PRODUCT MONOGRAPH

PrRiva PRAVASTATIN

(Pravastatin Sodium Tablets)

10, 20, and 40 mg

Lipid Metabolism Regulator

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NAME OF DRUG

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THERAPEUTIC CLASSIFICATION

Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

Riva PRAVASTATIN (Pravastatin Sodium) is one of a new class of lipid-lowering compounds known as HMG-CoA reductase inhibitors (statins) 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. Pravastatin is isolated from a strain of *Penicillium citrinum.* The active drug substance is the hydroxyacid form.

Riva 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 Low Density Lipoproteins (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 Very Low Density Lipoproteins (VLDL), the LDL precursor.

Epidemiologic and clinical investigations have associated the risk of coronary artery disease (CAD) with elevated levels of Total-C, LDL-C, and decreased levels of HDL-C. These abnormalities of lipoprotein metabolism are considered as major contributors to the development of the disease. Other factors, e.g. interactions between lipids/lipoproteins and endothelium, platelets and macrophages, have also been incriminated in the development of human atherosclerosis and of its complications.

In long-term, prospective clinical trials effective treatment of hypercholesterolemia/dyslipidemia has consistently been associated with a reduction in the risk of CAD.

Treatment with pravastatin sodium has been shown to reduce circulating Total-C, LDL-C, and apolipoprotein B, modestly reduce VLDL-C and trigylcerides (TG) while producing increases of variable magnitude in HDL-C and apolipoprotein A. Clinical trials suggest that pravastatin sodium's effect on reducing clinical events appears to incorporate both cholesterol modification and some ancillary mechanism.

Pravastatin has complex pharmacokinetic characteristics (see under PHARMACOLOGY).

A two-way, single-dose crossover comparative bioavailability study of Riva Pravastatin Tablets 40 mg, and Pravachol® Tablets 40 mg has been performed in healthy male volunteers in the fasting state. A summary of the bioavailability data is tabulated below.

Summary Table of the Comparative Bioavailability Data
Fasted Study (1 x 40 mg pravastatin)

Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratio of Geometric Means (%)	90% Confidence Intervals
	Pravastatin Tablets 40 mg	Pravachol®* 40 mg		
AUC_T (ng.h/mL)	159.739 185.267 (58.4)	157.204 183.145 (62.3)	101.61	92.77-111.30
AUC_I (ng.h/mL)	161.175 186.677 (58.2)	158.801 184.518 (61.9)	101.49	92.78-111.03
Cmax (ng/mL)	74.827 89.613 (65.4)	75.322 86.246 (61.2)	99.34	85.91-114.87
Tmax** (h)	1.13 [0.75-2.50]	1.00 [0.50-2.00]	N/A	N/A
T½*** (h)	2.24 (63.2)	2.23 (43.6)	N/A	N/A

* The reference product, Pravachol® 40 mg (manufactured by Bristol-Myers Squibb, Canada) was purchased in Canada.

**For Tmax, the median is presented with the range [min.-max.].

*** The T½ parameter is expressed as the arithmetic mean (% CV) only.

INDICATIONS AND CLINICAL USE

Therapy with lipid-altering agents should be considered a component of multiple risk factor intervention in those individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. *Riva* PRAVASTATIN (pravastatin sodium) should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other non-pharmacological measures alone has been inadequate (see NCEP Guidelines below).

Hypercholesterolemia

Riva PRAVASTATIN is indicated as an adjunct to diet [at least an equivalent of the American Heart Association (AHA) Step 1 diet] for the reduction of elevated Total and Low Density Lipoprotein Cholesterol (LDL-C) levels in patients with primary hypercholesterolemia (Types IIa and IIb), when the response to diet and other non-pharmacologic measures alone has been inadequate.

Prior to initiating therapy with *Riva* PRAVASTATIN, secondary causes for hypercholesterolemia, such as obesity, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy or alcoholism, should be excluded and it should be determined that patients for whom treatment with *Riva* PRAVASTATIN is being considered have an elevated LDL-C level as the cause for an elevated total serum cholesterol. A lipid profile should be performed to measure Total Cholesterol, High Density Lipoprotein Cholesterol (HDL-C) and Triglycerides (TG).

For patients with total triglycerides less than 4.52 mmol/L (400 mg/dL), LDL-C can be estimated using the following equation:

LDL-C (mmol/L) = Total Cholesterol - [(0.37 x triglycerides) + HDL-C]

LDL-C (mg/dL) = Total Cholesterol - [(0.16 x triglycerides) + HDL-C]

When total triglyceride levels exceed 4.52 mmol/L (400 mg/dL), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

The U.S. National Cholesterol Education Program's (NCEP) Treatment Guidelines are summarized below:

Definite Atherosclerotic Disease *	**Two or More Other Risk Factors** **	**LDL Cholesterol mmol/L (mg/dL)**	
		Drug Treatment Initiation Level	**Goal**
No	No	≥ 4.9 (≥ 190)	< 4.1 (< 160)
No	Yes	≥ 4.1 (≥ 160)	< 3.4 (< 130)
Yes	Yes or No	≥ 3.4 (≥ 130)	≤ 2.6 (≤ 100)

* Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

** Other risk factors (or coronary heart disease (CHD) include: age (males: ≥ 45 years; females: ≥ 55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C < 0.91 mmol/L (< 35 mg/dL); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥ 1.6 mmol/L (≥ 60 mg/dL).

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.

As with other lipid-lowering therapy, *Riva* PRAVASTATIN is not indicated when hypercholesterolemia is due to hyperalphalipoproteinemia (elevated HDL-C). The efficacy of pravastatin has not been evaluated in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e. hyperlipoproteinemia or dyslipoproteinemia types I, III, IV or V).

Primary Prevention of Coronary Events

In hypercholesterolemic patients without clinically evident coronary heart disease, *Riva* PRAVASTATIN is indicated to:

- Reduce the risk of myocardial infarction;
- Reduce the risk for undergoing myocardial revascularization procedures;
- Reduce the risk of total mortality by reducing cardiovascular deaths.

In the West of Scotland Study (WOS), the effect of pravastatin sodium treatment on fatal and non-fatal coronary heart disease (CHD) was assessed in 6 595 patients (aged 45 to 64 years) without a previous myocardial infarction, but with elevated LDL-C levels between 4 - 6.7 mmol/L (156-254 mg/dL). The patients were followed for a median of 4.8 years.

Pravastatin sodium significantly reduced the rate of first coronary events (either CHD death or non-fatal MI) by 31% (248 events in the placebo group [CHD death = 44, non-fatal MI = 204] vs 174 events in the pravastatin sodium group [CHD death = 31, non-fatal MI = 143], p = 0.0001). The effect of these cumulative cardiovascular event rates was evident after 6 months of treatment. The risk reduction with pravastatin sodium was similar and significant throughout the entire range of baseline LDL cholesterol levels. This reduction was also similar and significant across the age range studied with a 40% risk reduction for patients younger than 55 years and a 27% risk reduction for patients 55 years and older.

Pravastatin sodium also significantly decreased the risk for undergoing myocardial revascularization procedures (coronary artery bypass graft surgery by 37% [80 vs 51 patients, p = 0.009] and coronary angiography by 31% [128 vs 90, p = 0.007]). Cardiovascular deaths were decreased by 32% (73 vs 50, p = 0.03), and there was no increase in deaths from non-cardiovascular causes.

The West of Scotland Study excluded female patients, elderly subjects and most patients with familial hypercholesterolemia (FH). Consequently, it has not been established to what extent the findings of the WOS study can be extrapolated to these subpopulations of hypercholesterolemic patients (see HUMAN PHARMACOLOGY, Clinical Trials, Primary Prevention).

- In patients with heterozygous FH, optimal reduction in total and LDL cholesterol necessitates a combination drug therapy in the majority of patients (see SELECTED BIBLIOGRAPHY).

  (For homozygous FH see PRECAUTIONS, Use in Homozygous Familial Hypercholesterolemia).

- Because information on familial combined hyperlipidemic (FCH) patients is not available from the WOS study, the effect of pravastatin sodium in this subgroup of high risk dyslipidemic patients could not be assessed.

Secondary Prevention of Cardiovascular Events

In patients with total cholesterol in the normal to moderately elevated range who have clinically evident coronary heart disease, *Riva* PRAVASTATIN is indicated to:

- Reduce the risk of total mortality
- Reduce the risk of death due to coronary heart disease
- Reduce the risk of myocardial infarction
- Reduce the risk of undergoing myocardial revascularization procedures
- Reduce the risk of stroke and transient ischemic attack (TIA)
- Reduce total hospitalization

In the **L**ong-Term **I**ntervention with **P**ravastatin in **I**schemic **D**isease (LIPID) study, the effect of pravastatin sodium 40 mg daily was assessed in 9014 men and women with normal to elevated serum cholesterol levels (baseline Total-C = 155 - 271 mg/dL [4.0-7.0 mmol/L]; median Total-C = 218 mg/dL [5.66 mmol/L]; median LDL-C = 150 mg/dL [3.88 mmol/L]), and who had experienced either a myocardial infarction or had been hospitalized for unstable angina pectoris in the preceding 3 - 36 months.

Treatment with pravastatin sodium 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 sodium treated patients. The risk for fatal or nonfatal myocardial infarction was reduced by 29% ($p < 0.0001$). Pravastatin sodium 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 sodium treated patients. Pravastatin sodium also significantly reduced the risk for stroke by 19% ($p = 0.0477$). Treatment with pravastatin sodium significantly reduced the number of days of hospitalization per 100 person-years of follow-up by 15% ($p < 0.001$). The effect of pravastatin sodium on reducing CHD events was consistent regardless of age, gender, or diabetic status (see HUMAN PHARMACOLOGY, Clinical Trials, Secondary Prevention).

In the Cholesterol and Recurrent Events (CARE) study the effect of pravastatin sodium 40 mg daily on coronary heart disease death and nonfatal MI was assessed in 4159 men and women with normal serum cholesterol levels (baseline mean Total-C = 209 mg/dL [5.4 mmol/L]), and who had experienced a myocardial infarction in the preceding 3 - 20 months. Treatment with pravastatin sodium significantly reduced the rate of a recurrent coronary event (either CHD death or nonfatal MI) by 24% (274 patients with events [13.3%] in the placebo group vs. 212 patients [10.4%] in the pravastatin sodium group, p = 0.003). The reduction in risk for this combined endpoint was significant for both men and women; in women, the reduction in risk was 43% (p = 0.033). 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 sodium treated patients (391 [19.6%] vs 294 [14.2%] patients). Pravastatin sodium also significantly reduced the risk for stroke by 32% (p = 0.032), and stroke or transient ischemic attack (TIA) combined by 26% (124 [6.3%] vs 93 [4.7%] patients, p = 0.025) (see HUMAN PHARMACOLOGY, Clinical Trials, Secondary Prevention).

Pravastatin sodium was also found to reduce the rate of progression of atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower Total and LDL-cholesterol to target levels. In two trials including this type of patient[1] (i.e. in a secondary prevention intervention), pravastatin sodium monotherapy was shown to reduce the rate of progression of atherosclerosis as evaluated by quantitative angiography and B-mode ultrasound. This effect may be associated with an improvement in the coronary endpoints (fatal or non fatal myocardial infarction). In these trials, however, no effect was observed in all cause mortality (see HUMAN PHARMACOLOGY, Clinical Trials, Atherosclerotic Disease Progression).

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[1]Pravastatin Limitation of Atherosclerosis in the Coronary/Carotid Arteries (PLAC I and II)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations in liver function tests (see WARNINGS).

Pregnancy

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 such as *Riva* PRAVASTATIN (Pravastatin Sodium) decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, *Riva* PRAVASTATIN is contraindicated during pregnancy.

LACTATION and NURSING (see under PRECAUTIONS)

WARNINGS

Liver Dysfunction

HMG-CoA reductase inhibitors have been associated with biochemical abnormalities of liver function. As with other lipid-lowering agents, including non-absorbable 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 of 1142 (0.5%) patients treated with pravastatin in clinical trials (See ADVERSE REACTIONS). The increases usually appeared 3 to 12 months after the start of therapy with pravastatin sodium. These elevations were not associated with clinical signs and symptoms of liver disease and usually declined to pretreatment levels upon discontinuation of therapy. Patients rarely had persistent marked abnormalities possibly attributable to therapy. In the largest long-term placebo-controlled trial with pravastatin (Pravastatin Primary Prevention Study/ WOSCOPS), no patient with normal liver function after 12 weeks of treatment (N = 2875 pravastatin-treated patients) had subsequent ALT elevations greater than three times the upper limit of normal on two consecutive measurements. Two of these 2875 patients treated with pravastatin (0.07%) and one of 2 919 placebo patients (0.03%)

had elevations of AST greater than three times the upper limit of normal on two consecutive measurements during the 4.8 years (median treatment) of the study.

Liver function tests should be performed at baseline and at 12 weeks following initiation of therapy or the elevation of dose. 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 (ALAT) and aspartate aminotransferase (ASAT) equal or exceed three times the upper limit of normal and persist, therapy should be discontinued.**

Caution should be exercised when *Riva* PRAVASTATIN (Pravastatin Sodium) is administered to patients with a history of liver disease or heavy alcohol ingestion. Active liver disease or unexplained serum transaminase elevations are contraindications to the use of *Riva* PRAVASTATIN; if such condition develops during therapy, the drug should be discontinued.

Muscle Effects

Elevations of creatinine phosphokinase levels (CPK [MM fraction]), myalgia, myopathy, and rhabdomyolysis have been reported with the use of HMG-CoA reductase inhibitors, including pravastatin sodium.

Muscle weakness and rhabdomyolysis have been reported in patients receiving other HMG-CoA reductase inhibitors concomitantly with itraconozole and cyclosporine.

The benefits and risks of using HMG-CoA Reductase Inhibitors concomitantly with immunosuppressive drugs, fibrates, erythromycin, systemic azole derivative antifungal agents or lipid-lowering doses of niacin should be carefully considered.

Myalgia has been associated with pravastatin therapy. Rare cases of rhabdomyolysis associated with pravastatin (and macrocreatine kinase in one case) have been reported (see SELECTED BIBLIOGRAPHY).

Myopathy (markedly elevated CPK of greater than 10 times the upper limit of normal with myalgia) was very rarely reported in pravastatin treated 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 CPK.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness.

As with other statins, the risk of myopathy, including rhabdomyolysis, may be substantially increased by concomitant immunosuppressive therapy, including cyclosporines, and by concomitant therapy with gemfibrozil, erythromycin, or niacin (see also PRECAUTIONS).

Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with *Riva* PRAVASTATIN together with immunosupressants, fibric acid derivatives, or niacin (see HUMAN PHARMACOLOGY, Clinical Studies).

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 CPK elevations and musculoskeletal symptoms was seen. The combined use of pravastatin and fibrates should be avoided.

No information is available on the combined therapy of pravastatin with erythromycin.

Riva PRAVASTATIN therapy should be discontinued if marked elevation of CPK levels occurs or if myopathy is diagnosed or suspected.

Interruption of therapy with *Riva* PRAVASTATIN should be considered in any patient with an acute, serious condition, suggestive of a myopathy or having a risk factor predisposing to the development of renal failure or rhabdomyolysis, such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine or electrolyte disorders and uncontrolled seizures.

PRECAUTIONS

General

Before instituting therapy with *Riva* PRAVASTATIN (Pravastatin Sodium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight and obese patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). The patient should be advised to inform subsequent physicians of the prior use of *Riva* PRAVASTATIN.

Pravastatin may elevate creatine phosphokinase and transaminase levels. This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Effect on the Lens

Current data from clinical trials do not indicate an adverse effect of pravastatin on the human lens.

Homozygous Familial Hypercholesterolemia

Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. Most HMG-CoA reductase inhibitors are less or not effective in this subgroup of hypercholesterolemic patients (see SELECTED BIBLIOGRAPHY).

Effect on Lipoprotein (a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in the Lipoprotein (a) [Lp(a)] level. Further research is ongoing to elucidate the significance of Lp(a) variations. Therefore, until further experience is obtained, where feasible, it is suggested that measurements of serum Lp(a) be followed up in patients placed on pravastatin therapy (see SELECTED BIBLIOGRAPHY).

Effect on CoQ10 Levels (Ubiquinone)

A significant short-term decrease in plasma CoQ10 levels in patients treated with pravastatin sodium has been observed. Longer clinical trials have also shown reduced serum ubiquinone levels during treatment with pravastatin and other HMG-CoA reductase inhibitors. The clinical significance of a potential long-term statin-induced deficiency of CoQ10 has not yet been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY).

Carcinogenesis

A 21-month oral study in mice, with doses of 10 to 100 mg/kg daily of pravastatin did not demonstrate any carcinogenic potential. In a 2-year oral study in rats, a statistically significant increase in the incidence of hepatocellular carcinoma was observed in male rats given 100 mg/kg daily (125 times the maximum human dose) of pravastatin. This change was not seen in male rats given 40 mg/kg daily (50 times the recommended human dose) or less, or in female rats at any dose level.

Use in Pregnancy

***Riva* PRAVASTATIN is contraindicated during 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, *Riva* PRAVASTATIN should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of potential hazards. If a woman becomes pregnant while taking *Riva* PRAVASTATIN, *Riva* PRAVASTATIN 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 breast milk. Because of the potential for adverse reactions in nursing infants, if the mother is being treated with *Riva* PRAVASTATIN, nursing should be discontinued or treatment with *Riva* PRAVASTATIN stopped.

Pediatric Use

Only limited experience with the use of statins in children is available (see SELECTED BIBLIOGRAPHY). There is no experience to date with the use of pravastatin in such patients. Treatment in these patients is not recommended at this time.

Elderly

Pharmacokinetic evaluation of pravastatin in patients over the age of 65 years indicates an increased AUC. There were no reported increases in the incidence of adverse effects in these or other studies involving patients in that age group. As a precautionary measure, the lowest dose should be administered initially (see SELECTED BIBLIOGRAPHY).

Use in Patients with Impaired Renal Function

There have been no studies on the use of pravastatin in patients with renal failure. As a precautionary measure, the lowest dose should be used in these patients. (See WARNINGS, Muscle Effects).

Hypersensitivity

With lovastatin an apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocytes sedimentation rate (ESR) increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever and malaise.

Although to date hypersensitivity syndrome has not been described as such, in few instances eosinophilia and skin eruptions appear to be associated with pravastatin sodium treatment. If hypersensitivity is suspected, *Riva* PRAVASTATIN should be discontinued. Patients should be advised to report promptly any signs of hypersensitivity such as angioedema, urticaria, photosensitivity, polyarthralgia, fever, and malaise.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such could theoretically blunt adrenal and/or gonadal steroid production.

In one long-term study investigating the endocrine function in hypercholesterolemic patients, pravastatin sodium exhibited no effect upon basal and stimulated cortisol levels, as well as on aldosterone secretion. Although no change was reported in the testicular function, conflicting results were observed in the analysis of sperm motility after administration of pravastatin sodium. A case of reversible impotence has been reported in a 57-year old man administered pravastatin 20 mg/day and metoprolol (see SELECTED BIBLIOGRAPHY). A causal relationship to therapy with pravastatin sodium has not been established. Further studies are needed to clarify the effects of HMG-CoA reductase inhibitors on male fertility. Furthermore, the effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with *Riva* PRAVASTATIN who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones.

Patients With Severe Hypercholesterolemia

Higher doses (40 mg/day) required for some patients with severe hypercholesterolemia are associated with increased plasma levels of pravastatin. **Caution should be exercised in such patients who are also significantly renally impaired or elderly** (see WARNINGS, Muscle Effects).

DRUG INTERACTIONS

Concomitant Therapy with Other Lipid Metabolism Regulators

Combined drug therapy should be approached with caution as information from controlled studies is limited.

Bile Acid Sequestrants

Preliminary evidence suggests that the cholesterol-lowering effects of pravastatin sodium and the bile acid sequestrants, cholestyramine/colestipol are additive.

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

Gemfibrozil, nicotinic acid, and probucol

Gemfibrozil, nicotinic acid and probucol do not statistically significantly affect the bioavailability of pravastatin. However, in a limited size clinical trial, a trend toward CPK elevations and musculoskeletal symptoms was seen in patients treated concurrently with pravastatin and gemfibrozil. No results are available from clinical studies involving combination of pravastatin with probucol.

Myopathy, including rhabdomyolysis, has occurred in patients who were receiving co-administration of HMG-CoA reductase inhibitors with fibric acid derivatives and niacin, particularly in subjects with pre-existing renal insufficiency. (See WARNINGS, Muscle Effects).

Other Concomitant Therapy

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are administered with drugs that inhibit the cytochrome P-450 enzyme system. *In vitro* and *in vivo* data indicate that pravastatin is not metabolized by cytochrome P450 3A4 to a clinically significant extent. This has been shown in studies with known cytochrome P450 3A4 inhibitors.

<u>Digoxin</u>

Coadministration of digoxin and other HMG-CoA reductase inhibitors has been shown to increase the steady state digoxin concentrations. The potential effects of coadministration of digoxin and pravastatin sodium are not known. As a precautionary measure, patients taking digoxin should be closely monitored.

<u>Antipyrine</u>

Antipyrine was used as a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Pravastatin had no effect on the pharmacokinetics of antipyrine.

Coumarin Anticoagulants

Pravastatin had no clinically significant effect on prothrombin time when administered in a study to normal elderly subjects who were stabilized on warfarin.

Antacids and Cimetidine

On the average, antacids (one hour prior to pravastatin sodium) reduce and cimetidine increases the bioavailability of pravastatin. These changes were not statistically significant. The clinical significance of these interactions is not known but is probably minimal as judged from the interaction with food (see under HUMAN PHARMACOLOGY).

No information is available regarding interactions with erythromycin (see under WARNINGS, Muscle Effects).

Although specific interaction studies were not performed during clinical trials, no noticeable drug interactions were reported when pravastatin sodium was added to diuretics, antihypertensives, angiotensin converting-enzyme (ACE) inhibitors, calcium channel blockers, or nitroglycerin.

Propranolol

Co-administration of propranolol and pravastatin reduced the AUC values by 23% and 16% respectively.

Cyclosporine

In a multicentre study, the AUC values of pravastatin were shown to be five-fold higher in the presence of cyclosporine. There was no accumulation of pravastatin after multiple doses (see DOSAGE AND ADMINISTRATION and SELECTED BIBLIOGRAPHY).

ADVERSE REACTIONS

In seven randomized double blind placebo-controlled trials involving over 21,500 patients treated with pravastatin (N = 10,784) 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.

Clinical adverse events probably or possibly related, or of uncertain relationship to therapy, occurring in at least 0.5% of patients treated with pravastatin or placebo in these long-term morbidity/mortality trials are shown in the table below:

	PRAVASTATIN SODIUM (N = 10,784) %	**PLACEBO (N = 10,719) %**
Cardiovascular		
Angina pectoris	3.1	3.4
Disturbance rhythm subjective	0.8	0.7
Hypertension	0.7	0.9
Edema	0.6	0.6
Myocardial infarction	0.5	0.7
Gastrointestinal		
Dyspepsia / heartburn	3.5	3.7
Nausea / vomiting	1.4	1.6
Flatulence	1.2	1.1
Constipation	1.2	1.3
Diarrhea	0.9	1.1
Abdominal pain	0.9	1.0
Distention abdomen	0.5	0.5

	PRAVASTATIN SODIUM (N = 10,784) %	**PLACEBO** (N = 10,719) %
Musculoskeletal		
Musculoskeletal pain (includes arthralgia)	5.9	5.7
Muscle cramp	2.0	1.8
Myalgia	1.4	1.4
Musculoskeletal trauma	0.5	0.3
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
Paresthesia	0.9	0.9
Numbness	0.5	0.4
General		
Fatigue	3.4	3.3
Chest pain	2.6	2.6
Weight gain	0.6	0.7
Influenza	0.6	0.5
Special Senses		
Vision disturbance (includes blurred vision)	1.5	1.3
Disturbance eye (includes eye inflammation)	0.8	0.9
Hearing abnormality (includes tinnitus and hearing loss)	0.6	0.5
Lens opacity	0.5	0.4

	PRAVASTATIN SODIUM (N = 10,784) %	**PLACEBO** (N = 10,719) %
Dermatologic		
Rash	2.1	2.2
Pruritis	0.9	1.0
Renal / Genitourinary		
Urinary abnormality (includes dysuria and nocturia)	1	0.8
Respiratory		
Dyspnea	1.6	1.6
Upper respiratory infection	1.3	1.3
Cough	1.0	1.0
Sinus abnormality (includes sinusitis)	0.8	0.8
Pharyngitis	0.5	0.6

The following additional events were reported in either uncontrolled clinical trials or in marketed use: pruritis, scalp hair abnormalities, skin dryness, abnormal stool, appetite change, chest pain (noncardiovascular), weakness, excess sweating, hot flashes, paresthesia, equilibrium disturbance, mood changes, eye symptoms (including soreness, dryness or itching), tinnitus and impotence (See Endocrine Function), dermatitis, urticaria, sexual dysfunction, libido change, fever, allergy, vertigo, memory impairment, tremor, neuropathy and taste disturbance.

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 erythematosus-like syndrome, pancreatitis and thrombocytopenia. A causal association with pravastatin has not been established for these events.

The following have also been reported with other statins: hepatitis, cholestatic jaundice, anorexia, psychic disturbances including anxiety, hypospermia and hypersensitivity (see PRECAUTIONS).

Lens

Current data from clinical trials do not indicate an adverse effect of pravastatin on the human lens.

Laboratory Test Abnormalities

Increases in serum transaminases and in creatine phosphokinase (CPK) in patients treated with pravastatin sodium have been discussed (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been two reports of overdosage with pravastatin, both of which were asymptomatic and not associated with clinical laboratory abnormalities.

In the event of overdosage, treatment should be symptomatic and supportive, and appropriate therapy instituted. Until further experience is obtained, no specific therapy of overdosage can be recommended. The dialyzability of pravastatin and its metabolites is not known.

DOSAGE AND ADMINISTRATION

Prior to initiating *Riva* PRAVASTATIN (pravastatin sodium), the patient should be placed on at least an equivalent of the American Heart Association (AHA) Step 1 diet, which should be continued during treatment. If appropriate, a program of weight control and physical exercise should be implemented.

Hypercholesterolemia and Coronary Heart Disease

The recommended starting dose is 10 to 20 mg once daily at bedtime. If serum cholesterol is markedly elevated (i.e. severe hypercholesterolemia) [e.g. Total Cholesterol greater than 7.75 mmol/L (300 mg/dL)] dosage may be initiated at 40 mg per day. *Riva* PRAVASTATIN may be taken without regard to meals. (See PRECAUTIONS).

Since the maximal effect of a given dose is seen within four weeks, periodic lipid determinations should be performed and dosage adjusted according to the patient's response to therapy. **Consideration should be given to reducing the dosage of *Riva* PRAVASTATIN if cholesterol levels fall below the targeted range, such as that recommended by the Second Report of the U.S. National Cholesterol Education Program (NCEP), as well as the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias** (see SELECTED BIBLIOGRAPHY). The recommended dosage range is 10 to 40 mg administered once a day at bedtime.

Concomitant Therapy

Some patients may require combination therapy with one or more lipid-lowering agents. Pharmacokinetic interaction with pravastatin administered concurrently with nicotinic acid, probucol, or gemfibrozil did not statistically significantly affect the bioavailability of pravastatin. The combined use of pravastatin and fibrates should however generally be avoided (see WARNINGS, Muscle Effects). No results are available from clinical studies involving the concomitant administration of pravastatin with probucol.

The lipid-lowering effects of *Riva* PRAVASTATIN on Total and Low Density Lipoprotein Cholesterol are additive when combined with a bile acid-binding resin. However, when administering a bile acid-binding resin (e.g. cholestyramine, colestipol) and pravastatin, *Riva* PRAVASTATIN should not be administered concomitantly, but should be given either one hour or more before or at least four hours following the resin (See Drug Interactions, Concomitant Therapy with Other Lipid Metabolism Regulators).

In patients taking cyclosporine, with or without other immunosuppressive drugs, concomitantly with pravastatin, therapy should be initiated with 10 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. (See PRECAUTIONS - DRUG INTERACTIONS, Other Concomitant Therapy, Cyclosporine).

INFORMATION TO THE PATIENT

Full prescribing information is available to the physician and pharmacist.

Riva PRAVASTATIN is the proprietary name of Cobalt Pharmaceuticals Inc. for pravastatin sodium.

Riva PRAVASTATIN lowers the level of cholesterol, particularly Low Density Lipoprotein (LDL) cholesterol, in the blood. *Riva* PRAVASTATIN reduces cholesterol production by the liver and induces some changes of cholesterol transport and disposition in the blood and tissues.

Riva PRAVASTATIN is available only with your physician's prescription. It is to be used as an adjunct to a medically recommended and carefully supervised diet for the long-term treatment of hypercholesterolemia and is not a substitute for such a diet. This has been shown to decrease the chances of experiencing a first or second heart attack, or stroke, and may help prevent heart disease if caused by cholesterol clogging the blood vessels, or slow the progression of atherosclerosis (hardening) of the arteries that nourish your heart, so-called coronary heart disease (CHD). In addition, depending on your condition, your physician may recommend an appropriate regimen of exercise, weight control, and other measures.

Use only as specifically directed. Do not alter the dosage unless ordered to do so by your physician. Check with your physician before discontinuing medication since this may result in an increase of your blood lipids.

BEFORE USING THIS MEDICATION, you should have told your physician if:

- you have already taken *Riva* PRAVASTATIN or any other lipid lowering agent of the same class - for example fluvastatin (LESCOL), lovastatin (MEVACOR), simvastatin (ZOCOR), or atorvastatin (LIPITOR) - and have developed an allergy or intolerance to any of them;
- you suffer from liver disease;
- you are pregnant, intend to become pregnant or are breast feeding, or intend to breast-feed;
- you are taking any other medication, particularly corticosteroids, cyclosporine (SANDIMMUNE®), gemfibrozil (LOPID®), and anticoagulant [e.g. warfarin (WARFILONE®)], erythromycin, or digoxin.

PROPER USE OF THIS MEDICINE

- Riva PRAVASTATIN should be taken as a single dose at bedtime, as prescribed by your physician.
- Your physician will monitor your clinical condition and your blood tests at regular intervals. It is important to have these check-ups done on schedule. Please keep your appointments accurately.

- Avoid excessive alcohol intake.
- Notify your physician about any illness which may develop during your treatment with Riva PRAVASTATIN and about any new prescription or non-prescription medication you may take. If you require medical help for other reasons, inform the attending physician that you are taking Riva PRAVASTATIN.
- Notify your physician if you are going to have major surgery or have sustained a severe injury.
- Notify your physician of any muscle pain, tenderness or weakness developing during treatment with Riva PRAVASTATIN (see SIDE EFFECTS).
- The safety of Riva PRAVASTATIN in adolescents and children has not been established.
- Riva PRAVASTATIN is contraindicated during pregnancy since its use in the event of pregnancy may harm the unborn. Only female patients who are highly unlikely to conceive can be candidates for Riva PRAVASTATIN treatment. In the event of pregnancy during treatment, *Riva* PRAVASTATIN should be discontinued and the physician should be informed.

SIDE EFFECTS

Along with its intended action, any medication may cause unwanted effects.

Check with your physician as soon as possible if any of the following side effects occurs: aching muscles, muscle cramping, tiredness or weakness, fever and blurred vision.

Other side effects may occasionally occur which usually do not require stopping treatment. They may come and go during treatment without any particular danger, but you should mention them to your physician, without undue delay, if they become persistent or bothersome. Such adverse experiences include abdominal pain, constipation, diarrhea, nausea, headache, dizziness and skin rashes.

THIS MEDICINE IS PRESCRIBED FOR YOUR SPECIFIC MEDICAL PROBLEM AND FOR YOUR OWN USE ONLY. DO NOT GIVE TO OTHER PEOPLE.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

IF YOU NEED ANY FURTHER INFORMATION, ASK YOUR PHYSICIAN OR YOUR PHARMACIST.

PHARMACEUTICAL INFORMATION

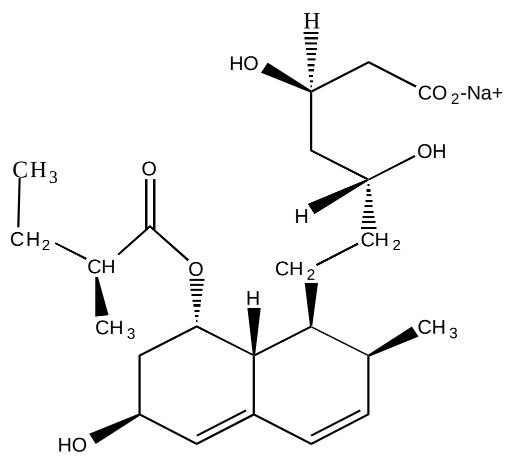
I. DRUG SUBSTANCE

Proper Name: Pravastatin sodium

Chemical Name: Pravastatin sodium is designated chemically as [1S-[1α(βS*,δS*) 2α,6α,8β(R*), 8aα]]-1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthaleneheptanoic acid, monosodium salt.

Empirical Formula: $C_{23}H_{35}O_7 \cdot Na$

Structural Formula:



Molecular Weight: 446.52

Description: Pravastatin is a white to off white, crystalline powder that is freely soluble in water and methanol, soluble in ethanol, slightly soluble in n-octanol, and practically insoluble in acetonitrile, acetone, chloroform and ether.

II. COMPOSITION

Each Riva PRAVASTATIN (pravastatin sodium) tablet for oral administration contains 10 mg, 20 mg or 40 mg of pravastatin sodium and the following non-medicinal ingredients:

lactose monohydrate	croscarmellose sodium
microcrystalline cellulose	povidone
magnesium aluminium silicate	talc
magnesium stearate	

Riva PRAVASTATIN contains the following colouring components:

10 mg tablets: Red 30 Iron Oxide

20 mg tablets: Yellow 10 Iron Oxide

40 mg tablets: Lake Blend Green

III. STORAGE RECOMMENDATIONS

Riva PRAVASTATIN (pravastatin sodium) should be stored at room temperature (15-30°C). Protect from moisture and light.

DOSAGE FORMS AND AVAILABILITY

Riva PRAVASTATIN 10 mg tablets, are pink to peach rounded, rectangular-shaped biconvex tablets, with “**>**” on one side and “PV” 10 on the other side. Available in HDPE bottles of 100's & 500's and Foil Aluminum Cold Formable unit dose blisters of 10's (cartons of 30 tablets).

Riva PRAVASTATIN 20 mg tablets are yellow, rounded, rectangular-shaped biconvex tablets, with “**>**” on one side and “PV” 20 on the other side. Available in HDPE bottles of 100's & 500's and Foil Aluminum Cold Formable unit dose blisters of 10's (cartons of 30 tablets).

Riva PRAVASTATIN 40 mg tablets are green, rounded, rectangular-shaped biconvex tablets, with “**>**” on one side and “PV” 40 on the other side. Available in HDPE bottles of 100's & 500's and Foil Aluminum Cold Formable unit dose blisters of 10's (cartons of 30 tablets).

PHARMACOLOGY

HUMAN PHARMACOLOGY

In both normal volunteers and patients with hypercholesterolemia, treatment with *Riva* PRAVASTATIN (pravastatin sodium) reduced total-C, LDL-C, apolipoprotein B, VLDL-C and TG while increasing HDL-C and apolipoprotein A. The mechanism of action of *Riva* PRAVASTATIN (pravastatin sodium) is complex. Inhibition of hepatic VLDL synthesis and/or secretion occurs, leading to a decrease in LDL precursor formation. The reduction in hepatic cellular pools of cholesterol, resulting from the specific and reversible inhibition of HMG-CoA reductase activity, leads to an increase in the fractional catabolic rate of IDL and LDL via increased expression of LDL receptors on the surface of hepatic cells. Through a combination of these and possibly other unknown metabolic effects, a decline in the serum level of cholesterol results.

Pharmacokinetics

Pravastatin sodium is administered orally in the active form. Following oral ingestion, pravastatin is rapidly absorbed with peak plasma levels attained at about 1 to 1.5 hours. Average oral absorption of pravastatin, based on urinary recovery of radiolabelled drug after oral and intravenous dosing, is 34%; average absolute bioavailability of the parent drug is 17%. The therapeutic response to *Riva* PRAVASTATIN is similar, whether taken with meals or one hour prior to meals, even though the presence of food in the gastrointestinal tract causes a reduction in systemic bioavailability.

Percent Decrease in LDL-C

Pravastatin	10 mg bid	20 mg bid
With meals	- 25%	- 37%
Before meals*	- 26%	- 36%

* administered one hour or more prior to eating.

Pravastatin undergoes extensive first pass extraction in the liver (estimated hepatic extraction ratio, 66%), its primary site of action, and is excreted in the bile. Therefore, plasma levels of the drug are probably of limited value in predicting therapeutic effectiveness. Nevertheless, measurement of plasma pravastatin concentrations by gas chromatography and mass-spectrometry showed dose proportionality for area under the concentration-time curve (AUC) and maximum and steady-state plasma levels. Steady-state areas under the plasma concentration-time-curves and maximum (C_{MAX}) or minimum (C_{MIN}) plasma concentrations showed no accumulation following once or twice-daily administration of pravastatin sodium tablets.

Protein binding of pravastatin is approximately 50%. The plasma elimination half-life of pravastatin is between 1.5 and 2 hours (2.5 - 3 hours in hypercholesterolemic subjects). Approximately 20% of a radiolabelled oral dose is excreted in the urine and 70% in the feces. Pravastatin is extensively metabolized. The major metabolite is the 3 α-hydroxy isomer, which has one-tenth to one-fortieth of the inhibitory activity of the parent compound on HMG-CoA reductase.

After intravenous administration to healthy subjects, approximately 47% of the total drug clearance occurs via renal excretion of intact pravastatin, and about 53% is cleared by non-renal routes, i.e. biliary excretion and biotransformation.

Studies of pravastatin sodium administered as a single dose to healthy elderly male and female subjects (age 65 to 78 years) indicated a 30 - 50% increase in plasma levels.

No studies have been carried out in patients with renal insufficiency.

Clinical Trials

Hypercholesterolemia

Riva PRAVASTATIN (pravastatin sodium) is highly effective in reducing total and LDL cholesterol in patients with primary hypercholesterolemia. A marked response is seen within one week, and the maximum therapeutic response usually occurs within four weeks. The response is maintained during extended periods of therapy. In addition, pravastatin sodium is effective in reducing the progressive cause of atherosclerosis and risk of coronary events, decreasing total mortality, decreasing death due to coronary heart disease, and decreasing the incidence of stroke, in hypercholesterolemic patients with atherosclerotic cardiovascular disease. Pravastatin sodium is also effective in reducing the risk of CHD death (fatal MI and sudden death) plus non-fatal MI with no increase in deaths from non-cardiovascular causes in hypercholesterolemic patients without previous myocardial infarction. Risk reduction is evident within 6 months of the initiation of treatment (see Figure 1).

Single daily doses of pravastatin sodium are effective. As shown in the table which follows, the Total-C and LDL-C lowering effects are the same whether pravastatin sodium is administered in single or divided (bid) doses. 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.

The results of a multicentre, double-blind regimen response comparative study of placebo and pravastatin, given to parallel groups of patients for 8 weeks are as follows:

SINGLE-DAILY VERSUS TWICE-DAILY DOSING*

Pravastatin	N	Total-C	LDL-C	HDL-C	TG
40 mg qam	41	- 23 %	- 30%	+ 4%	- 11%
40 mg qpm	33	- 26%	- 33%	+ 8%	- 24%
20 mg bid	44	- 27%	- 34%	+ 8%	- 25%

* Evening doses were administered at least 3 hours after the evening meal. Morning doses were administered at least 1 hour prior to breakfast.

Patients with primary hypercholesterolemia (71% Familial or Familial Combined, 29% Non-Familial). Baseline mean LDL-C = 6.34 mmo1/L (245.4 mg/dL)

In multicenter, double-blind studies of patients with primary hypercholesterolemia, pravastatin sodium administered in daily doses ranging from 5 mg to 80 mg to over 1100 patients was compared with placebo. Pravastatin sodium significantly decreased Total-C and LDL-C levels, and Total-C/HDL-C and LDL-C/HDL-C ratios. In addition, pravastatin slightly increased HDL-C and decreased VLDL-C and plasma TG levels.

Dose-response effects on lipids from two studies evaluated after 8 weeks of administering pravastatin sodium once or twice-daily are illustrated in the tables below.

DOSE-RESPONSE RESULTS*

(Once-Daily Administration at Bedtime)

Pravastatin	N	Total-C	LDL-C	HDL-C	TG
5 mg qd	16	- 14%	- 19%	+ 5%	- 14%
10 mg qd	18	- 16%	- 22%	+ 7%	- 15%
20 mg qd	19	- 24%	- 32%	+ 2%	- 11%
40 mg qd	18	- 25%	- 34%	+ 12%	- 24%

* Patients with primary hypercholesterolemia (28% Familial or Familial Combined, 72% Non-Familial). Baseline mean LDL-C = 5.68 mmol/L (219.6 mg/dL)

DOSE-RESPONSE RESULTS*

(BID Administration)

Pravastatin	N	Total-C	LDL-C	HDL-C	TG
5 mg bid	59	- 15 %	- 20%	+ 7%	- 14%
10 mg bid	53	- 18%	- 24%	+ 6%	- 17%
20 mg bid	56	- 24%	- 31%	+ 5%	- 17%

* Patients with primary hypercholesterolemia (70% Familial or Familial Combined, 30% Non-Familial), Baseline mean LDL-C = 6.06 mmol/L (234.5 mg/dL)

Pravastatin sodium is also effective when given with a bile acid-binding resin. In a study of pravastatin sodium administered alone or in combination with cholestyramine, marked reductions in the level of LDL-

C were observed. In addition, pravastatin sodium attenuated the increase in TG levels observed with cholestyramine alone. (The results of the study cited in the table which follows should be interpreted in the context of the exceptionally high rate of patient compliance with the bile acid-binding resin [70% of patients were taking 20 or 24 g daily].)

COMPARISON WITH CHOLESTYRAMINE RESIN*

	N	Total-C	LDL-C	HDL-C	TG
Pravastatin					
20 mg bid	49	- 24%	- 32%	+ 6%	- 10%
40 mg bid	52	- 30%	- 39%	+ 5%	- 15%
Resin Alone**	41	- 22%	- 31%	+ 2%	+ 16%
Combination					
20 mg bid & Resin**	49	-38%	-52%	+ 5%	- 1

* Patients with primary hypercholesterolemia (68% Familial or Familial Combined; 32% Non-Familia1). Baseline mean LDL-C = 6.09 mmol/L (235.3 mg/dL)

* * The dose of resin used in this study was 24 g.

Primary Prevention of Coronary Events

Pravastatin sodium has been shown to be effective in reducing the risk of coronary heart disease (CHD) death plus non-fatal MI in hypercholesterolemic patients without previous myocardial infarction.

In the West of Scotland Study (WOS), the effect of pravastatin sodium on fatal and non-fatal coronary heart disease (CHD) was assessed in 6595 patients. The patient population consisted of men 45 - 64 years of age, without a previous MI, and with LDL-C levels between 4 - 6.7 mmol/L (156 - 254 mg/dL). In this randomized, double-blind, placebo-controlled study, patients were treated with standard care, including dietary advice, and either pravastatin sodium 40 mg daily (n = 3302) or placebo (n = 3293) for a median duration of 4.8 years.

Pravastatin sodium significantly reduced the risk of CHD death plus non-fatal MI by 31% (248 patients in the placebo group [CHD death = 44, non-fatal MI = 204] vs 174 patients in the pravastatin sodium group [CHD death = 31, non-fatal MI = 143], p = 0.0001). As shown in the figure below, divergence in the cumulative event rate curves for this endpoint begins within 6 months of treatment. This reduction was similar and significant throughout the entire range of baseline LDL cholesterol levels with a 37% risk reduction for LDL cholesterol 4 - 4.8 mmol/L (156 - 188 mg/dL) (p = 0.003) and a 27% risk reduction for LDL cholesterol 4.9 - 6.7 mmol/L (189 - 254 mg/dL) (p = 0.03). This reduction was also similar and significant for all age groups studied with a 40% risk reduction for patients younger than 55 years (p = 0.002) and 27% risk reduction for patients 55 years and older (p = 0.009).

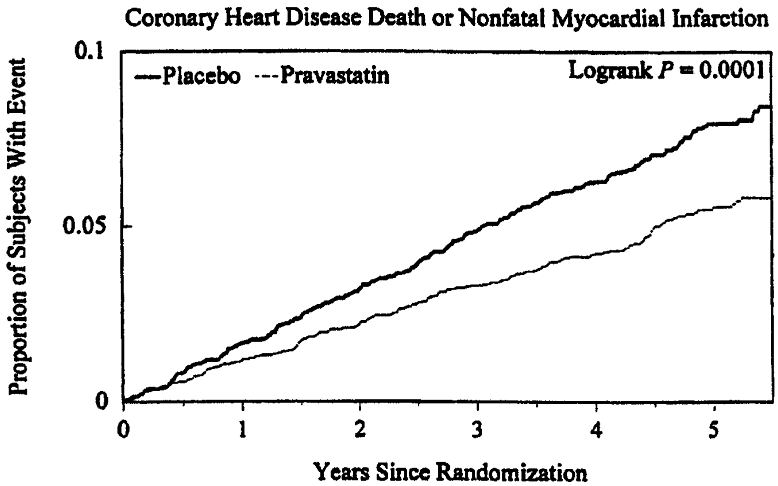


Figure 1

Total cardiovascular deaths were reduced by 32% (73 vs 50, p = 0.03) and overall mortality by 22% (135 vs 106, p = 0.051). There was no statistically significant difference between treatment groups in non-cardiovascular mortality, including cancer deaths. Pravastatin sodium also decreased the risk for undergoing myocardial revascularization procedures (coronary artery bypass graft surgery or coronary angioplasty) by 37% (80 vs 51 patients, p = 0.009) and coronary angiography by 31 % (128 vs 90, p = 0.007).

Secondary Prevention of Cardiovascular Events

Pravastatin sodium has been shown to be 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 **L**ong-Term **I**ntervention with **P**ravastatin in **I**schemic **D**isease (LIPID) study, the effect of pravastatin sodium 40 mg daily was assessed in 9014 men and women with normal to elevated serum cholesterol levels (baseline Total-C = 155-271 mg/dL [4.0 - 7.0 mmol/L]; median Total-C = 218 mg/dL [5.66 mmol/L]; median LDL-C = 150 mg/dL [3.88 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, 47% were receiving beta blockers, and 76% 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 sodium 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 sodium treated patients. The risk for fatal or nonfatal myocardial infarction was reduced by 29% ($p < 0.0001$). Pravastatin sodium 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 sodium treated patients. Pravastatin sodium also significantly reduced the risk for stroke by 19% ($p = 0.0477$). Treatment with pravastatin sodium significantly reduced the number of days of hospitalization per 100 person-years of follow-up by 15% ($p < 0.001$). The effect of pravastatin sodium on reducing CHD events was consistent regardless of age, gender, or diabetic status. Among patients who qualified with a history of myocardial infarction, pravastatin sodium 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 sodium 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 40 mg daily on coronary heart disease death and nonfatal MI was assessed in 4159 men and women with normal serum cholesterol levels (baseline mean Total-C = 209 mg/dL [5.4 mmol/L]), and who had experienced a myocardial infarction in the preceding 3 - 20 months. At baseline, 83% of patients were receiving aspirin, 55% had undergone PTCA/CABG, 40% were receiving beta blockers, and 82% were receiving antihypertensive medication. 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% (274 patients with events [13.3%] in the placebo group vs. 212 patients [10.4%] in the pravastatin group, p = 0.003). The reduction in risk for this combined endpoint was significant for both men and women; in women, the reduction in risk was 43% (p = 0.033). 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 (391 [19.6%] vs. 294 [14.2%] patients). Pravastatin also significantly reduced the risk for stroke by 32%

(p = 0.032), and stroke or transient ischemic attack (TIA) combined by 26% (124 [6.3%] vs. 93 [4.7%] patients, p = 0.025).

Atherosclerotic Disease Progression

In two controlled trials [PLAC I, PLAC II] in patients with moderate hypercholesterolemia and atherosclerotic cardiovascular disease, pravastatin was effective in reducing the progressive course of atherosclerosis as evaluated by quantitative angiography and B-mode ultrasound. This effect may be associated with an improvement in the coronary endpoints (fatal or non fatal MI). No difference in total mortality was detected during the 3 years of double-blind therapy.

In PLAC I (Pravastatin Limitation of Atherosclerosis in the Coronary Arteries), a 3-year, placebo-controlled, multicentre, randomized trial, of 408 patients with moderate hypercholesterolemia (baseline LDL-C range = 3.37 - 4.92 mmol/L (130 - 190 mg/dL)) and coronary artery disease, treatment with pravastatin reduced the rate of narrowing of the coronary artery lumen diameter as determined by quantitative angiography. The analyses of clinical cardiovascular events showed a favorable effect of pravastatin therapy on events that occurred > 90 days after randomization, as well as for events from the time of randomization. This effect was not accompanied by an improvement in the total mortality endpoint. In PLAC II (Pravastatin Lipids and Atherosclerosis in the Carotid Arteries), a 3-year, placebo-controlled trial, in 151 patients with moderate hypercholesterolemia (baseline LDL-C range = 3.76 - 4.92 mmol/L (145 - 190 mg/dL)) and coronary and carotid atherosclerosis, treatment with pravastatin significantly reduced the rate of progression of atherosclerosis in common carotid artery, as measured by

B-mode ultrasound. The rate of progression of the mean-maximum intimal-medial thickness (IMT) was not significantly reduced. There was a decrease in the incidence of coronary events of borderline significance. No difference in total mortality was observed during the 3 years of double-blind therapy.

Solid Organ Transplant

Myopathy has not been observed in clinical trials involving a total of 100 post-transplant patients (76 cardiac and 24 renal) treated concurrently for two 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.

ANIMAL PHARMACOLOGY

Cell/Tissue Selective Inhibition of Cholesterol Synthesis

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.

In suspensions of freshly isolated rat hepatocytes and in one-day cultures of rat hepatocytes, pravastatin sodium showed potent inhibition of ^{14}C incorporation into cholesterol. In cultured human skin fibroblasts and other non hepatic cell types, pravastatin inhibited cholesterol synthesis 400 times less than in hepatocytes.

The accumulation of ^{14}C-pravastatin was concentration and time dependent in hepatocytes and barely detectable in fibroblasts.

In tissue slices from rats given oral doses of pravastatin sodium, cholesterol synthesis was inhibited by more than 90% in liver and ileum slices and was substantially lower or not detectable in other tissue slices such as prostate, testes and adrenal.

In the intact rat lens, pravastatin sodium inhibited cholesterol synthesis 10 times less than in liver from the same animals. The inhibition of sterol synthesis in lens epithelial lines derived from the mouse and the rabbit was 400 to 1500 times less than in rat hepatocytes.

Specificity as an Inhibitor of HMG-CoA Reductase

The incorporation of ^{14}C-mevalonate, the product of HMG-CoA reductase reaction into sterols, was not affected in hepatocytes, fibroblasts, or CHO cells at concentrations of pravastatin sodium at least 20 times greater than those that inhibited ^{14}C-acetate incorporation into cholesterol.

At concentrations 500 times greater than those that inhibited acetate incorporation into cholesterol, pravastatin sodium did not alter the rate of incorporation of ^{14}C-acetate into total cell phospholipids in hepatocytes and the distribution of the radiolabel into the separate classes of phospholipids. Pravastatin sodium did not reduce the rate of incorporation of ^{14}C-acetate into triglycerides. These results demonstrate that pravastatin does not act in the sterol pathway at any step beyond the synthesis of mevalonate nor does it inhibit the enzymes required for the biosynthesis of two other major classes of lipids.

The inhibitory activity of pravastatin on the enzyme HMG-CoA reductase was 10^6 times greater than that demonstrated by pravastatin for HMG-CoA lyase. The active site of this enzyme, which also employs HMG-CoA as substrate, does not recognize pravastatin.

General pharmacology

The effect of pravastatin sodium on major physiologic systems and isolated tissue and its agonist and antagonist effects towards principal neurohumoral transmitters or histamine, behavioral effects, convulsive threshold and tissue- or activity-specific effects were evaluated in animals or *in vitro* tissue preparations.

With the exception of a moderate inhibition of gastric secretion at a dose of 300 mg/kg in rats, pravastatin sodium had no effect in any of these pharmacologic tests at doses of 1000 mg/kg in some species.

Pharmacokinetics

Studies in rats, dogs, and humans demonstrated that pravastatin sodium given orally has low bioavailability because of extensive first-pass hepatic extraction. Therefore, most of an oral dose of pravastatin sodium is delivered directly to the liver, the primary site of pharmacologic activity .

A relatively low extent of binding of pravastatin to plasma proteins was found in rats, dogs, monkeys, and humans. The highest concentrations of ^{14}C-pravastatin were found in the excretory organs and the GI tract in rats (N = 3 - 5), one dog, and one monkey. Similar metabolic patterns and appreciable fecal excretion in rats, dogs, monkeys, and man were also evident in these studies.

Dogs are unique as compared to all other species tested, including man, in that they have a much greater systemic exposure to pravastatin. Pharmacokinetic data from a study in dogs at a dose of 1.1 mg/kg (comparable to a 40 mg dose in humans) showed that the elimination of pravastatin is slower in dogs than in humans. Absolute bioavailability is two times greater in dogs compared to humans and estimated renal and hepatic extraction of pravastatin are about one-tenth and one-half, respectively, than those in humans. When concentrations of pravastatin in plasma or serum of rats, dogs, rabbits, monkeys, and humans were compared, the exposure in dogs was dramatically higher, based on both C_{MAX} and AUC. The mean AUC value in man at a therapeutic dose of 40 mg is approximately 100 times less than that in the dog at the no-effect dose of 12.5 mg/kg, and approximately 180 times lower than that in dogs at the threshold dose of 25 mg/kg for cerebral hemorrhage.

Placental Transfer

Low levels of radioactivity were found in the fetuses of rats dosed orally with radiolabeled pravastatin sodium. Pravastatin sodium was also found to be secreted in the milk of rats.

TOXICOLOGY

Acute Toxicity

Species	Sex (N)	Route	LD50 (mg/kg)
Mouse	M (50) F (50)	Oral	10590 8939
Mouse	M (50) F (50)	i.v.	2114 2011
Mouse	M (50) F (50)	s.c.	2975 3667
Rat	M (20) F (20)	Oral	> 12000 > 12000
Rat	M (50) F (50)	i.v.	443 440
Rat	M (50) F (50)	s.c.	3172 4455
Dog	M(4)	Oral	> 800

Signs of toxicity in mice were decreased activity, irregular respiration, ptosis, lacrimation, soft stool, diarrhea, urine-stained abdomen, ataxia, creeping behavior, loss of righting reflex, hypothermia, urinary incontinence, pilo-erection convulsion and/or prostration.

Signs of toxicity in rats were soft stool, diarrhea, decreased activity, irregular respiration, waddling gait, ataxia, loss of righting reflex and/or weight loss.

Subacute and Chronic Toxicity

The spectrum of effects produced by pravastatin in mice, rats, rabbits, dogs and monkeys shown on the following table is not unexpected in view of the magnitude of the dosage levels employed and the potency of pravastatin against the HMG-CoA reductase.

TARGET ORGANS OBSERVED IN ANIMAL STUDIES

Organ	Mouse	Rat	Rabbit	Dog	Monkey
Liver, neoplastic effect	−	+	−	−	−
Liver, non-neoplastic effect	+	+	+	−	+
Kidney	−	−	+	−	+
Skeletal muscle	−	+	+	−	−
Brain	−	−	−	+	−

\+ = Organ affected in some way by drug treatment

− = No effect observed in this organ in these species

On a mg/kg basis, rabbits appear to be more sensitive to the nephrotoxic effects of pravastatin sodium than monkeys, the only other species that exhibited renal toxicity. In rabbits, renal dysfunction and hepatic effects were observed at doses ≥ 25 mg/kg/day. In monkeys, hepatotoxicity and nephrotoxicity occurred at doses of 100 mg/kg/day. The threshold dose for renal toxicity in rabbits is 31 times greater than the maximum human dose.

SIGNIFICANT ADVERSE CHANGES

	Pravastatin	
	Minimal Toxic Dose (mg/kg/day)	No-effect Dose (mg/kg/day)
Mice		
Single-cell necrosis in the liver	40	20
Elevated serum transaminase activity	20	10
Rats		
Hepatic tumors	100	40
Foci of hepato-cellular alteration	30	12
Elevated transaminase activity	100	50
Skeletal-muscle myolysis	400	250
Rabbits		
Death	400	100
Hepatocellular necrosis	100	25
Renal tubular degeneration	25	6.25
Skeletal-muscle myolysis	100	25
Elevated serum transaminase activity	100	25
Dogs		
Death	25	12.5
Cerebral hemorrhage	25	12.5
Monkeys		
Death	200	100
Hepatocellular necrosis	100	50
Renal tubular degeneration	100	50
Elevated serum transaminase activity	100	50

Noteworthy findings in these studies included varying degrees of hepatotoxicity in all species tested, renal toxicity in rabbits and monkeys, skeletal-muscle lesions in rabbits, CNS symptoms and death secondary to cerebral hemorrhage in dogs, and an increased incidence of hepatic lesions and evidence of hepatocarcinoma (the latter at 100 mg/kg) in rats treated for 2 years. In all cases, these changes occurred only at daily doses of 20 mg/kg or more (more than 25 times the maximum human dose).

The findings from the chronic toxicity in dogs are detailed on the following pages.

Species/ Strain	Sex	N/Dose	Dose (mg/kg/day)	Route	Time	Effects
Subacute Toxicity						
Dog Beagle	M F	3 3	0, 12.5, 50 or 200	Oral (capsule)	5 weeks	200 mg/kg: One dog died and 4 dogs sacrificed on days 11 to 22 after exhibiting ataxia and/or convulsions, salivation, urinary incontinence and/or defecation. Ecchymotic lesions (hemorrhagic foci) in the brain.
Dog Beagle	M F	6 6	0 or 100 (2M, 2F controls) (4M, 4F treated)	Oral (capsule)	13 weeks	100 mg/kg: One death (F) on day 42 preceded by marked decrease in activity, serous salivation and vomiting. Diapedetic hemorrhage and degeneration of venular endothelial cells in one F and the F that died.
Chronic Toxicity						
Dog Beagle	M F	4M, 4F at 12.5 and 25 - 6M, 6F at 0, 50, & 100	0, 12.5, 25, 50 or 100	Oral (capsule)	2 years	25 mg/kg: Two F sacrificed during weeks 60 and 61. One had lesions consistent with idiopathic coagulopathy. The other showed clinical signs of CNS toxicity prior to sacrifice and had brain lesions.[1] 50 mg/kg: All dogs showed clinical signs of CNS toxicity; 5/6 dogs had brain lesions.[1] 100 mg/kg: Three M and 5 F died or sacrificed between weeks 2 and 24. One M died in week 76. All dogs showed clinical signs of CNS toxicity prior to death/sacrifice. Nine/nine dogs had brain lesions.

[1] Brain lesions (primarily in the piriform lobes) were characterized by discrete multifocal perivascular capilary and venular hemorrhages. In more severe lesions, there was an increased number of focal perivascular hemorrhages and associated early degenerative neutrophil changes including vacuolization, edema, and mild neutrophil infiltration. Larger vascular elements were not involved. No vascular endothelial changes were present, based on light- and electron-microscopic studies.

Chronic Toxicity (cont'd)

In dogs, pravastatin sodium was toxic at high doses and caused cerebral hemorrhage with clinical evidence of acute CNS toxicity (e.g. ataxia, convulsions). A dose-response relationship with respect to the incidence of CNS toxicity was clearly evident. In dogs, the threshold dose for CNS toxicity is 25 mg/kg. The high systemic exposure to orally administered pravastatin in dogs (refer to PHARMACOKINETICS) may be related to a greater bioavailability and slower elimination of pravastatin and likely plays an important role in the development of CNS lesions that occur in the dog.

Cerebral hemorrhages have not been observed to date in any other laboratory species and the CNS toxicity in dogs may represent a species-specific effect.

Reproduction and Teratology

Aside from a slight maternal toxicity in rabbits at 50 mg/kg and in rats at 1000 mg/kg, there were no treatment-related findings.

In rabbits and rats at doses greater than 60 and 600 times respectively the maximum human dose, pravastatin sodium exerted no untoward effects on reproduction through the F_1 generation in rats and did not cause any fetal or anatomic abnormalities through the F_1 generation in rabbits and the F_2 generation rats.

Carcinogenicity and Mutagenicity

In mice and rats, treated for 21 months with oral doses 25 and 50 times the maximum human dose respectively (i.e. 20 mg/kg daily and 40 mg/kg daily), pravastatin sodium was found to be non-carcinogenic. After 86 and 104 weeks of dosing in mice and rats respectively, at oral doses 125 times the maximum human dose (i.e. 100 mg/kg daily), statistically significant increases in the incidence of hepatocellular carcinoma were observed in male rats only.

In *in vivo* mutagenicity tests with i.p. doses up to 1400 mg/kg and in *in vitro* mutagenicity tests at concentrations up to 10000 ug/mL or plate, pravastatin sodium was found to be nonmutagenic.

Pravastatin was found to be non-genotoxic.

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