS IN LONG-TERM MORBIDITY AND MORTALITY TRIALS

	Pravastatin N=10,764 (%)	Placebo N=10,719 (%)
CARDIOVASCULAR		
Angina Pectoris	3.1	3.4
DERMATOLOGIC		
Rash	2.1	2.2
GASTROINTESTINAL		
Dyspepsia/heartburn	3.5	3.7
Abdominal pain	2.4	2.5
Nausea/vomiting	1.6	1.6
Flatulence	1.2	1.1
Constipation	1.2	1.3
GENERAL		
Fatigue	3.4	3.3
Chest pain	2.6	2.6
MUSCULOSKELETAL		
Musculoskeletal pain (includes arthralgia)	6.0	5.8
Muscle cramp	2.0	1.8
Myalgia	1.4	1.4
NERVOUS SYSTEM		
Dizziness	2.2	2.1
Headache	1.9	1.8
Sleep disturbance	1.0	0.9
Depression	1.0	1.0
Anxiety/nervousness	1.0	1.2
RENAL/GENITOURINARY		
Abnormality urination (includes dysuria, frequency, nocturia)	1.0	0.8
RESPIRATORY		
Dyspnea	1.6	1.6
Upper respiratory infection	1.3	1.3
Cough	1.0	1.0
SPECIAL SENSES		
Vision disturbance (includes blurred vision, diplopia)	1.6	1.3

In addition, the following adverse drug experiences occurred with an overall incidence of <1.0% in the combined clinical trials, and have also been reported with other drugs in this class. These ADEs occurred with a similar frequency in both treatment groups. The numbers in parentheses refer to the incidence (%) in pravastatin and placebo treated patients, respectively:

Dermatologic: pruritus (0.9 vs. 1.0); dermatitis (0.4 vs. 0.5); dryness skin (0.2 vs. 0.1); scalp/hair abnormality, including alopecia (0.1 vs. 0.1); urticaria (0.1 vs. 0.1);

Endocrine/Metabolic: sexual dysfunction (0.7 vs. 0.7), libido change (0.3 vs. 0.3);

Gastrointestinal: decreased appetite (0.3 vs. 0.3);

General: fever (0.2 vs. 0.2), flushing (0.1 vs. 0.1);

Immunologic: allergy (0.1 vs. 0.1), edema head/neck (0.1 vs. 0.1);

Musculoskeletal: muscle weakness (0.1 vs. <0.1);

Nervous System: paresthesia (0.9 vs. 0.9); vertigo (0.4 vs. 0.4); insomnia (0.3 vs. 0.2); memory impairment (0.3 vs. 0.3); tremor (0.1 vs. 0.1); neuropathy, including peripheral neuropathy (0.1 vs. 0.1);

Special Senses: lens opacity (0.5 vs. 0.4), taste disturbance (0.1 vs. 0.1).

These events have also been reported during postmarketing experience with LIPOSTAT.

Postmarketing Experience

In addition to the events listed above, the following adverse events have been reported very rarely from worldwide postmarketing experience: angioedema, jaundice (including cholestatic), hepatitis and fulminant hepatic necrosis, lupus erythematous-like syndrome, pancreatitis and thrombocytopenia. A causal association with **LIPOSTAT** has not been established for these events. LFT abnormalities have also been reported.

Lens

In 820 patients treated with **LIPOSTAT** for periods up to a year or more, there was no evidence that **LIPOSTAT** was associated with cataract formation. In extensions of the placebo controlled short term trials, 294 patients (92 on placebo/control, 202 on LIPOSTAT) were evaluated using the Lens Opacity Classification (a sophisticated method of lens assessment) at six months and one year following the initiation of treatment. When compared with the baseline evaluation, the final examination revealed the following:

	LIPOSTAT Number of patients (%)	Placebo/Control Number of patients (%)
Improved	29 (14%)	13 (14%)
No change	142 (70%)	63 (68%)
Worsened	31 (15%)	16 (17%)
Total	202	92

There was no statistically significant difference in the change in lens opacity between the control and pravastatin treatment groups during this time interval.

Comparative data indicate that pravastatin is 100-fold less potent than both lovastatin and simvastatin (other HMG-CoA reductase inhibitors) inhibiting cholesterol biosynthesis in rat lens and 40-fold less potent than lovastatin in inhibiting cholesterol biosynthesis in rabbit lens. Furthermore, unlike lovastatin, cataracts have not been observed in animal studies (beagle dogs) when chronic oral doses of pravastatin from 15 to 125 times the maximum recommended human dose were administered for two years.

Laboratory Abnormalities

Increases in serum transaminases and in creatine kinase (CK, CPK) in patients treated with LIPOSTAT have been discussed (see PRECAUTIONS).

Concomitant Therapy

Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, and probucol. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myositis has been reported with the combination of gemfibrozil (Lopid®) and lovastatin (see PRECAUTIONS).

OVERDOSAGE

There is limited experience with overdose of pravastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures instituted as required.

PHARMACOLOGY

Uses

LIPOSTAT (Pravastatin Sodium) designated chemically as [1S-[1α(βS*,δS*)2α,6α, 8β(R*),8aα]]-1,2,6,7,8,8a-hexahyro-β,δ,6-trihydroxy-1-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthaleneheptanoic acid, monosodium salt, is one of a new class of lipid-lowering compounds, the HMG-CoA reductase inhibitors, that reduce cholesterol biosynthesis. These agents are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate.

Actions

PRAVASTATIN produces its lipid-lowering effect in two ways: First, as a consequence of its reversible inhibition of HMG-CoA reductase activity, it effects modest reductions in intracellular pools of cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL. Second, pravastatin inhibits LDL production by inhibiting hepatic synthesis of VLDL, the LDL precursor. In vitro and animal studies have shown that pravastatin, a hydrophilic HMG-CoA reductase inhibitor, is tissue selective such that inhibitory activity is highest in those tissues with the highest rates of cholesterol synthesis, such as the liver and ileum. Unlike other HMG-CoA reductase inhibitors, pravastatin has less effect on cholesterol synthesis in other tissues. In animal studies, pravastatin was not detected in the cerebrospinal fluid.

Clinical and pathologic studies have shown that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (a membrane transport complex for LDL) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C. In multicenter clinical trials those pharmacologic and/or non-pharmacologic interventions that lowered Total-C and LDL-C and increased HDL-C reduced the rate of cardiovascular events (both fatal and nonfatal myocardial infarctions) and improved survival. In both normal volunteers and patients with hypercholesterolemia, treatment with pravastatin reduced Total-C, LDL-C, apolipoprotein B, VLDL-C and TG while increasing HDL-C and apolipoprotein A. In epidemiologic studies, higher levels of high sensitivity C-reactive protein (hs-CRP), a marker of inflammation, were associated with an increased risk of a subsequent cardiovascular event in apparently healthy subjects as well as in patients with coronary heart disease (CHD). Pravastatin treatment reduced hs-CRP levels in a long-term study of patients with CHD. (See Clinical Studies.) Pravastatin reduced the adverse effect the level of Lp(a) or fibrinogen, which are known independent biochemical risk markers for coronary heart disease. In controlled trials in patients with moderate hypercholesterolemia with or without atherosclerotic cardiovascular disease, pravastatin monotherapy reduced the progression of atherosclerosis, and cardiovascular events (eg., fatal and non-fatal MI) or death.

Pharmacokinetics

LIPOSTAT is administered orally in the active form. It is rapidly absorbed, with peak plasma levels attained 1 to 1.5 hours following ingestion. Based on urinary recovery of radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. While the presence of food in the gastrointestinal tract reduces systemic bioavailability, the lipid-lowering effects of the drug are similar whether taken with or without food.

Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio=0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance. In vitro studies demonstrated that pravastatin is transported into hepatocytes with substantially less uptake into other cells. In view of pravastatin's extensive hepatic uptake and metabolism, plasma levels are of limited value in predicting lipid-lowering efficacy. Pravastatin plasma concentrations including, area under the concentration-time curve (AUC), peak (C_{max}), and steady-state minimum (C_{min}) are directly proportional to administered dose. Pravastatin administered once daily at bedtime was more effective than after a morning dose despite a lower systemic bioavailability. Steady-state AUCs, C_{max} and Cmin plasma concentrations showed no evidence of drug accumulation following once or twice daily administration of **LIPOSTAT** tablets. Approximately 50% of the circulating drug is bound to plasma proteins.

Mean pravastatin Cmax and AUC values for pediatric subjects pooled across age and gender were similar to those values observed in adults after a 20 mg oral dose.

The plasma elimination half-life ($T_{1/2}$) of pravastatin (oral) is between 1.5 and 2 hours. Approximately 20% of a radiolabeled oral dose is excreted in urine and 70% in the feces. After intravenous administration of radiolabeled pravastatin to normal volunteers, approximately 47% of total body clearance was via renal excretion and 53% by nonrenal routes (i.e., biliary excretion and biotransformation). Accumulation of drug and/or metabolites may occur in patients with renal or hepatic insufficiency, although, as there are dual routes of elimination, the potential exists for compensatory excretion by the alternate route. The major degradation product of pravastatin is the 3-α-hydroxy isomeric metabolite. This metabolite has one-tenth to one-fortieth the HMG-CoA reductase inhibitory activity of the parent compound.

Clinical Studies

LIPOSTAT is highly effective in reducing Total-C, LDL-C, TG in patients with heterozygous familial combined, nonfamilial (non-FH) forms of hypercholesterolemia, and mixed dyslipidemia. A therapeutic response is seen within 1 week, and the maximum response usually is achieved within 4 weeks. This response was maintained during extended periods of therapy.

A single daily dose administered in the evening is as effective as the same total daily dose given twice a day. Once daily administration in the evening appears to be marginally more effective than once daily administration in the morning, perhaps because hepatic cholesterol is synthesized mainly at night.

In multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin significantly decreased Total-C, LDL-C, and Total-C/HDL-C and LDL-C/HDL-C ratios, decreased VLDL-C and plasma TG levels, and increased HDL-C. Whether administered once or twice daily, a clear dose-response relationship (i.e., lipid-lowering) was seen by 1 to 2 weeks following the initiation of treatment.

Primary Hypercholesterolemia Study Dose Response of LIPOSTAT® Once Daily Administration At Bedtime

Dose	Total-C	LDL-C	HDL-C	TG
5 mg	-14%	-19%	+ 5%	-14%
10 mg	-16%	-22%	+ 7%	-15%
20 mg	-24%	-32%	+ 2%	-11%
40 mg	-25%	-34%	+12%	-24%

In a pooled analysis of two multicenter, double-blind, placebo-controlled studies in patients with primary hypercholesterolemia, treatment with pravastatin at a daily dose of 80 mg increased HDL-C and significantly decreased Total-C, LDL-C, and TG from baseline after 6 weeks. The efficacy results of the individual studies were consistent with the pooled data. Mean percent changes from baseline after 6 weeks of treatment were: Total-C (-27%), LDL-C (-37%), HDL-C (+3%) and TG (-19%).

Prevention of Coronary Heart Disease: LIPOSTAT is effective in reducing the risk of coronary heart disease (CHD) death (fatal MI and sudden death) plus non-fatal MI and improving survival in hypercholesterolemic patients without previous myocardial infarction.

The West of Scotland Study (WOS) was a randomized, double-blind, placebo-controlled trial among 6595 male patients (45-66 years) with moderate to severe hypercholesterolemia (LDL-C=156-254 mg/dL [4-6.6 mmol/L]), and without a previous MI. Patients were treated with standard care, including dietary advice, and either pravastatin (N=3302) or placebo (N=3293) for a median duration of 4.8 years. The study was designed to assess the effect of pravastatin on fatal and non-fatal coronary heart disease (CHD). Pravastatin significantly reduced the risk of CHD death plus non-fatal MI by 31% (p=0.0001). The effect on these cumulative cardiovascular event rates was evident as early as 6 months of treatment. This reduction was similar and significant throughout the entire range of LDL-C entered levels and age groups studied. A significant reduction of 32% (p=0.03) in total cardiovascular deaths was observed. When adjusted for baseline risk factors, a 24% (p=0.039) reduction in overall mortality was also observed among patients treated with pravastatin.

There was no statistically significant difference between treatment groups in non-cardiovascular mortality, including cancer death. Pravastatin also decreased the risk for undergoing myocardial revascularization procedures (coronary artery bypass graft surgery or coronary angioplasty) by 37% (p=0.009) and coronary angiography by 31% (p=0.007).

Cardiovascular Disease: LIPOSTAT is effective in reducing the risk for total mortality, CHD death, recurrent coronary events (including myocardial infarction), frequency of stroke or transient ischemic attacks (TIA), need for myocardial revascularization procedures, and need for hospitalization in patients with a history of either myocardial infarction or unstable angina pectoris.

In the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study, the effect of pravastatin was assessed in 9014 men and women with average to elevated serum cholesterol levels (baseline Total-C=155-271 mg/dL [4.0-7.0 mmol/L]; mean Total-C=219 mg/dL [5.66 mmol/L]), and who had experienced either a myocardial infarction or had been hospitalized for unstable angina pectoris in the preceding 3-36 months. Patients with a wide range of baseline levels of triglycerides were included (≤443 mg/dL [5.0 mmol/L]) and enrollment was not restricted by baseline levels of HDL cholesterol. At baseline, 82% of patients were receiving aspirin and76% were receiving antihypertensive medication. Patients in this multicenter, double-blind, placebo-controlled study participated for a mean of 5.6 years (median=5.9 years). Treatment with pravastatin significantly reduced the risk for CHD death by 24% (p=0.0004). The risk for coronary events (either CHD death or nonfatal MI) was significantly reduced by 24% (p<0.0001) in the pravastatin treated patients. The risk for fatal or nonfatal myocardial infarction was reduced by 29% (p<0.0001). Pravastatin reduced both the risk for total mortality by 23% (p<0.0001) and cardiovascular mortality by 25% (p<0.0001). The risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) was significantly reduced by 20% (p<0.0001) in the pravastatin treated patients. Pravastatin also significantly reduced the risk for stroke by 19% (p=0.0477). Treatment with pravastatin significantly reduced the number of days of hospitalization per 100 person-years of follow-up by 15% (p<0.001). The effect of pravastatin on reducing CHD events was consistent regardless of age, gender, or diabetic status. Among patients who qualified with a history of myocardial infarction, pravastatin significantly reduced the risk for total mortality and for fatal or non-fatal MI (risk reduction for total mortality = 21%, p=0.0016; risk reduction for fatal or non-fatal MI=25%, p=0.0008). Among patients who qualified with a history of hospitalization for unstable angina pectoris, pravastatin significantly reduced the risk for total mortality and for fatal or non-fatal MI (risk reduction for total mortality = 26%, p=0.0035; risk reduction for fatal or non-fatal MI = 37%, p=0.0003).

In the Cholesterol and Recurrent Events (CARE) study the effect of pravastatin on coronary heart disease death and nonfatal MI was assessed in 4159 men and women with average (normal) serum cholesterol levels (baseline mean Total-C=209 mg/dL), and who had experienced a myocardial infarction in the preceding 3-20 months. Patients in this double-blind, placebo-controlled study participated for an average of 4.9 years. Treatment with pravastatin significantly reduced the rate of a recurrent coronary event (either CHD death or nonfatal MI) by 24% (p=0.003). The reduction in risk for this combined endpoint was significant for both men and women. The risk of undergoing revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) was significantly reduced by 27% (p<0.001) in the pravastatin treated patients. Pravastatin also significantly reduced the risk for stroke by 32% (p=0.032), and stroke or transient ischemic attack (TIA) combined by 26% (p=0.025).

In a controlled study of 782 patients within the CARE trial, pravastatin therapy appeared to reduce the adverse effects of inflammation, as evidenced by hs-CRP levels ≥.95th percentile, in patients with CHD. In the placebo group (n=438), the relative risk for recurrent coronary events was increased by 79% (p<0.05) in subjects with inflammation compared to subjects without inflammation, while for pravastatin-treated subjects (n=344) this increase was 16% (NS).

In a follow-up study, hs-CRP levels were measured at baseline and after five years in 472 CARE patients who were assigned to pravastatin treatment. Median hs-CRP levels by 37.8% and median levels by 21.6% when compared with placebo, independent of the amount of lipid lowering.

Atherosclerotic Disease Progression and Clinical Cardiovascular Events: Pravastatin monotherapy was effective in reducing both the progression of atherosclerosis and cardiovascular event rates in two controlled trials among patients with moderate hypercholesterolemia and atherosclerotic cardiovascular disease.

The Pravastatin Limitation of Atherosclerosis in the Coronary Arteries trial (PLAC I) was a 3-year, randomized, double-blind, placebo-controlled, multicenter trial involving 408 patients with moderate hypercholesterolemia (baseline mean LDL-C=163 mg/dL, Total-C=231 mg/dL) and coronary disease. Pravastatin monotherapy resulted in a significantly reduced rate of coronary artery lumen narrowing as determined by quantitative angiography, in a prospectively planned analysis of clinical events occurring from 90 days after initiating therapy to allow for maximum lipid lowering effect, treatment with pravastatin resulted in a 74% reduction in the rate of myocardial infarction (fatal and nonfatal) [p=0.006], and a 62% reduction for the combined endpoint of nonfatal myocardial infarction or all cause death [p=0.02]. For the entire study duration, myocardial infarction (fatal and non-fatal) rate was reduced by 60% [p=0.0498].

The Pravastatin Limitation of Atherosclerosis in the Carotid Arteries trial (PLAC II) was a 3-year, randomized, double-blind, placebo-controlled trial among 151 patients with moderate hypercholesterolemia (baseline mean LDL-C=164 mg/dL, Total-C=234 mg/dL), and coronary and carotid atherosclerosis. Pravastatin significantly reduced the rate of progression of atherosclerosis in the common carotid artery as measured by B-mode ultrasound. A reduction of 80% in the rate of myocardial infarction (fatal and nonfatal) [p=0.018], and a 81% reduction for the combined endpoint of nonfatal myocardial infarction or all cause death [p=0.049] were also observed among patients treated with pravastatin.

In an analysis of pooled clinical cardiovascular events from the PLAC I and PLAC II trials, treatment with pravastatin was associated with a 67% reduction in the event rates for myocardial infarction (fatal and nonfatal) [p=0.002], and a 55% reduction for the combined endpoint of nonfatal myocardial infarction or all cause death [p=0.009].

Solid Organ Transplantation: The safety and efficacy of pravastatin treatment in patients receiving immunosuppressive therapy following cardiac and kidney transplantation were assessed in two prospective, randomized controlled studies. Patients were treated concurrently with either pravastatin (20-40 mg) or no pravastatin, and a standard immunosuppressive regimen of cyclosporine and prednisone. Cardiac transplant patients also received azathioprine as part of the immunosuppressive regimen. Treatment with pravastatin significantly reduced the rate of cardiac rejection with hemodynamic compromise at one year (p=0.005), improved one-year survival (p=0.025), and lowered the risk of coronary vasculopathy in the transplant as determined by angiography and autopsy (p=0.049). In patients following kidney transplantation, pravastatin significantly reduced the incidence of biopsy-proven acute rejection episodes (p=0.01), the incidence of multiple rejections episodes (p=0.05), and the use of pulse injections of both methylprednisolone (p=0.01) and OKT3 (p=0.02). Plasma lipid levels were favorably altered by pravastatin treatment. Pravastatin was well-tolerated with no significant increases in creatine phosphokinase or hepatic transaminases. In addition, there were no reported cases of myositis or rhabdomyolysis.

Pediatric Use: A double-blind placebo-controlled study in 214 pediatric patients with heterozygous familial hypercholesterolemia was conducted over 2 years. Children (8-13 years) were randomized to placebo or 20 mg of pravastatin and the adolescents (aged 14-18 years) were randomized to placebo or 40 mg of pravastatin. There was a significant mean percent reduction in LDL-C of -22.9% and also in total cholesterol (-17.2%) from the pooled data analysis, similar to demonstrated efficacy in adults on 20 mg of pravastatin. Reductions were also observed in ApoB. In subjects receiving pravastatin, there were no differences seen in any of the monitored endocrine parameters [ACTH, cortisol, DHEAS, FSH, LH, TSH, estradiol (girls) or testosterone (boys)] relative to placebo. There were no developmental differences, testicular volume changes or Tanner score differences observed relative to placebo.

PRESENTATION

LIPOSTAT tablets for oral administration providing 10mg, 20mg or 40mg pravastatin sodium.

STORAGE

Do not store above 25° C. Keep tightly closed (protect from moisture). Protect from light.

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