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PHYSICIANS' DESK REFERENCE®

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Tranxene—Cont.

Thereafter, gradually reduce the daily dose to 7.5 to 15 mg. Discontinue drug therapy as soon as patient's condition is stable.

The maximum recommended total daily dose is 90 mg. Avoid excessive reductions in the total amount of drug administered on successive days.

As an Adjunct to Antiepileptic Drugs:

In order to minimize drowsiness, the recommended initial dosages and dosage increments should not be exceeded.

Adults: The maximum recommended initial dose in patients over 12 years old is 7.5 mg three times a day. Dosage should be increased by no more than 7.5 mg every week and should not exceed 90 mg/day.

Children (9-12 years): The maximum recommended initial dose is 7.5 mg two times a day. Dosage should be increased by no more than 7.5 mg every week and should not exceed 60 mg/day.

DRUG INTERACTIONS

If TRANXENE is to be combined with other drugs acting on the central nervous system, careful consideration should be given to the pharmacology of the agents to be employed. Animal experience indicates that clorazepate dipotassium prolongs the sleeping time after hexobarbital or after ethyl alcohol, increases the inhibitory effects of chlorpromazine, but does not exhibit monoamine oxidase inhibition. Clinical studies have shown increased sedation with concurrent hypnotic medications. The actions of the benzodiazepines may be potentiated by barbiturates, narcotics, phenothiazines, monoamine oxidase inhibitors or other antidepressants.

If TRANXENE tablets are used to treat anxiety associated with somatic disease states, careful attention must be paid to possible drug interaction with concomitant medication.

In bioavailability studies with normal subjects, the concurrent administration of antacids at therapeutic levels did not significantly influence the bioavailability of TRANXENE tablets.

OVERDOSAGE

Overdosage is usually manifested by varying degrees of CNS depression ranging from slight sedation to coma. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken.

The treatment of overdosage should consist of the general measures employed in the management of overdosage of any CNS depressant. Gastric evacuation either by the induction of emesis, lavage, or both, should be performed immediately. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated. Hypotension, though rarely reported, may occur with large overdoses. In such cases the use of agents such as Levophed® Bitartrate (norepinephrine bitartrate injection, USP) or Aramine® Injection (metaraminol bitartrate injection, USP) should be considered.

While reports indicate that individuals have survived overdoses of clorazepate dipotassium as high as 450 to 675 mg, these doses are not necessarily an accurate indication of the amount of drug absorbed since the time interval between ingestion and the institution of treatment was not always known. Sedation in varying degrees was the most common physiological manifestation of clorazepate dipotassium overdosage. Deep coma when it occurred was usually associated with the ingestion of other drugs in addition to clorazepate dipotassium.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS should be consulted prior to use.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Studies in rats and monkeys have shown a substantial difference between doses producing tranquilizing, sedative and toxic effects. In rats, conditioned avoidance response was inhibited at an oral dose of 10 mg/kg; sedation was induced at 32 mg/kg; the LD_{50} was 1320 mg/kg. In monkeys aggressive behavior was reduced at an oral dose of 0.25 mg/kg; sedation (ataxia) was induced at 7.5 mg/kg; the LD_{50} could not be determined because of the emetic effect of large doses, but the LD_{50} exceeds 1600 mg/kg.

Twenty-four dogs were given clorazepate dipotassium orally in a 22-month toxicity study; doses up to 75 mg/kg were given. Drug-related changes occurred in the liver; weight was increased and cholestasis with minimal hepatocellular damage was found, but lobular architecture remained well preserved.

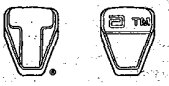
Eighteen rhesus monkeys were given oral doses of clorazepate dipotassium from 3 to 36 mg/kg daily for 52 weeks. All treated animals remained similar to control animals. Although total leucocyte count remained within normal limits it tended to fall in the female animals on the highest doses. Examination of all organs revealed no alterations attributable to clorazepate dipotassium. There was no damage to liver function or structure.

Reproduction Studies: Standard fertility, reproduction, and teratology studies were conducted in rats and rabbits. Oral doses in rats up to 150 mg/kg and in rabbits up to 15 mg/kg produced no abnormalities in the fetuses. TRANXENE did not alter the fertility indices or reproductive capacity of adult animals. As expected, the sedative effect of high doses interfered with care of the young by their mothers (*see Usage in Pregnancy*).

HOW SUPPLIED

TRANXENE® 3.75 mg, scored T-TAB® tablets are supplied as blue-colored tablets bearing the Abbott logo, the distinctive T shape and a two-letter Abbo-Code designation, TL:
Bottles of 100 ..... (**NDC** 0074-4389-13).
ABBO-PAC® unit dose packages:
100 ..... (**NDC** 0074-4389-11).

7.5 mg scored T-TAB® tablets are supplied as peach-colored tablets bearing the Abbott logo, the distinctive T shape and a two-letter Abbo-Code designation, TM:
Bottles of 100 ..... (**NDC** 0074-4390-13).
Bottles of 500 ..... (**NDC** 0074-4390-53).
ABBO-PAC® unit dose packages:
100 ..... (**NDC** 0074-4390-11).



15 mg scored T-TAB® tablets are supplied as lavender-colored tablets bearing the Abbott logo, the distinctive T shape and a two-letter Abbo-Code designation, TN:
Bottles of 100 ..... (**NDC** 0074-4391-13).
ABBO-PAC® unit dose packages:
100 ..... (**NDC** 0074-4391-11).

TRANXENE®-S[redacted]se tablets are supplied as tan-colored tablets bearing the Abbott logo and a two-letter Abbo-Code designation, TY:
Bottles of 100 ..... (**NDC** 0074-2997-13).
TRANXENE®-SD™ HALF-STRENGTH 11.25 mg single dose tablets are supplied as blue-colored tablets bearing the Abbott logo and a two-letter Abbo-Code designation, TX:
Bottles of 100 ..... (**NDC** 0074-2699-13).
T-TAB, tablet appearance and shape are trademarks of Abbott Laboratories.
Recommended storage: Store below 77°F (25°C)
U.S. Design Pat. No. D–300,879
Ref. 03-5051-R15
Abbott Laboratories
North Chicago, IL 60064, U.S.A.
Revised: April, 2001
Shown in Product Identification Guide, pages 303, 304

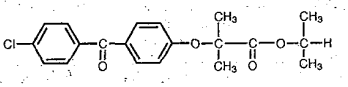
TRICOR®

℞

[tri cŏr]
(fenofibrate tablets)

DESCRIPTION

TRICOR (*fenofibrate tablets*), is a lipid regulating agent available as tablets for oral administration. Each tablet contains 54 mg or 160 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4C1$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79–82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each tablet contains colloidal silicon dioxide, crospovidone, lactose monohydrate, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulfate, sodium stearyl fumarate, talc, titanium dioxide, and xanthan gum. In addition, individual tablets contain:

54 mg tablets: D&C Yellow No. 10, FD&C Yellow No. 6, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.

The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of 54 mg and 160 mg tablets are equivalent under fed conditions to 67 and 200 mg capsules, respectively.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

The absorption of fenofibrate is increased when administered with food. With fenofibrate tablets, the extent of absorption is increased by approximately 35% under fed as compared to fasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77–87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

TRICOR has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabo-

lized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal insufficiency

In a study in patients with severe renal impairment (creatinine clearance <50 mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of TRICOR should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4–6 hours after a bile acid binding resin to avoid impeding its absorption (see WARNINGS and PRECAUTIONS).

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose equivalent to 160 mg TRICOR per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. TRICOR therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. TRICOR therapy also lowered triglycerides and raised HDL-C (see Table 1).

[See table above]

In a subset of the subjects, measurements of apo B were conducted. TRICOR treatment significantly reduced apo B from baseline to endpoint as compared with placebo (−25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials[1] of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 160 mg TRICOR per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

[See table 2 at top of next page]

The effect of TRICOR on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

TRICOR is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

TRICOR is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of TRICOR therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia[2].

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers, are sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS).

Table 1
[redacted]t Change in Lipid Parameters at End of Treatment†

Treat[redacted]	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	−18.7%*	−20.6%*	+11.0%*	−28.9%*
Placebo (n=285)	−0.4%	−2.2%	+0.7%	+7.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa)				
Mean baseline lipid values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	−22.4%*	−31.4%*	+9.8%*	−23.5%*
Placebo (n=141)	+0.2%	−2.2%	+2.6%	+11.7%
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL (Type IIb)				
Mean baseline lipid values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	[redacted]
All FEN (n=126)	−16.8%*	−20.1%*	+14.6%*	
Placebo (n=116)	−3.0%	−6.6%	+2.3%	

†Duration of study treatment was 3 to 6 months.
*p=.<0.05 vs. Placebo

Fredrickson Classification of Hyperlipoproteinemias

Type	Lipoprotein Elevated	Lipid Elevation Major	Lipid Elevation Minor
I (rare)	chylomicrons	TG	↑↔C
IIa	LDL	C	–
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	–
IV	VLDL	TG	↑↔C
V (rare)	chylomicrons, VLDL	TG	↑↔

C=cholesterol
TG=triglycerides
LDL=low density lipoprotein
VLDL=very low density lipoprotein
IDL=intermediate density lipoprotein

[See second table at top of next page]

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.

CONTRAINDICATIONS

TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

TRICOR is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

TRICOR is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 107 mg to 160 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 107 mg to 160 mg TRICOR per day and was 0% in those receiving dosages equivalent to 54 mg or less TRICOR per day, or placebo.

Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRICOR, and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TRICOR therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with TRICOR because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA Reductase Inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In a single-dose drug interaction study in 23 healthy adults the concomitant administration of TRICOR and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolite 3a-hydroxy iso-pravastatin when compared to either drug given alone.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

Mortality: The effect of TRICOR on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations: In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate tablets), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to TRICOR.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91–1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carci-

Continued on next page

Tricor—Cont.

noma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94–5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS

Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting TRICOR therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of TRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 160 mg per day.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs 0%, and rash in 1.4 vs 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during postmarketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration.

Skeletal muscle: The use of fibrates alone, including TRICOR, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions

Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take TRICOR at least 1 hour before or 4–6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including TRICOR, there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRICOR with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Table 2
Effects of TRICOR in Patients With Fredrickson Type IV/V Hyperlipidemia

Study 1	Placebo				TRICOR			
Baseline TG levels 350 to 499 mg/dL	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**
Triglycerides	28	449	450	−0.5	27	432	223	−46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	−44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	−9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	−44.7*
Study 2	**Placebo**				**TRICOR**			
Baseline TG levels 500 to 1500 mg/dL	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**
Triglycerides	44	710	750	7.2	48	726	308	−54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	−50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	−13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	−4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	−49.4*

* = p<0.05 vs. Placebo

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

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-years risk >20%)	<100	≥100	≥130 (100–129: drug optional)††
2+ Risk Factors 10-year risk ≤20%)	<130	[redacted]	10-year risk 10%–20%: ≥130 10-Year risk <10%: ≥160
0–1 Risk Factor †††	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

† CHD = coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

††† 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter^2 of surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter^2 surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter^2 surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/meter^2 surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Pregnancy Category C: Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6–15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 postpartum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4%**	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 200 mg TRICOR
**Significantly different from Placebo

10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table above. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

[See table above]

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.

CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.

DIGESTIVE SYSTEM: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.

ENDOCRINE SYSTEM: Diabetes mellitus

HEMIC AND LYMPHATIC SYSTEM: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.

METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.

MUSCULOSKELETAL SYSTEM: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.

NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.

RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, pneumonia, laryngitis, and sinusitis.

SKIN AND APPENDAGES: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.

SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.

UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, kidney function abnormal, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving TRICOR, and should continue this diet during treatment with TRICOR. TRICOR tablets should be given with meals, thereby optimizing the bioavailability of the medication.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRICOR is 160 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 54 to 160 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 160 mg per day.

Treatment with TRICOR should be initiated at a dose of 54 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 54 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRICOR if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

TRICOR® (fenofibrate tablets) is available in two strengths:

54 mg yellow tablets, imprinted with ⊐ and Abbo-Code identification letters "TA", available in bottles of 90 (**NDC** 0074-4009-90).

160 mg white tablets, imprinted with ⊐ and Abbo-Code identification letters "TC", available in bottles of 90 (**NDC** 0074-4013-90).

Storage

Store at controlled room temperature, 15–30°C (59–86°F). Keep out of the reach of children. Protect from moisture.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by Laboratoires Fournier, S.A., 21300 Chenôve, France

Made in France

REFERENCES

1. GOLDBERG AC, *et al.* Fenofibrate for the Treatment of Type IV and V Hyperlipoproteinemias: A Double-Blind, Placebo-Controlled Multicenter US Study. *Clinical Therapeutics,* 11, pp. 69–83, 1989.
2. NIKKILA EA. Familial Lipoprotein Lipase Deficiency and Related Disorders of Chylomicron Metabolism. In Stanbury J.B., *et al.* (eds.): *The Metabolic Basis of Inherited Disease,* 5th edition, McGraw-Hill, 1983, Chap. 30, pp. 622–642.
3. BROWN WV, *et al.* Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study In Patients with Type IIA or IIB Hyperlipidemia. *Arteriosclerosis.* 6, pp. 670–678, 1986.

Revised: August, 2001

Ref.: 03-5034-R1

ABBOTT LABORATORIES

NORTH CHICAGO, IL 60064, USA

Shown in Product Identification Guide, page 304

VICODIN® Ⓜ ℞

(hydrocodone bitartrate and acetaminophen tablets, USP)

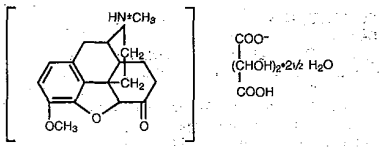
5 mg/500 mg

℞ only

DESCRIPTION

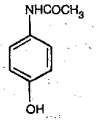
Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is: 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ M.W. 494.50

Acetaminophen, 4′-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ M.W. 151.16

Each VICODIN tablet contains:

Hydrocodone Bitartrate	5 mg
Acetaminophen	500 mg

In addition each tablet contains the following inactive ingredients: colloidal silicon dioxide, starch, croscarmellose sodium, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, povidone, and stearic acid.

Meets USP Dissolution Test 2.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalmic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxy- metabolites. See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug. See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

VICODIN tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

Patients known to be hypersensitive to other opioids may exhibit cross-sensitivity to hydrocodone.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Continued on next page

Table 4: Adverse Events Occurring in ≥2.5% of PLAVIX Patients in CAPRIE

Body System Event	% Incidence (% Discontinuation) PLAVIX [n=9599]	Aspirin [n=9586]
Body as a Whole—general disorders		
Chest Pain	8.3 (0.2)	8.3 (0.3)
Accidental/Inflicted Injury	7.9 (0.1)	7.3 (0.1)
Influenza-like symptoms	7.5 (<0.1)	7.0 (<0.1)
Pain	6.4 (0.1)	6.3 (0.1)
Fatigue	3.3 (0.1)	3.4 (0.1)
Cardiovascular disorders, general		
Edema	4.1 (<0.1)	4.5 (<0.1)
Hypertension	4.3 (<0.1)	5.1 (<0.1)
Central & peripheral nervous system disorders		
Headache	7.6 (0.3)	7.2 (0.2)
Dizziness	6.2 (0.2)	6.7 (0.3)
Gastrointestinal system disorders		
Abdominal pain	5.6 (0.7)	7.1 (1.0)
Dyspepsia	5.2 (0.6)	6.1 (0.7)
Diarrhea	4.5 (0.4)	3.4 (0.3)
Nausea	3.4 (0.5)	3.8 (0.4)
Metabolic & nutritional disorders		
Hypercholesterolemia	4.0 (0)	4.4 (<0.1)
Musculo-skeletal system disorders		
Arthralgia	6.3 (0.1)	6.2 (0.1)
Back Pain	5.8 (0.1)	5.3 (<0.1)
Platelet, bleeding, & clotting disorders		
Purpura/Bruise	5.3 (0.3)	3.7 (0.1)
Epistaxis	2.9 (0.2)	2.5 (0.1)
Psychiatric disorders		
Depression	3.6 (0.1)	3.9 (0.2)
Respiratory system disorders		
Upper resp tract infection	8.7 (<0.1)	8.3 (<0.1)
Dyspnea	4.5 (0.1)	4.7 (0.1)
Rhinitis	4.2 (0.1)	4.2 (<0.1)
Bronchitis	3.7 (0.1)	3.7 (0)
Coughing	3.1 (<0.1)	2.7 (<0.1)
Skin & appendage disorders		
Rash	4.2 (0.5)	3.5 (0.2)
Pruritus	3.3 (0.3)	1.6 (0.1)
Urinary system disorders		
Urinary tract infection	3.1 (0)	3.5 (0.1)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Adverse events occurring in ≥2.0% of patients on PLAVIX in the CURE controlled clinical trial are shown below regardless of relationship to PLAVIX.

Table 5: Adverse Events Occurring in ≥2.0% of PLAVIX Patients in CURE

Body System Event	% Incidence (% Discontinuation) PLAVIX (+ aspirin)* [n=6259]	Placebo (+ aspirin)* [n=6303]
Body as a Whole—general disorders		
Chest Pain	2.7 (<0.1)	2.8 (0.0)
Central & peripheral nervous system disorders		
Headache	3.1 (0.1)	3.2 (0.1)
Dizziness	2.4 (0.1)	2.0 (<0.1)
Gastrointestinal system disorders		
Abdominal pain	2.3 (0.3)	2.8 (0.3)
Dyspepsia	2.0 (0.1)	1.9 (<0.1)
Diarrhea	2.1 (0.1)	2.2 (0.1)

* Other standard therapies were used as appropriate.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving PLAVIX (clopidogrel bisulfate) in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE).

Autonomic Nervous System Disorders: Syncope, Palpitation. *Body as a Whole—general disorders:* Asthenia, Fever, Hernia. *Cardiovascular disorders:* Cardiac failure. *Central and peripheral nervous system disorders:* Cramps legs, Hypoaesthesia, Neuralgia, Paresthesia, Vertigo. *Gastrointestinal system disorders:* Constipation, Vomiting. *Heart rate and rhythm disorders:* Fibrillation atrial. *Liver and biliary system disorders:* Hepatic enzymes increased. *Metabolic and nutritional disorders:* Gout, hyperuricemia, non-protein nitrogen (NPN) increased. *Musculo-skeletal system disorders:* Arthritis, Arthrosis. *Platelet, bleeding & clotting disorders:* GI hemorrhage, hematoma, platelets decreased. *Psychiatric disorders:* Anxiety, Insomnia. *Red blood cell disorders:* Anemia. *Respiratory system disorders:* Pneumonia, Sinusitis. *Skin and appendage disorders:* Eczema, Skin ulceration. *Urinary system disorders:* Cystitis. *Vision disorders:* Cataract, Conjunctivitis.

Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received PLAVIX in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE).

Body as a whole: Allergic reaction, necrosis ischemic. *Cardiovascular disorders:* Edema generalized. *Gastrointestinal system disorders:* Gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic. *Liver and Biliary system disorders:* Bilirubinemia, hepatitis infectious, liver fatty. *Platelet, bleeding and clotting disorders:* hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, Thrombocytopenia. *Red blood cell disorders:* Anemia aplastic, anemia hypochromic. *Reproductive disorders, female:* Menorrhagia. *Respiratory system disorders:* Hemothorax. *Skin and appendage disorders:* Bullous eruption, rash erythematous, rash maculopapular, urticaria. *Urinary system disorders:* Abnormal renal function, acute renal failure. *White cell and reticuloendothelial system disorders:* Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutrophils decreased.

Postmarketing Experience

The following events have been reported spontaneously from worldwide postmarketing experience:

- *Body as a whole:*
  —hypersensitivity reactions, anaphylactoid reactions
- *Central and Peripheral Nervous System disorders:*
  —confusion, hallucinations, taste disorders
- *Liver and Biliary system disorders:*
  —abnormal liver function test, hepatitis (non-infectious)
- *Platelet, Bleeding and Clotting disorders:*
  —cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage)
  —agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP)—see WARNINGS.
  —conjunctival, ocular and retinal bleeding
- *Respiratory system disorders:*
  —bronchospasm
- *Skin and Appendage disorders:*
  —angioedema, erythema multiforme
- *Urinary system disorders:*
  —glomerulopathy, abnormal creatinine levels

OVERDOSAGE

One case of deliberate overdosage with PLAVIX was reported in the large, CAPRIE controlled clinical study. A 34-year-old woman took a single 1,050-mg dose of PLAVIX (equivalent to 14 standard 75-mg tablets). There were no associated adverse events. No special therapy was instituted, and she recovered without sequelae.

No adverse events were reported after single oral administration of 600 mg (equivalent to 8 standard 75-mg tablets) of PLAVIX in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75 mg of PLAVIX per day.

A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.

Recommendations About Specific Treatment:

Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of PLAVIX if quick reversal is required.

DOSAGE AND ADMINISTRATION

The recommended daily dose of PLAVIX is 75 mg once daily.

Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

The recommended daily dose of PLAVIX is 75 mg once daily.

Acute Coronary Syndrome

For patients with acute coronary syndrome (unstable angina/non-Q-wave MI), PLAVIX should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with PLAVIX. In CURE, most patients with Acute Coronary Syndrome also received heparin acutely (see **CLINICAL STUDIES**).

PLAVIX can be administered with or without food.

No dosage adjustment is necessary for elderly patients or patients with renal disease. (See **Clinical Pharmacology: Special Populations.**)

HOW SUPPLIED

PLAVIX (clopidogrel bisulfate) is available as a pink, round, biconvex, film-coated tablet debossed with "75" on one side and "1171" on the other. Tablets are provided as follows:

NDC 63653-1171-6 bottles of 30
NDC 63653-1171-1 bottles of 90
NDC 63653-1171-5 bottles of 500
NDC 63653-1171-3 blisters of 100

Storage

Store at 25° C (77° F); excursions permitted to 15°–30° C (59°–86° F) [See USP Controlled Room Temperature]

Distributed by:
Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership
New York, NY 10016

Sanofi-Synthelabo
Bristol-Myers Squibb Company

PLAVIX® is a registered trademark of Sanofi-Synthelabo

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B1-B001-06-02
1171DIM-14
51-021345-03

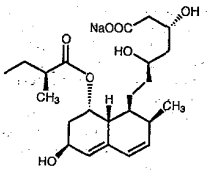
Shown in Product Identification Guide, page 310

PRAVACHOL® ℞
(pravastatin sodium) Tablets
Rx only

DESCRIPTION

PRAVACHOL® (pravastatin sodium) is one of a new class of lipid-lowering compounds, the HMG-CoA reductase inhibitors, which 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 sodium is designated chemically as 1-Naphthalene-heptanoic acid, 1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, [1S-[1α(βS*,δS*),2α,6α, 8β(R*),8aα]]-. Structural formula:



$C_{23}H_{35}NaO_7$ MW 446.52

Pravastatin sodium is an odorless, white to off-white, fine or crystalline powder. It is a relatively polar hydrophilic compound with a partition coefficient (octanol/water) of 0.59 at a pH of 7.0. It is soluble in methanol and water (>300 mg/mL), slightly soluble in isopropanol, and practically insoluble in acetone, acetonitrile, chloroform, and ether.

PRAVACHOL is available for oral administration as 10 mg, 20 mg, 40 mg and 80 mg tablets. Inactive ingredients include: croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. The 10 mg tablet also contains Red Ferric Oxide, the 20 mg and 80 mg tablets also contain Yellow Ferric Oxide, and the 40 mg tablet also contains Green Lake Blend (mixture of D&C Yellow No. 10-Aluminum Lake and FD&C Blue No. 1-Aluminum Lake).

CLINICAL PHARMACOLOGY

Cholesterol and triglycerides in the bloodstream circulate as part of lipoprotein complexes. These complexes can be separated by density ultracentrifugation into high (HDL), intermediate (IDL), low (LDL), and very low (VLDL) density lipoprotein fractions. Triglycerides (TG) and cholesterol synthesized in the liver are incorporated into very low density lipoproteins (VLDLs) and released into the plasma for delivery to peripheral tissues. In a series of subsequent steps, VLDLs are transformed into intermediate density lipoproteins (IDLs), and cholesterol-rich low density lipoproteins (LDLs). High density lipoproteins (HDLs), containing apolipoprotein A, are hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver.

PRAVACHOL 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.

Clinical and pathologic studies have shown that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (Apo 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. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk

Continued on next page

Pravachol—Cont.

factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. In both normal volunteers and patients with hypercholesterolemia, treatment with PRAVACHOL reduced Total-C, LDL-C, and apolipoprotein B. PRAVACHOL also reduced VLDL-C and TG and produced increases in HDL-C and apolipoprotein A. The effects of pravastatin on Lp (a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown. Although pravastatin is relatively more hydrophilic than other HMG-CoA reductase inhibitors, the effect of relative hydrophilicity, if any, on either efficacy or safety has not been established.

In one primary (West of Scotland Coronary Prevention Study – WOS)[1] and two secondary (Long-term Intervention with Pravastatin in Ischemic Disease – LIPID[2] and the Cholesterol and Recurrent Events – CARE[3]) prevention studies, PRAVACHOL has been shown to reduce cardiovascular morbidity and mortality across a wide range of cholesterol levels (see **Clinical Studies**).

Pharmacokinetics/Metabolism

PRAVACHOL is administered orally in the active form. In clinical pharmacology studies in man, pravastatin is rapidly absorbed, with peak plasma levels of parent compound 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 1 hour prior, to meals.

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 apparently extensive first-pass hepatic metabolism, plasma levels may not necessarily correlate perfectly with 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. Systemic bioavailability of pravastatin administered following a bedtime dose was decreased 60% compared to that following an AM dose. Despite this decrease in systemic bioavailability, the efficacy of pravastatin administered once daily in the evening, although not statistically significant, was marginally more effective than that after a morning dose. This finding of lower systemic bioavailability suggests greater hepatic extraction of the drug following the evening dose. Steady-state AUCs, C_{max} and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily administration of PRAVACHOL (pravastatin sodium) tablets. Approximately 50% of the circulating drug is bound to plasma proteins. Following single dose administration of ^{14}C-pravastatin, the elimination half-life ($t^1/_2$) for total radioactivity (pravastatin plus metabolites) in humans is 77 hours.

Pravastatin, like other HMG-CoA reductase inhibitors, has variable bioavailability. The coefficient of variation, based on between-subject variability, was 50% to 60% for AUC.

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 non-renal routes (i.e., biliary excretion and biotransformation). Since there are dual routes of elimination, the potential exists both for compensatory excretion by the alternate route as well as for accumulation of drug and/or metabolites in patients with renal or hepatic insufficiency.

In a study comparing the kinetics of pravastatin in patients with biopsy confirmed cirrhosis (N=7) and normal subjects (N=7), the mean AUC varied 18-fold in cirrhotic patien and 5-fold in healthy subjects. Similarly, the pe pravastatin values varied 47-fold for cirrhotic patients co pared to 6-fold for healthy subjects.

Biotransformation pathways elucidated for pravastatin i clude: (a) isomerization to 6-epi pravastatin and the 3 hydroxyisomer of pravastatin (SQ 31,906), (b) enzyma ring hydroxylation to SQ 31,945, (c) ω-1 oxidation of the ester side chain, (d) β-oxidation of the carboxy side chain, (e) ring oxidation followed by aromatization, (f) oxidation of a hydroxyl group to a keto group, and (g) conjugation. The major degradation product is the 3α-hydroxy isomeric metabolite, which has one-tenth to one-fortieth the HMG-CoA reductase inhibitory activity of the parent compound.

In a single oral dose study using pravastatin 20 mg, the mean AUC for pravastatin was approximately 27% greater and the mean cumulative urinary excretion (CUE) approximately 19% lower in elderly men (65 to 75 years old) compared with younger men (19 to 31 years old). In a similar study conducted in women, the mean AUC for pravastatin was approximately 46% higher and the mean CUE approximately 18% lower in elderly women (65 to 78 years old) compared with younger women (18 to 38 years old). In both studies, C_{max}, T_{max} and ($t^1/_2$) values were similar in older and younger subjects.

Table 1 LIPID — Primary and Secondary Endpoints

	Number (%) of Subjects			
	Pravastatin 40 mg (N = 4512)	Placebo (N = 4502)	Risk Reduction	*P*-value
Primary Endpoint				
CHD mortality	287 (6.4)	373 (8.3)	24%	0.0004
Secondary Endpoints				
Total mortality	498 (11.0)	633 (14.1)	23%	<0.0001
CHD mortality or non-fatal MI	557 (12.3)	715 (15.9)	24%	<0.0001
Myocardial revascularization procedures (CABG or PTCA)	584 (12.9)	706 (15.7)	20%	<0.0001
Stroke				
All-cause	169 (3.7)	204 (4.5)	19%	0.0477
Non-hemorrhagic	154 (3.4)	196 (4.4)	23%	0.0154
Cardiovascular mortality	331 (7.3)	433 (9.6)	25%	<0.0001

Table 2 CARE — Primary and Secondary Endpoints

	Number (%) of Subjects			
	Pravastatin 40 mg (N = 2081)	Placebo (N = 2078)	Risk Reduction	*P*-value
Primary Endpoint				
CHD mortality or nonfatal MI*	212 (10.2)	274 (13.2)	24%	0.003
Secondary Endpoints				
Myocardial revascularization procedures (CABG or PTCA)	294 (14.1)	391 (18.8)	27%	<0.001
Stroke or TIA	93 (4.5)	124 (6.0)	26%	0.029

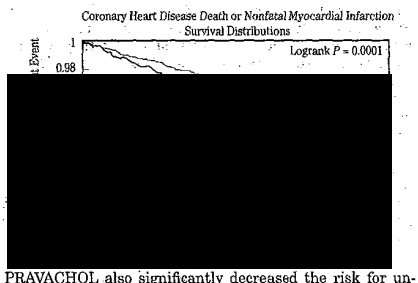
* The risk reduction due to treatment with PRAVACHOL was consistent in both sexes.

Clinical Studies

Prevention of Coronary Heart Disease

In the Pravastatin Primary Prevention Study (West of Scotland Coronary Prevention Study – WOS),[1] the effect of PRAVACHOL (pravastatin sodium) on fatal and nonfatal coronary heart disease (CHD) was assessed in 6595 men 45–64 years of age, without a previous myocardial infarction (MI), and with LDL-C levels between 156–254 mg/dL (4–6.7 mmol/L). In this randomized, double-blind, placebo-controlled study, patients were treated with standard care, including dietary advice, and either PRAVACHOL 40 mg daily (N=3302) or placebo (N=3293) and followed for a median duration of 4.8 years. Median (25th, 75th percentile) percent changes from baseline after 6 months of pravastatin treatment in Total C, LDL-C, TG, and HDL were −20.3 (−26.9, −11.7), −27.7 (−36.0, −16.9), 9.1 (−27.6, 12.5), and 6.7 (−2.1, 15.6), respectively.

PRAVACHOL significantly reduced the rate of first coronary events (either coronary heart disease (CHD) death or nonfatal MI) by 31% [248 events in the placebo group (CHD death=44, nonfatal MI=204) vs 174 events in the PRAVACHOL group (CHD death=31, nonfatal MI=143), p=0.0001 (see figure below)]. The risk reduction with PRAVACHOL 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. The Pravastatin Primary Prevention Study included only men and therefore it is not clear to what extent these data can be extrapolated to a similar population of female patients.



PRAVACHOL also significantly decreased the risk for undergoing myocardial revascularization procedures (coronary artery bypass graft [CABG] surgery or percutaneous transluminal coronary angioplasty [PTCA]) 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 death from non-cardiovascular causes.

Secondary Prevention of Cardiovascular Events

In the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID)[2] study, the effect of PRAVACHOL (pravastatin sodium) 40 mg daily, was assessed in 9014 patients (7498 men; 1516 women; 3514 elderly patients [age ≥65 years]; 782 diabetic patients) who had experienced either an MI (5754 patients) or had been hospitalized for unstable angina pectoris (3260 patients) in the preceding 3–36 months. Patients in this multicenter, double-blind, placebo-controlled study participated for an average of 5.6 years (median of 5.9 years) and at randomization had total cholesterol between 114 and 563 mg/dL (mean 219 mg/dL), LDL-C between 46 and 274 mg/dL (mean 150 mg/dL), triglycerides between 35 and 2710 mg/dL (mean 160 mg/dL), and HDL-C between 1 and 103 mg/dL (mean 37 mg/dL). At baseline, 82% of patients were receiving aspirin and 76% were receiving antihypertensive medication. Treatment with PRAVACHOL significantly reduced the risk for total mortality by reducing coronary death (see **Table 1**). The risk reduction due to treatment with PRAVACHOL on CHD mortality was consistent regardless of age. PRAVACHOL significantly reduced the risk for total mortality (by reducing CHD death) and CHD events (CHD mortality or nonfatal MI) in patients who qualified with a history of either MI or hospitalization for unstable angina pectoris.

[See table 1 above]

In the Cholesterol and Recurrent Events (CARE)[3] study the effect of PRAVACHOL, 40 mg daily, on coronary heart disease death and nonfatal MI was assessed in 4159 patients (3583 men and 576 women) who had experienced a myocardial infarction in the preceding 3–20 months and who had normal (below the 75th percentile of the general population) plasma total cholesterol levels. Patients in this double-blind, placebo controlled study participated for an average of 4.9 years and had a mean baseline total cholesterol of 209 mg/dL. LDL cholesterol levels in this patient population ranged from 101 mg/dL–180 mg/dL (mean = 139 mg/dL). At baseline, 84% of patients were receiving aspirin and 82% were taking antihypertensive medications. Median (25th, 75th percentile) percent changes from baseline after 6 months of pravastatin treatment in Total C, LDL-C, TG, and HDL were −22.0 (−28.4, −14.9), −32.4 (−39.9, −23.7), −11.0 (−26.5, 8.6), and 5.1 (−2.9, 12.7), respectively. Treatment with PRAVACHOL (pravastatin sodium) significantly reduced the rate of first recurrent coronary events (either CHD death or nonfatal MI), the risk of undergoing revascularization procedures (PTCA, CABG), and the risk for stroke or transient ischemic attack (TIA) (see **Table 2**).

[See table 2 above]

In the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I)[4] study, the effect of pravastatin therapy on coronary atherosclerosis was assessed by coronary angiography in patients with coronary disease and moderate hypercholesterolemia (baseline LDL-C range = 130–190 mg/dL). In this double-blind, multicenter, controlled clinical trial angiograms were evaluated at baseline and at three years in 264 patients. Although the difference between pravastatin and placebo for the primary endpoint (per-patient change in mean coronary artery diameter) and one of two secondary endpoints (change in percent lumen diameter stenosis) did not reach statistical significance, for the secondary endpoint of change in minimum lumen diameter, statistically significant slowing of disease was seen in the pravastatin treatment group (p=0.02).

In the Regression Growth Evaluation Statin Study (REGRESS)[5], the effect of pravastatin on coronary atherosclerosis was assessed by coronary angiography in 885 patients with angina pectoris, angiographically documented coronary artery disease and hypercholesterolemia (baseline total cholesterol range = 160–310 mg/dL). In this double-blind, multicenter, controlled clinical trial, angiograms were evaluated at baseline and at two years in 653 patients (323 treated with pravastatin). Progression of coronary atherosclerosis was significantly slowed in the pravastatin group as assessed by changes in mean segment diameter (p=0.037) and minimum obstruction diameter (p=0.001).

Analysis of pooled events from PLAC I, the Pravastatin, Lipids and Atherosclerosis in the Carotids Study (PLAC II)[6], REGRESS, and the Kuopio Atherosclerosis Prevention Study (KAPS)[7] (combined N=1891) showed that treatment with pravastatin was associated with a statistically significant reduction in the composite event rate of fatal and nonfatal myocardial infarction (46 events or 6.4% for placebo versus 21 events or 2.4% for pravastatin, p=0.001). The predominant effect of pravastatin was to reduce the rate of nonfatal myocardial infarction.

Primary Hypercholesterolemia (Fredrickson Type IIa and IIb)

PRAVACHOL (pravastatin sodium) is highly effective in reducing Total-C, LDL-C and Triglycerides (TG) in patients

with heterozygous familial, presumed familial combined and non-familial (non-FH) forms of primary hypercholesterolemia, and mixed dyslipidemia. A therapeutic response is seen within 1 week, and the maximum response usually is achieved within 4 weeks. This response is maintained during extended periods of therapy. In addition, PRAVACHOL is effective in reducing the risk of acute coronary events in hypercholesterolemic patients with and without previous myocardial infarction.

A single daily dose is as effective as the same total daily dose given twice a day. In multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin in daily doses ranging from 10 mg to 40 mg consistently and significantly decreased Total-C, LDL-C, TG, and Total-C/HDL-C and LDL-C/HDL-C ratios; (see **Table 3**).

In a pooled analysis of two multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin at a daily dose of 80 mg (N = 277) significantly decreased Total-C, LDL-C, and TG. The 25th and 75th percentile changes from baseline in LDL-C for pravastatin 80 mg were −43% and −30%. The efficacy results of the individual studies were consistent with the pooled data (see **Table 3**).

Treatment with PRAVACHOL modestly decreased VLDL-C and PRAVACHOL across all doses produced variable increased in HDL-C (see **Table 3**).

Table 3 Primary Hypercholesterolemia Studies: Dose Response of PRAVACHOL Once Daily Administration

Dose	Total-C	LDL-C	HDL-C	TG
Mean Percent Changes From Baseline After 8 Weeks*				
Placebo (N = 36)	−3%	−4%	+1%	−4%
10 mg (N = 18)	−16%	−22%	+7%	−15%
20 mg (N = 19)	−24%	−32%	+2%	−11%
40 mg (N = 18)	−25%	−34%	+12%	−24%
Mean Percent Changes From Baseline After 6 Weeks**				
Placebo (N = 162)	0%	−1%	−1%	+1%
80 mg (N = 277)	−27%	−37%	+3%	−19%

*a multicenter, double-blind, placebo-controlled study
**pooled analysis of 2 multicenter, double-blind, placebo-controlled studies

In another clinical trial, patients treated with pravastatin in combination with cholestyramine (70% of patients were taking cholestyramine 20 or 24 g per day) had reductions equal to or greater than 50% in LDL-C. Furthermore, pravastatin attenuated cholestyramine-induced increases in TG levels (which are themselves of uncertain clinical significance).

Hypertriglyceridemia (Fredrickson Type IV)

The response to pravastatin in patients with Type IV hyperlipidemia (baseline TG >200 mg/dL and LDL-C <160 mg/dL) was evaluated in a subset of 429 patients from the Cholesterol and Recurrent Events (CARE) study. For pravastatin-treated subjects, the median (min, max) baseline triglyceride level was 246.0 (200.5, 349.5) mg/dL (see **Table 4**).

Table 4 Patients With Fredrickson Type IV Hyperlipidemia Median (25th,75th percentile) Percent Change From Baseline

	Pravastatin 40 mg (N=429)	Placebo (N=430)
Triglycerides	−21.1 (−34.8, 1.3)	−6.3 (−23.1, 18.3)
Total-C	−22.1 (−27.1, −14.8)	0.2 (−6.9, 6.8)
LDL-C	−31.7 (−39.6, −21.5)	0.7 (−9.0, 10.0)
HDL-C	7.4 (−1.2, 17.7)	2.8 (−5.7, 11.7)
Non-HDL-C	−27.2 (−34.0, −18.5)	−0.8 (−8.2, 7.0)

Dysbetalipoproteinemia (Fredrickson Type III)

The response to pravastatin in two double-blind crossover studies of 46 patients with genotype E2/E2 and Fredrickson Type III dysbetalipoproteinemia is shown in **Table 5**.

Table 5 Patients With Fredrickson Type III Dysbetalipoproteinemia Median (min, max) Percent Change From Baseline

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max) Pravastatin 40 mg (N=20)
Study 1		
Total-C	386.5 (245.0, 672.0)	−32.7 (−58.5, 4.6)
Triglycerides	443.0 (275.0, 1299.0)	−23.7 (−68.5, 44.7)
VLDL-C*	206.5 (110.0, 379.0)	−43.8 (−73.1, −14.3)
LDL-C*	117.5 (80.0, 170.0)	−40.8 (−63.7, 4.6)
HDL-C	30.0 (18.0, 88.0)	6.4 (−45.0, 105.6)
Non-HDL-C	344.5 (215.0, 646.0)	−36.7 (−66.3, 5.8)
*N=14		
Study 2		
Total-C	340.3 (230.1, 448.6)	−31.4 (−54.5, −13.0)
Triglycerides	343.2 (212.6, 845.9)	−11.9 (−56.5, 44.8)
VLDL-C	145.0 (71.5, 309.4)	−35.7 (−74.7, 19.1)
LDL-C	128.6 (63.8, 177.9)	−30.3 (−52.2, 13.5)
HDL-C	38.7 (27.1, 58.0)	5.0 (−17.7, 66.7)
Non-HDL-C	295.8 (195.3, 421.5)	−35.5 (−81.0, −13.5)

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 Levels 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
0–1 Risk factor[c]	< 160	≥ 160	≥ 190 (160–189: LDL-lowering drug optional)

[a] CHD, coronary heart disease.
[b] Some authorities recommend the 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 judgement 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.

INDICATIONS AND USAGE

Therapy with PRAVACHOL (pravastatin sodium) should be considered in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence or absence of coronary heart disease, and other risk factors.

Primary Prevention of Coronary Events

In hypercholesterolemic patients without clinically evident coronary heart disease, PRAVACHOL is indicated to:
— Reduce the risk of myocardial infarction
— Reduce the risk of undergoing myocardial revascularization procedures
— Reduce the risk of cardiovascular mortality with no increase in death from non-cardiovascular causes

Secondary Prevention of Cardiovascular Events

In patients with clinically evident coronary heart disease, PRAVACHOL is indicated to:
— Reduce the risk of total mortality by reducing coronary death
— Reduce the risk of myocardial infarction
— Reduce the risk of undergoing myocardial revascularization procedures
— Reduce the risk of stroke and stroke/transient ischemic attack (TIA)
— Slow the progression of coronary atherosclerosis

Hyperlipidemia

PRAVACHOL is indicated as an adjunct to diet to reduce elevated Total-C, LDL-C, Apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb).[8]

PRAVACHOL is indicated as adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV).

PRAVACHOL is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.

Lipid-altering agents 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 NCEP Guidelines below).

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

$$\text{LDL-C} = \text{Total-C} - \text{HDL-C} - \tfrac{1}{5}\,\text{TG}$$

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

Lipid determinations should be performed at intervals of no less than four weeks and dosage adjusted according to the patients response to therapy.

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

[See table at top of page]

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 Treatment 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.

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

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

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

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 are contraindicated during pregnancy and in nursing mothers. **Pravastatin 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 immediately and the patient apprised of the potential hazard to the fetus (see **PRECAUTIONS: Pregnancy**).

WARNINGS

Liver Enzymes

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. In three long-term (4.8–5.9 years), placebo-controlled clinical trials (WOS, LIPID, CARE; see **CLINICAL PHARMACOLOGY: Clinical Studies**), 19,592 subjects (19,768 randomized), were exposed to pravastatin or placebo. In an analysis of serum transaminase values (ALT, AST), incidences of marked abnormalities were compared between the pravastatin and placebo treatment groups; a marked abnormality was defined as a post-treatment test value greater than three times the upper limit of normal for subjects with pretreatment values less than or equal to the upper limit of normal, or four times the pretreatment value for subjects with pretreatment values greater than the upper limit of normal but less than 1.5 times the upper limit of normal. Marked abnormalities of ALT or AST occurred with similar low frequency (≤1.2%) in both treatment groups. Overall, clinical trial experience showed that liver function test abnormalities observed during pravastatin therapy were usually asymptomatic, not associated with cholestasis, and did not appear to be related to treatment duration.

It is recommended that liver function tests be performed prior to the initiation of therapy, prior to the elevation of the dose, and when otherwise clinically indicated.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of pravastatin (see **CONTRAINDICATIONS**). Caution should be exercised when pravastatin is administered to patients who have a recent history of liver disease, have signs that may suggest liver disease (e.g., unexplained aminotransferase elevations, jaundice), or are heavy users of alcohol (see **CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabo-**

Continued on next page

Pravachol—Cont.

lism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Patients who develop increased transaminase levels or signs and symptoms of liver disease should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of pravastatin therapy is recommended.

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see **ADVERSE REACTIONS**). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper normal limit, was rare (<0.1%) in pravastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates. However, neither myopathy nor significant increases in CPK levels have been observed in three reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to two years concurrently with pravastatin 10–40 mg and cyclosporine. Some of these patients also received other concomitant immunosuppressive therapies. Further, in clinical trials involving small numbers of patients who were treated concurrently with pravastatin and niacin, there were no reports of myopathy. Also, myopathy was not reported in a trial of combination pravastatin (40 mg/day) and gemfibrozil (1200 mg/day), although 4 of 75 patients on the combination showed marked CPK elevations versus one of 73 patients receiving placebo. There was a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy (see **PRECAUTIONS: Drug Interactions**). **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.**

PRECAUTIONS

General

PRAVACHOL (pravastatin sodium) may elevate creatine phosphokinase and transaminase levels (see **ADVERSE REACTIONS**). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

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.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (tZ\x) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever (see **WARNINGS: Skeletal Muscle**).

Drug Interactions

Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See **WARNINGS: Skeletal Muscle**

Cytochrome P450 3A4 Inhibitors: 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 (see diltiazem and itraconazole below). Other examples of cytochrome P450 3A4 inhibitors include ketoconazole, mibefradil, and erythromycin.

Diltiazem— Steady-state levels of diltiazem (a known, weak inhibitor of P450 3A4) had no effect on the pharmacokinetics of pravastatin. In this study, the AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 3.6 and 4.3, respectively.

Itraconazole—The mean AUC and C_{max} for pravastatin were increased by factors of 1.7 and 2.5, respectively, when given with itraconazole (a potent P450 3A4 inhibitor which also inhibits p-glycoprotein transport) as compared to placebo. The mean $t^1/_2$ was not affected by itraconazole, suggesting that the relatively small increases in C_{max} and AUC were due solely to increased bioavailability rather than a decrease in clearance, consistent with inhibition of p-glycoprotein transport by itraconazole. This drug transport system is thought to affect bioavailability and excretion of HMG-CoA reductase inhibitors, including pravastatin. The AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 19 and 17, respectively, when given with itraconazole.

Antipyrine: Since concomitant administration of pravastatin had no effect on the clearance of antipyrine, interactions with other drugs metabolized via the same hepatic cytochrome isozymes are not expected.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See **DOSAGE AND ADMINISTRATION: Concomitant Therapy**.)

Warfarin: Concomitant administration of 40 mg pravastatin had no clinically significant effect on prothrombin time when administered in a study to normal elderly subjects who were stabilized on warfarin.

Cimetidine: The $AUC_{0-12\ hr}$ for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given 20 mg pravastatin and 0.2 mg digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Cyclosporine: Some investigators have measured cyclosporine 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 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, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended. (See **WARNINGS: Skeletal Muscle**.)

In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL) (pravastatin sodium) *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity

CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day. These effects in dogs were observed at approximately 59 times the human dose of 80 mg/day, based on AUC. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). These effects in rats were observed at approximately 12 times the human dose (HD) of 80 mg, based on body surface area mg/m^2 and at approximately 4 times the human dose, based on AUC.

In a 2-year study in mice fed pravastatin at doses of 250 and 500 mg/kg/day, there was an increased incidence of hepatocellular carcinomas in males and females at both 250 and 500 mg/kg/day ($p<0.0001$). At these doses, lung adenomas in females were increased ($p=0.013$). These effects in mice were observed at approximately 15 times (250 mg/kg/day) and 23 times (500 mg/kg/day) the human dose of 80 mg, based on AUC. In another 2-year study in mice with doses up to 100 mg/kg/day (producing drug exposures approximately 2 times the human dose of 80 mg, based on AUC), there were no drug-induced tumors.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X.

See **CONTRAINDICATIONS**.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 10× (rabbit) or 120× (rat) the human exposure based on surface area (mg/meter^2). Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review[9] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a three-to-four-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with PRAVACHOL (pravastatin sodium) during pregnancy (see **CONTRAINDICATIONS**), treatment should be immediately discontinued as soon as pregnancy is recognized. PRAVACHOL should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Nursing Mothers

A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see **CONTRAINDICATIONS**).

Pediatric Use

Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time.

Geriatric Use

Two secondary prevention trials with pravastatin (CARE and LIPID) included a total of 6,593 subjects treated with pravastatin 40 mg for periods ranging up to 6 years. Across these two studies, 36.1% of pravastatin subjects were aged 65 and older and 0.8% were aged 75 and older. The beneficial effect of pravastatin in elderly subjects in reducing cardiovascular events and in modifying lipid profiles was similar to that seen in younger subjects. The adverse event profile in the elderly was similar to that in the overall population. Other reported clinical experience has not identified differences in responses to pravastatin between elderly and younger patients.

Mean pravastatin AUCs are slightly (25–50%) higher in elderly subjects than in healthy young subjects, but mean

C_{max}, T_{max} and $t^1/_2$ values are similar in both age groups and substantial accumulation of pravastatin would not be expected in the elderly (see **CLINICAL PHARMACOLOGY: Pharmacokinetics/ Metabolism**).

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. (See also **PRECAUTIONS: Geriatric Use** section).

Adverse Clinical Events

Short-Term Controlled Trials

All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials up to 4 months duration are identified in **Table 6**; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

[See table at right]

The safety and tolerability of PRAVACHOL (pravastatin sodium) at a dose of 80 mg in two controlled trials with a mean exposure of 8.6 months was similar to that of PRAVACHOL (pravastatin sodium) at lower doses except that 4 out of 464 patients taking 80 mg of pravastatin had a single elevation of CK >10X ULN compared to 0 out of 115 patients taking 40 mg of pravastatin.

Long-Term Controlled Morbidity and Mortality Trials

Adverse event data were pooled from seven double-blind placebo-controlled trials (West of Scotland Coronary Prevention study [WOS]; Cholesterol and Recurrent Events study [CARE]; Long-term Intervention with Pravastatin in Ischemic Disease study [LIPID]; Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study [PLAC I]; Pravastatin, Lipids and Atherosclerosis in the Carotids study [PLAC II]; Regression Growth Evaluation Statin Study [REGRESS]; and Kuopio Atherosclerosis Prevention Study [KAPS]) involving a total of 10,764 patients treated with pravastatin 40 mg and 10,719 patients treated with placebo. The safety and tolerability profile in the pravastatin group was comparable to that of the placebo group. Patients were exposed to pravastatin for a mean of 4.0 to 5.1 years in WOS, CARE, and LIPID and 1.9 to 2.9 years in PLAC I, PLAC II, KAPS, and REGRESS. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Collectively, these seven trials represent 47,613 patient-years of exposure to pravastatin. Events believed to be of probable, possible, or uncertain relationship to study drug, occurring in at least 1% of patients treated with pravastatin in these studies are identified in **Table 7**.

Table 7 Adverse Events in ≥1 Percent of Patients Treated with Pravastatin 40 mg in Long-Term Placebo-Controlled Trials

Body System/Event	Pravastatin (N = 10,764) % of patients	Placebo (N = 10,719) % of patients
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		
Urinary Abnormality (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 burred vision, diplopia)	1.6	1.3

Events of probable, possible, or uncertain relationship to study drug that occurred in <1.0% of pravastatin-treated patients in the long-term trials included the following; frequencies were similar in placebo-treated patients:

Table 6 Adverse Events in >2% of Patients Treated with Pravastatin 10–40 mg in Short-Term Placebo-Controlled Trials

	All Events		Events Attributed to Study Drug	
Body System/Event	Pravastatin (N = 900) % of patients	Placebo (N = 411) % of patients	Pravastatin (N = 900) % of patients	Placebo (N = 411) % of patients
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo

Dermatologic: pruritus, dermatitis, dryness of skin, scalp hair abnormality (including alopecia), urticaria.
Endocrine/Metabolic: sexual dysfunction, libido change.
Gastrointestinal: decreased appetite.
General: fever, flushing.
Immunologic: allergy, edema head/neck.
Musculoskeletal: muscle weakness.
Nervous System: paresthesia, vertigo, insomnia, memory impairment, tremor, neuropathy (including peripheral neuropathy).
Special Senses: lens opacity, taste disturbance.

Postmarketing Experience

In addition to the events reported above, as with other drugs in this class, the following events have been reported rarely during postmarketing experience with PRAVACHOL (pravastatin sodium), regardless of causality assessment:
Musculoskeletal: myopathy, rhabdomyolysis.
Nervous System: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), peripheral nerve palsy.
Hypersensitivity: anaphylaxis, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, asthenia, photosensitivity, chills, malaise, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, cirrhosis, fulminant hepatic necrosis, hepatoma.
Dermatologic: A variety of skin changes (e.g., nodules, discoloration, dryness of mucous membranes, changes to hair/nails).
Reproductive: gynecomastia.
Laboratory Abnormalities: elevated alkaline phosphatase, and bilirubin; thyroid function abnormalities.

Laboratory Test Abnormalities

Increases in serum transaminase (ALT, AST) values and CPK have been observed (see **WARNINGS**).
Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with HMG-CoA reductase inhibitors.

Concomitant Therapy

Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See **WARNINGS: Skeletal Muscle** and **PRECAUTIONS: Drug Interactions**.)

OVERDOSAGE

To date, there has been limited experience with overdosage of pravastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures should be instituted as required. (See **WARNINGS**.)

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving PRAVACHOL (pravastatin sodium) and should continue on this diet during treatment with PRAVACHOL (see NCEP Treatment Guidelines for details on dietary therapy).
The recommended starting dose is 40 mg once daily. PRAVACHOL can be administered as a single dose at any time of the day, with or without food. In patients with a history of significant renal or hepatic dysfunction, a starting dose of 10 mg daily is recommended.
Since the maximal effect of a given dose is seen within 4 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. If a daily dose of 40 mg does not achieve desired cholesterol levels, 80 mg once daily is recommended.
In patients taking immunosuppressive drugs such as cyclosporine (see **WARNINGS: Skeletal Muscle**) concomitantly with pravastatin, therapy should begin with 10 mg of pravastatin once-a-day at bedtime and titration to higher doses should be done with caution. Most patients treated with this combination received a maximum pravastatin dose of 20 mg/day.

Concomitant Therapy

The lipid-lowering effects of PRAVACHOL 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, PRAVACHOL should be given either 1 hour or more before or at least 4 hours following the resin. See also **ADVERSE REACTIONS: Concomitant Therapy**.

HOW SUPPLIED

PRAVACHOL® (pravastatin sodium) Tablets are supplied as:

10 mg tablets: Pink to peach, rounded, rectangular-shaped, biconvex with a P embossed on one side and PRAVACHOL 10 engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5154-05). Bottles contain a desiccant canister.

20 mg tablets: Yellow, rounded, rectangular-shaped, biconvex with a P embossed on one side and PRAVACHOL 20 engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5178-05) and bottles of 1000 (NDC 0003-5178-75). Bottles contain a desiccant canister.

40 mg tablets: Green, rounded, rectangular-shaped, biconvex with a P embossed on one side and PRAVACHOL 40 engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5194-10). Bottles contain a desiccant canister.

80 mg tablets: Yellow, oval-shaped, biconvex with BMS embossed on one side and 80 engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5195-10) and bottles of 500 (NDC 0003-5195-12). Bottles contain a desiccant canister.

Unimatic® unit-dose packs containing 100 tablets are also available for the **20 mg** (NDC 0003-5178-06) potency.

Continued on next page

Pravachol—Cont.

Storage

Store at 25°C (77°F); excursions permitted to 15°–30° C (59°–86°F) [see USP Controlled Room Temperature]. Keep tightly closed (protect from moisture). Protect from light.

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Princeton, NJ 08543 U.S.A.

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Shown in Product Identification Guide, page 310

SERZONE®

℞

[ser' zōnē]

(nefazodone hydrochloride) Tablets

Rx only

(Patient Information Included)

Before prescribing SERZONE, the physician should be thoroughly familiar with the details of this prescribing information.

WARNING

Cases of life-threatening hepatic failure have been reported in patients treated with SERZONE.

The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000–300,000 patient-years of SERZONE treatment. The total patient-years is a summation of each patient's duration of exposure expressed in years. For example, 1 patient-year is equal to 2 patients each treated for 6 months, 3 patients each treated for 4 months, etc. (See WARNINGS.)

Ordinarily, treatment with SERZONE should not be initiated in with active liver disease or with elevated baseline serum transaminases. There is no evidence that pre-existing liver disease increases the likelihood of developing liver failure, however, baseline abnormalities can complicate patient monitoring.

Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur.

SERZONE should be discontinued if clinical signs or symptoms suggest liver failure (see PRECAUTIONS: Information for Patients). Patients who develop evidence of hepatocellular injury such as increased serum AST or serum ALT levels ≥ 3 times the upper limit of NORMAL, while on SERZONE should be withdrawn from the drug. These patients should be presumed to be at increased risk for liver injury if SERZONE is reintroduced. Accordingly, such patients should not be considered for re-treatment.

DESCRIPTION

SERZONE® (nefazodone hydrochloride) is an antidepressant for oral administration with a chemical structure unrelated to selective serotonin reuptake inhibitors, tricyclics, tetracyclics, or monoamine oxidase inhibitors (MAOI).

Nefazodone hydrochloride is a synthetically derived phenylpiperazine antidepressant. The chemical name for nefazodone hydrochloride is 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one monohydrochloride. The molecular formula is $C_{25}H_{32}ClN_5O_2 \cdot HCl$, which corresponds to a molecular weight of 506.5. The structural formula is:

Nefazodone hydrochloride is a nonhygroscopic, white crystalline solid. It is freely soluble in chloroform, soluble in propylene glycol, and slightly soluble in polyethylene glycol and water.

SERZONE is supplied as hexagonal tablets containing 50 mg, 100 mg, 150 mg, 200 mg, or 250 mg of nefazodone hydrochloride and the following inactive ingredients: microcrystalline cellulose, povidone, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and iron oxides (red and/or yellow) as colorants.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of nefazodone, as with other antidepressants, is unknown.

Preclinical studies have shown that nefazodone inhibits neuronal uptake of serotonin and norepinephrine.

Nefazodone occupies central 5-HT_2 receptors at nanomolar concentrations, and acts as an antagonist at this receptor. Nefazodone was shown to antagonize alpha$_1$-adrenergic receptors, a property which may be associated with postural hypotension. *In vitro* binding studies showed that nefazodone had no significant affinity for the following receptors: alpha$_2$ and beta adrenergic, 5-HT_{1A}, cholinergic, dopaminergic, or benzodiazepine.

Pharmacokinetics

Nefazodone hydrochloride is rapidly and completely absorbed but is subject to extensive metabolism, so that its absolute bioavailability is low, about 20%, and variable. Peak plasma concentrations occur at about one hour and the half-life of nefazodone is 2–4 hours.

Both nefazodone and its pharmacologically similar metabolite, hydroxynefazodone, exhibit nonlinear kinetics for both dose and time, with AUC and C_{max} increasing more than proportionally with dose increases and more than expected upon multiple dosing over time, compared to single dosing. For example, in a multiple-dose study involving BID dosing with 50, 100, and 200 mg, the AUC for nefazodone and hydroxynefazodone increased by about 4-fold with an increase in dose from 200 to 400 mg per day; C_{max} increased by about 3-fold with the same dose increase. In a multiple-dose study involving BID dosing with 25, 50, 100, and 150 mg, the accumulation ratios for nefazodone and hydroxynefazodone AUC, after 5 days of BID dosing relative to the first dose, ranged from approximately 3 to 4 at the lower doses (50–100 mg/day) and from 5 to 7 at the higher doses (200–300 mg/day); there were also approximately 2- to 4-fold increases in C_{max} after 5 days of BID dosing relative to the first dose, suggesting extensive and greater than predicted accumulation of nefazodone and its hydroxy metabolite with multiple dosing. Steady-state plasma nefazodone and metabolite concentrations are attained within 4 to 5 days of initiation of BID dosing or upon dose increase or decrease.

Nefazodone is extensively metabolized after oral administration by n-dealkylation and aliphatic and aromatic hydroxylation, and less than 1% of administered nefazodone is excreted unchanged in urine. Attempts to characterize three metabolites identified in plasma, hydroxynefazodone (HO-NEF), meta-chlorophenylpiperazine (mCPP), and a triazole-dione metabolite, have been carried out. The AUC (expressed as a multiple of the AUC for nefazodone dosed at 100 mg BID) and elimination half-lives for these three metabolites were as follows:

AUC Multiples and $T_{1/2}$ for Three Metabolites of Nefazodone (100 mg BID)

Metabolite	AUC Multiple	$T_{1/2}$
HO-NEF	0.4	1.5–4 h
mCPP	0.07	4–8 h
Triazole-dione	4.0	18 h

HO-NEF possesses a pharmacological profile qualitatively and quantitatively similar to that of nefazodone. mCPP has some similarities to nefazodone, but also has agonist activity at some serotonergic receptor subtypes. The pharmacological profile of the triazole-dione metabolite has not yet been well characterized. In addition to the above compounds, several other metabolites were present in plasma but have not been tested for pharmacological activity.

After oral administration of radiolabeled nefazodone, the mean half-life of total label ranged between 11 and 24 hours. Approximately 55% of the administered radioactivity was detected in urine and about 20–30% in feces.

Distribution—Nefazodone is widely distributed in body tissues, including the central nervous system (CNS). In humans the volume of distribution of nefazodone ranges from 0.22 to 0.87 L/kg.

Protein Binding—At concentrations of 25–2500 ng/mL nefazodone is extensively (>99%) bound to human plasma proteins *in vitro*. The administration of 200 mg BID of nefazodone for 1 week did not increase the fraction of unbound warfarin in subjects whose prothrombin times had been prolonged by warfarin therapy to 120–150% of the laboratory control (see **PRECAUTIONS: Drug Interactions**). While nefazodone did not alter the *in vitro* protein binding of chlorpromazine, desipramine, diazepam, diphenylhydantoin, lidocaine, prazosin, propranolol, or verapamil, it is unknown whether displacement of either nefazodone or these drugs occurs *in vivo*. There was a 5% decrease in the protein binding of haloperidol; this is probably of no clinical significance.

Effect of Food—Food delays the absorption of nefazodone and decreases the bioavailability of nefazodone by approximately 20%.

Renal Disease—In studies involving 29 renally impaired patients, renal impairment (creatinine clearances ranging from 7 to 60 mL/min/1.73m^2) had no effect on steady-state nefazodone plasma concentrations.

Liver Disease—In a multiple-dose study of patients with liver cirrhosis, the AUC values for nefazodone and HO-NEF at steady state were approximately 25% greater than those observed in normal volunteers.

Age/Gender Effects—After single doses of 300 mg to younger (18–45 years) and older patients (>65 years), C_{max} and AUC for nefazodone and hydroxynefazodone were up to twice as high in the older patients. With multiple doses, however, differences were much smaller, 10–20%. A similar result was seen for gender, with a higher C_{max} and AUC in women after single doses but no difference after multiple doses.

Treatment with SERZONE (nefazodone hydrochloride) should be initiated at half the usual dose in elderly patients, especially women (see **DOSAGE AND ADMINISTRATION**), but the therapeutic dose range is similar in younger and older patients.

Clinical Efficacy Trial Results

Studies in Outpatients with Depression

During its premarketing development, the efficacy of SERZONE was evaluated at doses within the therapeutic range in five well-controlled, short-term (6–8 weeks) clinical investigations. These trials enrolled outpatients meeting DSM-III or DSM-IIIR criteria for major depression. Among these trials, two demonstrated the effectiveness of SERZONE, and two provided additional support for that conclusion.

One trial was a 6-week dose-titration study comparing SERZONE in two dose ranges (up to 300 mg/day and up to 600 mg/day [mean modal dose for this group was about 400 mg/day], on a BID schedule) and placebo. The second trial was an 8-week dose-titration study comparing SERZONE (up to 600 mg/day; mean modal dose was 375 mg/day), imipramine (up to 300 mg/day), and placebo, all on a BID schedule. Both studies demonstrated SERZONE, at doses titrated between 300 mg to 600 mg/day (therapeutic dose range), to be superior to placebo on at least three of the following four measures: 17-Item Hamilton Depression Rating Scale or HDRS (total score), Hamilton Depressed Mood item, Clinical Global Impressions (CGI) Severity score, and CGI Improvement score. Significant differences were also found for certain factors of the HDRS (e.g., anxiety factor, sleep disturbance factor, and retardation factor). In the two supportive studies, SERZONE was titrated up to 500 or 600 mg/day (mean modal doses of 462 mg/day and 363 mg/day). In the fifth study, the differentiation in response rates between SERZONE and placebo was not statistically significant. Three additional trials were conducted using subtherapeutic doses of SERZONE.

Overall, approximately two thirds of patients in these trials were women, and an analysis of the effects of gender on outcome did not suggest any differential responsiveness on the basis of sex. There were too few elderly patients in these trials to reveal possible age-related differences in response. Since its initial marketing as an antidepressant drug product, additional clinical investigations of SERZONE have been conducted. These studies explored SERZONE's use under conditions not evaluated fully at the time initial marketing approval was granted.

Studies in "Inpatients"

Two studies were conducted to evaluate SERZONE's effectiveness in hospitalized depressed patients. These were 6-week, dose-titration trials comparing SERZONE (up to 600 mg/day) and placebo, on a BID schedule. In one study, SERZONE was superior to placebo. In this study, the mean modal dose of SERZONE was 503 mg/day, and 85% of these inpatients were melancholic; at baseline, patients were distributed at the higher end of the 7-point CGI Severity scale, as follows: 4=moderately ill (17%); 5=markedly ill (48%); 6=severely ill (32%). In the other study, the differentiation in response rates between SERZONE and placebo was not statistically significant. This result may be explained by the "high" rate of spontaneous improvement among the patients randomized to placebo.

Carcinogenesis, Mutagenesis and Impairment of Fertility
A reportedly apparent association between prolonged thyroid therapy and breast cancer has not been confirmed and patients on thyroid for established indications should not discontinue therapy. No confirmatory long-term studies in animals have been performed to evaluate carcinogenic potential, mutagenicity, or impairment of fertility in either males or females.

Pregnancy
Pregnancy Category A: Thyroid hormones do not readily cross the placental barrier. The clinical experience to date does not indicate any adverse effect on fetuses when thyroid hormones are administered to pregnant women. On the basis of current knowledge, thyroid replacement therapy to hypothyroid women should not be discontinued during pregnancy.

Nursing Mothers
Minimal amounts of thyroid hormones are excreted in human milk. Thyroid hormones are not associated with serious adverse reactions and do not have a known tumorigenic potential. However, caution should be exercised when thyroid hormones are administered to a nursing woman.

Pediatric Use
There is limited experience with *Triostat* in the pediatric population. Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
The most frequently reported adverse events were arrhythmia (6% of patients) and tachycardia (3%). Cardiopulmonary arrest, hypotension and myocardial infarction occurred in approximately 2% of patients. The following events occurred in approximately 1% or fewer of patients: angina, congestive heart failure, fever, hypertension, phlebitis and twitching.
In rare instances, allergic skin reactions have been reported with liothyronine sodium tablets.

OVERDOSAGE
Signs and Symptoms: Headache, irritability, nervousness, tremor, sweating, increased bowel motility and menstrual irregularities. Angina pectoris, arrhythmia, tachycardia, acute myocardial infarction or congestive heart failure may be induced or aggravated. Shock may also develop if there is untreated pituitary or adrenocortical failure. Massive overdosage may result in symptoms resembling thyroid storm.
Treatment of Overdosage: Dosage should be reduced or therapy temporarily discontinued if signs and symptoms of overdosage appear. Treatment may be reinstituted at a lower dosage. In normal individuals, normal hypothalamic-pituitary-thyroid axis function is restored in six to eight weeks after cessation of therapy following thyroid suppression.
Treatment is symptomatic and supportive. Oxygen may be administered and ventilation maintained. Cardiac glycosides may be indicated if congestive heart failure develops. Beta-adrenergic antagonists have been used advantageously in the treatment of increased sympathetic activity. Measures to control fever, hypoglycemia or fluid loss should be instituted if needed.

DOSAGE AND ADMINISTRATION
Adults
Myxedema coma is usually precipitated in the hypothyroid patient of long standing by intercurrent illness or drugs such as sedatives and anesthetics and should be considered a medical emergency. Therapy should be directed at the correction of electrolyte disturbances, possible infection, or other intercurrent illness in addition to the administration of intravenous liothyronine (T_3). Simultaneous glucocorticosteroids are required.
Triostat (liothyronine sodium injection) (T_3) is for intravenous administration only. It should not be given intramuscularly or subcutaneously.
- Prompt administration of an adequate dose of intravenous liothyronine (T_3) is important in determining clinical outcome.
- Initial and subsequent doses of *Triostat* should be based on continuous monitoring of the patient's clinical status and response to therapy.
- *Triostat* doses should normally be administered at least four hours—and not more than 12 hours—apart.
- Administration of at least 65 mcg/day of intravenous liothyronine (T_3) in the initial days of therapy was associated with lower mortality.
- There is limited clinical experience with intravenous liothyronine (T_3) at total daily doses exceeding 100 mcg/day.

No controlled clinical studies have been done with *Triostat*. The following dosing guidelines have been derived from data analysis of myxedema coma/precoma case reports collected by SmithKline Beecham Pharmaceuticals since 1963 and from scientific literature since 1956.
An initial intravenous *Triostat* dose ranging from 25 mcg to 50 mcg is recommended in the emergency treatment of myxedema coma/precoma in adults. In patients with known or suspected cardiovascular disease, an initial dose of 10 mcg to 20 mcg is suggested (see WARNINGS). However, both the initial dose and subsequent doses should be determined on the basis of continuous monitoring of the patient's clinical condition and response to *Triostat* therapy. Normally at least four hours should be allowed between doses to adequately assess therapeutic response and no more than 12 hours should elapse between doses to avoid fluctuations in hormone levels. Caution should be exercised in adjusting the dose due to the potential of large changes to precipitate adverse cardiovascular events. Review of the myxedema case reports indicates decreased mortality in patients receiving at least 65 mcg/day in the initial days of treatment. However, there is limited clinical experience at total daily doses above 100 mcg. See PRECAUTIONS—*Drug Interactions* for potential interactions between thyroid hormones and *digitalis* and *vasopressors*.

Pediatric Use
There is limited experience with *Triostat* in the pediatric population. Safety and effectiveness in pediatric patients have not been established.

Switching to Oral Therapy
Oral therapy should be resumed as soon as the clinical situation has been stabilized and the patient is able to take oral medication. When switching a patient to liothyronine sodium tablets from *Triostat*, discontinue *Triostat*, initiate oral therapy at a low dosage, and increase gradually according to the patient's response.
If L-thyroxine rather than liothyronine sodium is used in initiating oral therapy, the physician should bear in mind that there is a delay of several days in the onset of L-thyroxine activity and that intravenous therapy should be discontinued gradually.

HOW SUPPLIED
In packages of six 1 mL vials at a concentration of 10 mcg/mL.
NDC 52604-5210-6
Store between 2° and 8°C (35° and 46°F).
DATE OF ISSUANCE MARCH 1999
Manufactured by:
Taylor Pharmaceuticals
Decatur, IL 62522
Manufactured for:
JONES PHARMA INCORPORATED
(a wholly owned subsidiary of King Pharmaceuticals, Inc.)
St. Louis, MO 63146

LSOON Rev. 3/99
Printed in the U.S.A.
Shown in Product Identification Guide, page 320

Key Pharmaceuticals, Inc.
GALLOPING HILL ROAD
KENILWORTH, NJ 07033

(For product information, please see Schering Corporation.)

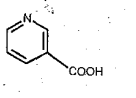
Knoll Laboratories/ Pharmaceuticals
Due to the acquisition of Knoll Laboratories, Knoll Pharmaceutical Company, by Abbott Laboratories, please refer to ABBOTT LABORATORIES for product information.

Kos Pharmaceuticals, Inc.
1001 BRICKELL BAY DRIVE
25TH FLOOR
MIAMI, FL 33131

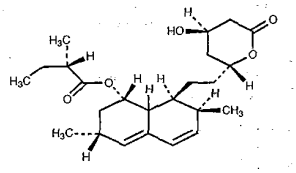
For medical information contact:
Drug Information Services
1-888-4-LIPIDS
1-888-454-7437

ADVICOR™ ℞
[ad' vĭ kor'']
(niacin extended-release and lovastatin tablets)
Rx Only

DESCRIPTION
ADVICOR contains niacin extended-release and lovastatin in combination. Niacin, a B-complex vitamin, and lovastatin, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, are both lipid-altering agents.
Niacin is nicotinic acid, or 3-pyridinecarboxylic acid. Niacin is a white, nonhygroscopic crystalline powder that is very soluble in water, boiling ethanol and propylene glycol. It is insoluble in ethyl ether. The empirical formula of niacin is $C_6H_5NO_2$ and its molecular weight is 123.11. Niacin has the following structural formula:



Lovastatin is [1S -[1(alpha)(R *), 3(alpha), 7(beta), 8(beta)(2S *, 4S *), 8a(beta)]]-1,2,3, 7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl) ethyl]-1-naphthalenyl 2-methylbutanoate. Lovastatin is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile. The empirical formula of lovastatin is $C_{24}H_{36}O_5$ and its molecular weight is 404.55. Lovastatin has the following structural formula:



ADVICOR tablets contain the labeled amount of niacin and lovastatin and have the following inactive ingredients: hydroxypropyl methylcellulose, povidone, stearic acid, polyethylene glycol, titanium dioxide, polysorbate 80. The individual tablet strengths (expressed in terms of mg niacin/mg lovastatin) contain the following coloring agents:
ADVICOR 500 mg/20 mg - synthetic red and yellow iron oxides.
ADVICOR 750 mg/20 mg - FD & C Yellow # 6 Aluminum Lake.
ADVICOR 1000 mg/20 mg - synthetic red, yellow, and black iron oxides.

CLINICAL PHARMACOLOGY
A variety of clinical studies have demonstrated that elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B-100 (Apo B) promote human atherosclerosis. Similarly, decreased levels of high-density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of TC and LDL-C, and inversely with the level of HDL-C.
Cholesterol-enriched triglyceride-rich lipoproteins, including very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and their remnants, can also promote atherosclerosis. Elevated plasma triglycerides (TG) are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG have not consistently been shown to be an independent risk factor for CHD.
As an adjunct to diet, the efficacy of niacin and lovastatin in improving lipid profiles (either individually, or in combination with each other, or niacin in combination with other statins) for the treatment of dyslipidemia has been well documented. The effect of combined therapy with niacin and lovastatin on cardiovascular morbidity and mortality has not been determined.

Effects on Lipids
ADVICOR
ADVICOR reduces LDL-C, TC, and TG, and increases HDL-C due to the individual actions of niacin and lovastatin. The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality.

Niacin
Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. Niacin (but not nicotinamide) in gram doses reduces LDL-C, Apo B, Lp(a), TG, and TC, and increases HDL-C. The increase in HDL-C is associated with an increase in apolipoprotein A-I (Apo A-I) and a shift in the distribution of HDL subfractions. These shifts include an increase in the HDL_2:HDL_3 ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL-C particle containing only Apo A-I). In addition, preliminary reports suggest that niacin causes favorable LDL particle size transformations, although the clinical relevance of this effect is not yet clear.

Lovastatin
Lovastatin has been shown to reduce both normal and elevated LDL-C concentrations. Apo B also falls substantially during treatment with lovastatin. Since each LDL-C particle contains one molecule of Apo B, and since little Apo B is found in other lipoproteins, this strongly suggests that lovastatin does not merely cause cholesterol to be lost from LDL-C, but also reduces the concentration of circulating LDL particles. In addition, lovastatin can produce increases of variable magnitude in HDL-C, and modestly reduces VLDL-C and plasma TG. The effects of lovastatin on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are not well characterized.

Mechanism of Action
Niacin
The mechanism by which niacin alters lipid profiles is not completely understood and may involve several actions, including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity (which may increase the rate of chylomicron triglyceride removal from plasma). Niacin decreases the rate of hepatic synthesis of VLDL-C and LDL-C, and does not appear to affect fecal excretion of fats, sterols, or bile acids.

Continued on next page

Advicor—Cont.

Lovastatin

Lovastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol. Lovastatin is a prodrug and has little, if any, activity until hydrolyzed to its active beta-hydroxyacid form, lovastatin acid. The mechanism of the LDL-lowering effect of lovastatin may involve both reduction of VLDL-C concentration and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C.

Pharmacokinetics

Absorption and Bioavailability

ADVICOR

In single-dose studies of ADVICOR, rate and extent of niacin and lovastatin absorption were bioequivalent under fed conditions to that from NIASPAN® and Mevacor® tablets, respectively. After administration of two ADVICOR 1000 mg/20 mg tablets, peak niacin concentrations averaged about 18 mcg/mL and occurred about 5 hours after dosing; about 72% of the niacin dose was absorbed according to the urinary excretion data. Peak lovastatin concentrations averaged about 11 ng/mL and occurred about 2 hours after dosing.

The extent of niacin absorption from ADVICOR was increased by administration with food. The administration of two ADVICOR 1000 mg/20 mg tablets under low-fat or high-fat conditions resulted in a 22 to 30% increase in niacin bioavailability relative to dosing under fasting conditions. Lovastatin bioavailability is affected by food. Lovastatin Cmax was increased 48% and 21% after a high- and a low-fat meal, respectively, but the lovastatin AUC was decreased 26% and 24% after a high- and a low-fat meal, respectively, compared to those under fasting conditions.

Niacin

Due to extensive and saturable first-pass metabolism, niacin concentrations in the general circulation are dose dependent and highly variable. Peak steady-state niacin concentrations were 0.6, 4.9, and 15.5 mcg/mL after doses of 1000, 1500, and 2000 mg NIASPAN once daily (given as two 500 mg, two 750 mg, and two 1000 mg tablets, respectively).

Lovastatin

Lovastatin appears to be incompletely absorbed after oral administration. Because of extensive hepatic extraction, the amount of lovastatin reaching the systemic circulation as active inhibitors after oral administration is low (<5%) and shows considerable inter-individual variation. Peak concentrations of active and total inhibitors occur within 2 to 4 hours after Mevacor administration.

Lovastatin absorption appears to be increased by at least 30% by grapefruit juice; however, the effect is dependent on the amount of grapefruit juice consumed and the interval between grapefruit juice and lovastatin ingestion.

With a once-a-day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady-state between the second and third days of therapy and were about 1.5 times those following a single dose of Mevacor.

Distribution

Niacin

Niacin is less than 20% bound to human serum proteins and distributes into milk. Studies using radiolabeled niacin in mice show that niacin and its metabolites concentrate in the liver, kidney, and adipose tissue.

Lovastatin

Both lovastatin and its beta-hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Distribution of lovastatin or its metabolites into human milk is unknown; however, lovastatin distributes into milk in rats. In animal studies, lovastatin concentrated in the liver, and crossed the blood-brain and placental barriers.

Metabolism

Niacin

Niacin undergoes rapid and extensive first-pass metabolism that is dose-rate specific and, at the doses used to treat dyslipidemia, saturable. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of NAD. It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans.

Lovastatin

Lovastatin undergoes extensive first-pass extraction and metabolism by cytochrome P450 3A4 in the liver, its primary site of action. The major active metabolites present in human plasma are the beta-hydroxyacid of lovastatin (lovastatin acid), its 6'-hydroxy derivative, and two additional metabolites.

Elimination

ADVICOR

Niacin is primarily excreted in urine mainly as metabolites. After a single dose of ADVICOR, at least 60% of the niacin dose was recovered in urine as unchanged niacin and its metabolites. The plasma half-life for lovastatin was about 4.5 hours in single-dose studies.

Niacin

The plasma half-life for niacin is about 20 to 48 minutes after oral administration and dependent on dose administered. Following multiple oral doses of NIASPAN, up to 12% of the dose was recovered in urine as unchanged niacin depending on dose administered. The ratio of metabolites recovered in the urine was also dependent on the dose administered.

Lovastatin

Lovastatin is excreted in urine and bile, based on studies of Mevacor. Following an oral dose of radiolabeled lovastatin in man, 10% of the dose was excreted in urine and 83% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug.

Special Populations

Hepatic

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency for either niacin or lovastatin (see **WARNINGS, Liver Dysfunction**).

Renal

No information is available on the pharmacokinetics of niacin in patients with renal insufficiency.

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

ADVICOR should be used with caution in patients with renal disease.

Gender

Plasma concentrations of niacin and metabolites after single- or multiple-dose administration of niacin are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating similar absorption for both genders. The gender differences observed in plasma niacin and metabolite levels may be due to gender-specific differences in metabolic rate or volume of distribution. Data from clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of NIASPAN and ADVICOR.

In a multiple-dose study, plasma concentrations of active and total HMG-CoA reductase inhibitors were 20 to 50% higher in women than in men. In two single-dose studies with ADVICOR, lovastatin concentrations were about 30% higher in women than men, and total HMG-CoA reductase inhibitor concentrations were about 20 to 25% greater in women.

In a multi-center, randomized, double-blind, active comparator study in patients with Type IIa and IIb hyperlipidemia, ADVICOR was compared to single-agent treatment (NIASPAN and lovastatin). The treatment effects of ADVICOR compared to lovastatin and NIASPAN differed for males and females with a significantly larger treatment effect seen for females. The mean percent change from baseline at endpoint for LDL-C, TG, and HDL-C by gender are as follows (Table 1):

Table 1. Mean percent change from baseline at endpoint for LDL-C, HDL-C and TG by gender

	ADVICOR 2000 mg/40 mg		NIASPAN 2000 mg		Lovastatin 40 mg	
	Women (n=22)	Men (n=30)	Women (n=28)	Men (n=28)	Women (n=21)	Men (n=38)
LDL-C	-47%	-34%	-12%	-9%	-31%	-31%
HDL-C	+33%	+24%	+22%	+15%	+3%	+7%
TG	-48%	-35%	-25%	-15%	-15%	-23%

Clinical Studies

In a multi-center, randomized, double-blind, parallel, 28-week, active-comparator study in patients with Type IIa and IIb hyperlipidemia, ADVICOR was compared to each of its components (NIASPAN and lovastatin). Using a forced dose-escalation study design, patients received each dose for at least 4 weeks. Patients randomized to treatment with ADVICOR initially received 500 mg/20 mg. The dose was increased at 4-week intervals to a maximum of 1000 mg/20 mg in one-half of the patients and 2000 mg/40 mg in the other half. The NIASPAN monotherapy group underwent a similar titration from 500 mg to 2000 mg. The patients randomized to lovastatin monotherapy received 20 mg for 12 weeks titrated to 40 mg for up to 16 weeks. Up to a third of the patients randomized to ADVICOR or NIASPAN discontinued prior to Week 28. In this study, ADVICOR decreased LDL-C, TG and Lp(a), and increased HDL-C in a dose-dependent fashion (Tables 2, 3, 4 and 5 below). Results from this study for LDL-C mean percent change from baseline (the primary efficacy variable) showed that:

1) LDL-lowering with ADVICOR was significantly greater than that achieved with lovastatin 40 mg only after 28 weeks of titration to a dose of 2000 mg/40 mg ($p<.0001$)
2) ADVICOR at doses of 1000 mg/20 mg or higher achieved greater LDL-lowering than NIASPAN ($p<.0001$)

The LDL-C results are summarized in Table 2.

[See table 2 above]

ADVICOR achieved significantly greater HDL-raising compared to lovastatin and NIASPAN monotherapy at all doses (Table 3).

[See table 3 above]

In addition, ADVICOR achieved significantly greater TG-lowering at doses of 1000 mg/20 mg or greater compared to lovastatin and NIASPAN monotherapy (Table 4).

[See table 4 above]

The Lp(a) lowering effects of ADVICOR and NIASPAN were similar, and both were superior to lovastatin (Table 5). The independent effect of lowering Lp(a) with NIASPAN or ADVICOR on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

[See table 5 at top of next page]

Table 2. LDL-C mean percent change from baseline

Week	ADVICOR n*	ADVICOR Dose (mg/mg)	ADVICOR LDL	NIASPAN n*	NIASPAN Dose (mg)	NIASPAN LDL	Lovastatin n*	Lovastatin Dose (mg)	Lovastatin LDL
Baseline	57	-	190.9 mg/dL	61	-	189.7 mg/dL	61	-	185.6 mg/dL
12	47	1000/20	-30%	46	1000	-3%	56	20	-29%
16	45	1000/40	-36%	44	1000	-6%	56	40	-31%
20	42	1500/40	-37%	43	1500	-12%	54	40	-34%
28	42	2000/40	-42%	41	2000	-14%	53	40	-32%

*n = number of patients remaining in the trial at each timepoint

Table 3. HDL-C mean percent change from baseline

Week	ADVICOR n*	ADVICOR Dose (mg/mg)	ADVICOR HDL	NIASPAN n*	NIASPAN Dose (mg)	NIASPAN HDL	Lovastatin n*	Lovastatin Dose (mg)	Lovastatin HDL
Baseline	57	-	45 mg/dL	61	-	47 mg/dL	61	-	43 mg/dL
12	47	1000/20	+20%	46	1000	+14%	56	20	+3%
16	45	1000/40	+20%	44	1000	+15%	56	40	+5%
20	42	1500/40	+27%	43	1500	+22%	54	40	+6%
28	42	2000/40	+30%	41	2000	+24%	53	40	+6%

*n = number of patients remaining in the trial at each timepoint

Table 4. TG median percent change from baseline

Week	ADVICOR n*	ADVICOR Dose (mg/mg)	ADVICOR TG	NIASPAN n*	NIASPAN Dose (mg)	NIASPAN TG	Lovastatin n*	Lovastatin Dose (mg)	Lovastatin TG
Baseline	57	-	174 mg/dL	61	-	186 mg/dL	61	-	171 mg/dL
12	47	1000/20	-32%	46	1000	-22%	56	20	-20%
16	45	1000/40	-39%	44	1000	-23%	56	40	-17%
20	42	1500/40	-44%	43	1500	-31%	54	40	-21%
28	42	2000/40	-44%	41	2000	-31%	53	40	-20%

*n = number of patients remaining in the trial at each timepoint

ADVICOR Long-Term Study

A total of 814 patients were enrolled in a long-term (52-week), open-label, single-arm study of ADVICOR. Patients were force dose-titrated to 2000 mg/40 mg over 16 weeks. After titration, patients were maintained on the maximum tolerated dose of ADVICOR for a total of 52 weeks. Five hundred-fifty (550) patients (68%) completed the study, and fifty-six percent (56%) of all patients were able to maintain a dose of 2000 mg/40 mg for the 52 weeks of treatment. The lipid-altering effects of ADVICOR peaked after 4 weeks on the maximum tolerated dose, and were maintained for the duration of treatment. These effects were comparable to what was observed in the double-blind study of ADVICOR (Tables 2-4).

INDICATIONS AND USAGE

ADVICOR is a fixed-dose combination product and is not indicated for initial therapy (see **DOSAGE AND ADMINISTRATION**). Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Initial medical therapy is indicated with a single agent as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate (see also Table 7 and the NCEP treatment guidelines[1]).

ADVICOR is indicated for the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb; Table 6) in:

- Patients treated with lovastatin who require further TG-lowering or HDL-raising who may benefit from having niacin added to their regimen
- Patients treated with niacin who require further LDL-lowering who may benefit from having lovastatin added to their regimen

Table 6. Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations	
		Major	Minor
I (rare)	Chylomicrons	TG	↑→TC
IIa	LDL	TC	-
IIb	LDL, VLDL	TC	TG
III (rare)	IDL	TC/TG	-
IV	VLDL	TG	↑→TC
V (rare)	Chylomicrons, VLDL	TG	↑→TC

TC = total cholesterol; TG = triglycerides; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein
↑→ = increased or no change

General Recommendations

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

LDL-C = TC– [(0.20 x TG) + HDL-C]

For TG levels > 400 mg/dL, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy. The NCEP Treatment Guidelines are summarized in Table 7.

[See table 7 above]

After the LDL-C goal has been achieved, if the TG is still ≥ 200 mg/dL, non-HDL-C (TC 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.

CONTRAINDICATIONS

ADVICOR is contraindicated in patients with a known hypersensitivity to niacin, lovastatin or any component of this medication, active liver disease or unexplained persistent elevations in serum transaminases (see **WARNINGS**), active peptic ulcer disease, or arterial bleeding.

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

Table 5. Lp(a) median percent change from baseline

Week	ADVICOR			NIASPAN			Lovastatin		
	n	Dose (mg/mg)	Lp(a)	n	Dose (mg)	Lp(a)	n	Dose (mg)	Lp(a)
Baseline	57	-	34 mg/dL	61	-	41 mg/dL	60	-	42 mg/dL
12	47	1000/20	-9%	46	1000	-8%	55	20	+8%
16	45	1000/40	-9%	44	1000	-12%	55	40	+8%
20	42	1500/40	-17%	43	1500	-22%	53	40	+6%
28	42	2000/40	-22%	41	2000	-32%	52	40	0%

*n = number of patients remaining in the trial at each timepoint

Table 7. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%:≥130 10-year risk <10%:≥160
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

†*CHD*, coronary heart disease
††Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
†††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.

WARNINGS

ADVICOR should not be substituted for equivalent doses of *immediate-release (crystalline) niacin*. For patients switching from immediate-release niacin to NIASPAN, therapy with NIASPAN should be initiated with low doses (i.e., 500 mg once daily at bedtime) and the NIASPAN dose should then be titrated to the desired therapeutic response (see DOSAGE AND ADMINISTRATION).

Liver Dysfunction

Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted *sustained-release (modified-release, timed-release)* niacin products for immediate-release (crystalline) niacin at equivalent doses.

ADVICOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of ADVICOR.

Niacin preparations and lovastatin preparations have been associated with abnormal liver tests. In studies using NIASPAN alone, 0.8% of patients were discontinued for transaminase elevations. In studies using lovastatin alone, 0.2% of patients were discontinued for transaminase elevations.[2] In three safety and efficacy studies involving titration to final daily ADVICOR doses ranging from 500 mg/10 mg to 2500 mg/40 mg, ten of 1028 patients (1.0%) experienced reversible elevations in AST/ALT to more than 3 times the upper limit of normal (ULN). Three of ten elevations occurred at doses outside the recommended dosing limit of 2000 mg/40 mg; no patient receiving 1000 mg/20 mg had 3-fold elevations in AST/ALT.

In clinical studies with ADVICOR, elevations in transaminases did not appear to be related to treatment duration; elevations in AST and ALT levels did appear to be dose related. Transaminase elevations were reversible upon discontinuation of ADVICOR.

Liver function tests should be performed on all patients during therapy with ADVICOR. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be monitored before treatment begins, every 6 to 12 weeks for the first 6 months, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and, if confirmed, then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued.

Skeletal Muscle

Lovastatin

Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (> 10 times ULN).

Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time. In a large, long-term, clinical safety and efficacy study (the EXCEL study)[3,4] with lovastatin, myopathy occurred in up to 0.2% of patients treated with lovastatin 20 to 80 mg for up to 2 years. When drug treatment was interrupted or discontinued in these patients, muscle symptoms and creatine kinase (CK) increases promptly resolved. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the EXCEL study design.

The risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Lovastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which share this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include cyclosporine, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin and clarithromycin, HIV protease inhibitors, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily).

ADVICOR

Myopathy and/or rhabdomyolysis have been reported when lovastatin is used in combination with lipid-altering doses (≥1g/day) of niacin. Physicians contemplating the use of ADVICOR, a combination of lovastatin and niacin, *should weigh the potential benefits and risks, and should* carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial month of treatment or during any period of upward dosage titration of either drug. Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

In clinical studies, no cases of rhabdomyolysis and one suspected case of myopathy have been reported in 1079 patients who were treated with ADVICOR at doses up to 2000 mg/40 mg for periods up to 2 years.

Patients starting therapy with ADVICOR should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness, or weakness. A CK level above 10 times ULN in a patient with unexplained muscle symptoms indicates myopathy. ADVICOR therapy should be discontinued if myopathy is diagnosed or suspected.

In patients with complicated medical histories predisposing to rhabdomyolysis, such as preexisting renal insufficiency, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with ADVICOR should be stopped for a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

Use of ADVICOR with other Drugs

The incidence and severity of myopathy may be increased by concomitant administration of ADVICOR with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates.

The use of ADVICOR in combination with fibrates should be avoided unless the benefit of further alterations in lipid *levels is likely to outweigh the increased risk of this drug* combination. In patients taking concomitant cyclosporine or fibrates, the dose of ADVICOR should generally not exceed 1000 mg/20 mg (see **DOSAGE AND ADMINISTRATION**), **as the risk of myopathy may increase at higher doses.** Interruption of ADVICOR therapy during a course of treatment with a systemic antifungal azole or a macrolide antibiotic should be considered.

Continued on next page

Advicor—Cont.

PRECAUTIONS

General

Before instituting therapy with a lipid-altering medication, an attempt should be made to control dyslipidemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see **INDICATIONS AND USAGE**).

Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during ADVICOR therapy. Frequent monitoring of liver function tests and blood glucose should be performed to ascertain that the drug is producing no adverse effects on these organ systems.

Diabetic patients may experience a dose-related rise in fasting blood sugar (FBS). In three clinical studies, which included 1028 patients exposed to ADVICOR (6 to 22% of whom had diabetes type II at baseline), increases in FBS above normal occurred in 46 to 65% of patients at any time during study treatment with ADVICOR. Fourteen patients (1.4%) were discontinued from study treatment: 3 patients for worsening diabetes, 10 patients for hyperglycemia and 1 patient for a new diagnosis of diabetes. In the studies in which lovastatin and NIASPAN were used as active controls, 24 to 41% of patients receiving lovastatin and 43 to 58% of patients receiving NIASPAN also had increases in FBS above normal. One patient (1.1%) receiving lovastatin was discontinued for hyperglycemia. Diabetic or potentially diabetic patients should be observed closely during treatment with ADVICOR, and adjustment of diet and/or hypoglycemic therapy may be necessary.

In one long-term study of 106 patients treated with ADVICOR, elevations in prothrombin time (PT) >3 X ULN occurred in 2 patients (2%) during study drug treatment. In a long-term study of 814 patients treated with ADVICOR, 7 patients were noted to have platelet counts <100,000 during study drug treatment. Four of these patients were discontinued, and one patient with a platelet count <100,000 had prolonged bleeding after a tooth extraction. Prior studies have shown that NIASPAN can be associated with dose-related reductions in platelet count (mean of -11% with 2000 mg) and increases of PT (mean of approximately +4%). Accordingly, patients undergoing surgery should be carefully evaluated. In controlled studies, ADVICOR has been associated with small but statistically significant dose-related reductions in phosphorus levels (mean of -10% with 2000 mg/40 mg). Phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia. In clinical studies with ADVICOR, hypophosphatemia was more common in males than in females. The clinical relevance of hypophosphatemia in this population is not known.

Niacin

Caution should also be used when ADVICOR is used in patients with unstable angina or in the acute phase of MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Elevated uric acid levels have occurred with niacin therapy; therefore, in patients predisposed to gout, niacin therapy should be used with caution. Niacin is rapidly metabolized by the liver, and excreted through the kidneys. ADVICOR is contraindicated in patients with significant or unexplained hepatic dysfunction (see **CONTRAINDICATIONS** and **WARNINGS**) and should be used with caution in patients with renal dysfunction.

Lovastatin

Lovastatin may elevate creatine phosphokinase and transaminase levels (see **WARNINGS** and **ADVERSE REACTIONS**). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Endocrine function—HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical studies with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to human chorionic gonadotropin (HCG). In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS toxicity—Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level (Cmax) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose which produced plasma drug levels (Cmax) which were about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Cataracts were seen in dogs treated with lovastatin for 11 and 28 weeks at 180 mg/kg/day and 1 year at 60 mg/kg/day.

Information for Patients

Patients should be advised of the following:

- to report promptly unexplained muscle pain, tenderness, or weakness (see **WARNINGS, Skeletal Muscle**);
- to take ADVICOR at bedtime, with a low-fat snack. Administration on an empty stomach is not recommended;
- to carefully follow the prescribed dosing regimen (see **DOSAGE AND ADMINISTRATION**);
- that flushing is a common side effect of niacin therapy that usually subsides after several weeks of consistent niacin use. Flushing may last for several hours after dosing, may vary in severity, and will, by taking ADVICOR at bedtime, most likely occur during sleep. If awakened by flushing, especially if taking antihypertensives, rise slowly to minimize the potential for dizziness and/or syncope;
- that taking aspirin (up to approximately 30 minutes before taking ADVICOR) or another non-steroidal anti-inflammatory drug (e.g., ibuprofen) may minimize flushing;
- to avoid ingestion of alcohol or hot drinks around the time of ADVICOR administration, to minimize flushing;
- should not be administered with grapefruit juice;
- that if ADVICOR therapy is discontinued for an extended length of time, their physician should be contacted prior to re-starting therapy; re-titration is recommended (see **DOSAGE AND ADMINISTRATION**);
- to notify their physician if they are taking vitamins or other nutritional supplements containing niacin or related compounds such as nicotinamide (see **Drug Interactions**);
- to notify their physician if symptoms of dizziness occur;
- if diabetic, to notify their physician of changes in blood glucose;
- that ADVICOR tablets should not be broken, crushed, or chewed, but should be swallowed whole.

Drug Interactions

Niacin

Antihypertensive Therapy—Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

Aspirin: Concomitant aspirin may decrease the metabolic clearance of niacin. The clinical relevance of this finding is unclear.

Bile Acid Sequestrants—An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding to cholestyramine. These results suggest that 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of ADVICOR.

Other—Concomitant alcohol or hot drinks may increase the side effects of flushing and pruritus and should be avoided around the time of ADVICOR ingestion. Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of ADVICOR.

Lovastatin

Serious skeletal muscle disorders, e.g., rhabdomyolysis, have been reported during concomitant therapy of lovastatin or other HMG-CoA reductase inhibitors with cyclosporine, itraconazole, ketoconazole, gemfibrozil, niacin, erythromycin, clarithromycin, nefazodone or HIV protease inhibitors. (See **WARNINGS, Skeletal Muscle**).

Coumarin Anticoagulants—In a small clinical study in which lovastatin was administered to warfarin-treated patients, no effect on PT was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two seconds increase in PT in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased PT have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, PT be determined before starting ADVICOR and frequently enough during early therapy to insure that no significant alteration of PT occurs. Once a stable PT has been documented, PT can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of ADVICOR is changed, the same procedure should be repeated.

Antipyrine—Lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites. However, since lovastatin is metabolized by the cytochrome P450 isoform 3A4 enzyme system, this does not preclude an interaction with other drugs metabolized by the same isoform.

Propranolol—In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin—In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Oral Hypoglycemic Agents—In pharmacokinetic studies of lovastatin in hypercholesterolemic, non-insulin dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide.

Drug/Laboratory Test Interactions

Niacin may produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. Niacin may also give false-positive reactions with cupric sulfate solution (Benedict's reagent) in urine glucose tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with ADVICOR regarding carcinogenesis, mutagenesis, or impairment of fertility.

Niacin

Niacin, administered to mice for a lifetime as a 1% solution in drinking water, was not carcinogenic. The mice in this study received approximately 6 to 8 times a human dose of 3000 mg/day as determined on a mg/m^2 basis. Niacin was negative for mutagenicity in the Ames test. No studies on impairment of fertility have been performed.

Lovastatin

In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose on a mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of lovastatin.)

There was an increase in incidence of papilloma in the nonglandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose-response relationship for hepatocellular carcinogenicity in males at drug exposures between 2 to 7 times that of human exposure at 80 mg/day (doses in rats were 5, 30, and 180 mg/kg/day).

An increased incidence of thyroid neoplasms in rats appears to be a response that has been seen with other HMG-CoA reductase inhibitors.

A drug in this class chemically similar to lovastatin was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhinurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X—See **CONTRAINDICATIONS**.

ADVICOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazard. Safety in pregnant women has not been established and there is no apparent benefit to therapy with ADVICOR dur-

ing pregnancy (see **CONTRAINDICATIONS**). Treatment should be immediately discontinued as soon as pregnancy is recognized.

Niacin

Animal reproduction studies have not been conducted with niacin or with ADVICOR. It is also not known whether niacin at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving niacin or ADVICOR for primary hypercholesterolemia (Types IIa or IIb) becomes pregnant, the drug should be discontinued.

Lovastatin

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[5] of approximately 100 prospectively followed pregnancies in women exposed to lovastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m^2 surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose).

Labor and Delivery

No studies have been conducted on the effect of ADVICOR, niacin or lovastatin on the mother or the fetus during labor or delivery, on the duration of labor or delivery, or on the growth, development, and functional maturation of the child.

Nursing Mothers

No studies have been conducted with ADVICOR in nursing mothers.

Because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of niacin and lovastatin (see **CONTRAINDICATIONS**), ADVICOR should not be taken while a woman is breastfeeding.

Niacin has been reported to be excreted in human milk. It is not known whether lovastatin is excreted in human milk. A small amount of another drug in this class is excreted in human breast milk.

Pediatric use

No studies in patients under 18 years-of-age have been conducted with ADVICOR. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug or its active ingredients is limited, treatment of pediatric patients with ADVICOR is not recommended at this time.

Geriatric Use

Of the 214 patients who received ADVICOR in double-blind clinical studies, 37.4% were 65 years-of-age and older, and of the 814 patients who received ADVICOR in open-label clinical studies, 36.2% were 65 years-of-age and older. Responses in LDL-C, HDL-C, and TG were similar in geriatric patients. No overall differences in the percentage of patients with adverse events were observed between older and younger patients. No overall differences were observed in selected chemistry values between the two groups except for amylase which was higher in older patients.

ADVERSE REACTIONS

Overview

In controlled clinical studies, 40/214 (19%) of patients randomized to ADVICOR discontinued therapy prior to study completion, 18/214 (8%) of discontinuations being due to flushing. In the same controlled studies, 9/94 (10%) of patients randomized to lovastatin and 19/92 (21%) of patients randomized to NIASPAN also discontinued treatment prior to study completion secondary to adverse events. Flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse events, and occurred in 53% to 83% of patients treated with ADVICOR. Spontaneous reports with NIASPAN and clinical studies with ADVICOR suggest that flushing may also be accompanied by symptoms of dizziness or syncope, tachycardia, palpitations, shortness of breath, sweating, chills, and/or edema.

Adverse Reactions Information

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. The adverse reaction information from clinical studies does, however provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described in this section reflect the exposure to ADVICOR in two double-blind, controlled clinical studies of 400 patients. The population was 28 to 86 years-of-age, 54% male, 85% Caucasian, 9% Black, and 7% Other, and had mixed dyslipidemia (Frederickson Types IIa and IIb).

In addition to flushing, other adverse events occurring in 5% or greater of patients treated with ADVICOR are shown in Table 8 below.

[See table 8 above]

Table 8. Treatment-Emergent Adverse Events in ≥ 5% of Patients
(Events Irrespective of Causality; Data from Controlled, Double-Blind Studies)

Adverse Event	ADVICOR	NIASPAN	Lovastatin
Total Number of Patients	214	92	94
Cardiovascular	**163 (76%)**	**66 (72%)**	**24 (26%)**
Flushing	152 (71%)	60 (65%)	17 (18%)
Body as a Whole	**104 (49%)**	**50 (54%)**	**42 (45%)**
Asthenia	10 (5%)	6 (7%)	5 (5%)
Flu Syndrome	12 (6%)	7 (8%)	4 (4%)
Headache	20 (9%)	12 (13%)	5 (5%)
Infection	43 (20%)	14 (15%)	19 (20%)
Pain	18 (8%)	3 (3%)	9 (10%)
Pain, Abdominal	9 (4%)	1 (1%)	6 (6%)
Pain, Back	10 (5%)	5 (5%)	5 (5%)
Digestive System	**51 (24%)**	**26 (28%)**	**16 (17%)**
Diarrhea	13 (6%)	8 (9%)	2 (2%)
Dyspepsia	6 (3%)	5 (5%)	4 (4%)
Nausea	14 (7%)	11 (12%)	2 (2%)
Vomiting	7 (3%)	5 (5%)	0
Metabolic and Nutrit. System	**37 (17%)**	**18 (20%)**	**13 (14%)**
Hyperglycemia	8 (4%)	6 (7%)	6 (6%)
Musculoskeletal System	**19 (9%)**	**9 (10%)**	**17 (18%)**
Myalgia	6 (3%)	5 (5%)	8 (9%)
Skin and Appendages	**3 (2%)**	**19 (21%)**	**11 (12%)**
Pruritus	14 (7%)	7 (8%)	3 (3%)
Rash	11 (5%)	11 (12%)	3 (3%)

Note: Percentages are calculated from the total number of patients in each column.

The following adverse events have also been reported with niacin, lovastatin, and/or other HMG-CoA reductase inhibitors, but not necessarily with ADVICOR, either during clinical studies or in routine patient management.

Body as a Whole: chest pain; abdominal pain; edema; chills; malaise

Cardiovascular: atrial fibrillation; tachycardia; palpitations, and other cardiac arrhythmias; orthostasis; hypotension; syncope

Eye: toxic amblyopia; cystoid macular edema; ophthalmoplegia; eye irritation

Gastrointestinal: activation of peptic ulcers and peptic ulceration; dyspepsia; vomiting; anorexia; constipation; flatulence, pancreatitis; hepatitis; fatty change in liver; jaundice; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma

Metabolic: gout

Musculoskeletal: muscle cramps; myopathy; rhabdomyolysis; arthralgia

Nervous: dizziness; insomnia; dry mouth; paresthesia; anxiety; tremor; vertigo; memory loss; peripheral neuropathy; psychic disturbances; dysfunction of certain cranial nerves

Skin: hyper-pigmentation; acanthosis nigricans; urticaria; alopecia; dry skin; sweating; and a variety of skin changes (e.g., nodules, discoloration, dryness of mucous membranes, changes to hair/nails)

Respiratory: dyspnea; rhinitis

Urogenital: gynecomastia; loss of libido; erectile dysfunction

Hypersensitivity reactions: An apparent hypersensitivity syndrome has been reported rarely, which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Other: migraine

Clinical Laboratory Abnormalities

Chemistry

Elevations in serum transaminases (see **WARNINGS - *Liver Dysfunction***), CPK and fasting glucose, and reductions in phosphorus. Niacin extended-release tablets have been associated with slight elevations in LDH, uric acid, total bilirubin, and amylase. Lovastatin and/or HMG-CoA reductase inhibitors have been associated with elevations in alkaline phosphatase, γ-glutamyl transpeptidase and bilirubin, and thyroid function abnormalities.

Hematology

Niacin extended-release tablets have been associated with slight reductions in platelet counts and prolongation in PT (see **WARNINGS**).

DRUG ABUSE AND DEPENDENCE

Neither niacin nor lovastatin is a narcotic drug. ADVICOR has no known addiction potential in humans.

OVERDOSAGE

Information on acute overdose with ADVICOR in humans is limited. Until further experience is obtained, no specific treatment of overdose with ADVICOR can be recommended. The patient should be carefully observed and given supportive treatment.

Niacin

The s.c. LD50 of niacin is 5 g/kg in rats.

The signs and symptoms of an acute overdose of niacin can be anticipated to be those of excessive pharmacologic effect: severe flushing, nausea/vomiting, diarrhea, dyspepsia, dizziness, syncope, hypotension, possibly cardiac arrhythmias and clinical laboratory abnormalities. Insufficient information is available on the potential for the dialyzability of niacin.

Lovastatin

After oral administration of lovastatin to mice the median lethal dose observed was >15 g/m^2.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdose have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g. The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The usual recommended starting dose for NIASPAN is 500 mg qhs. NIASPAN must be titrated and the dose should not be increased by more than 500 mg every 4 weeks up to a maximum dose of 2000 mg a day, to reduce the incidence and severity of side effects. Patients already receiving a stable dose of NIASPAN may be switched directly to a niacin-equivalent dose of ADVICOR.

The usual recommended starting dose of lovastatin is 20 mg once a day. Dose adjustments should be made at intervals of 4 weeks or more. Patients already receiving a stable dose of lovastatin may receive concomitant dosage titration with NIASPAN, and switch to ADVICOR once a stable dose of NIASPAN has been reached.

Flushing of the skin (see **ADVERSE REACTIONS**) may be reduced in frequency or severity by pretreatment with aspirin (taken up to approximately 30 minutes prior to ADVICOR dose) or other non-steroidal anti-inflammatory drugs. Flushing, pruritus, and gastrointestinal distress are also greatly reduced by slowly increasing the dose of niacin and avoiding administration on an empty stomach.

Equivalent doses of ADVICOR may be substituted for equivalent doses of NIASPAN but should not be substituted for other modified-release (sustained-release or time-release) niacin preparations or immediate-release (crystalline) niacin preparations (see WARNINGS). Patients previously receiving niacin products other than NIASPAN should be started on NIASPAN with the recommended NIASPAN titration schedule, and the dose should subsequently be individualized based on patient response.

ADVICOR should be taken at bedtime, with a low-fat snack, and the dose should be individualized according to patient response. ADVICOR tablets should be taken whole and should not be broken, crushed, or chewed before swallowing. The dose of ADVICOR should not be increased by more than

Continued on next page

Advicor—Cont.

500 mg daily (based on the NIASPAN component) every 4 weeks. The lowest dose of ADVICOR is 500 mg/20 mg. Doses of ADVICOR greater than 2000 mg/40 mg daily are not recommended. **If ADVICOR therapy is discontinued for an extended period (>7 days), reinstitution of therapy should begin with the lowest dose of ADVICOR.**

HOW SUPPLIED

ADVICOR is an unscored, capsule-shaped tablet containing either 500, 750, or 1000 mg of niacin in an extended-release formulation and 20 mg of lovastatin in an immediate-release formulation. Tablets are color-coated and debossed with "KOS" on one side and the tablet strength code on the other side. ADVICOR 500 mg/20 mg tablets are light yellow, code "502". ADVICOR 750 mg/20 mg tablets are light orange, code "752". ADVICOR 1000 mg/20 mg tablets are dark pink/light purple, code "1002". Tablets are supplied in bottles of 30, 90, or 180 tablets as shown below.

500 mg/20 mg tablets: bottles of 30 - NDC# 60598-006-30
bottles of 90 - NDC# 60598-006-90
bottles of 180 - NDC# 60598-006-18
750 mg/20 mg tablets: bottles of 30 - NDC# 60598-007-30
bottles of 90 - NDC# 60598-007-90
bottles of 180 - NDC# 60598-007-18
1000 mg/20 mg tablets: bottles of 30 - NDC# 60598-008-30
bottles of 90 - NDC# 60598-008-90
bottles of 180 - NDC# 60598-008-18

Store at room temperature (20° to 25°C or 68° to 77°F).
Rx Only

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Mfr. by:
KOS PHARMACEUTICALS, INC.
Miami, FL 33131

400161/1101
Printed in USA

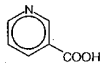
NIASPAN® ℞

[nīă-span]
niacin extended-release tablets

Rx Only

DESCRIPTION

NIASPAN® (niacin extended-release tablets), contain niacin, a B-complex vitamin and antihyperlipidemic agent. Niacin (nicotinic acid, or 3-pyridinecarboxylic acid) is a white, crystalline powder, very soluble in water, with the following structural formula:



$C_6H_5NO_2$ M.W. = 123.11

NIASPAN® is an unscored, off-white tablet for oral administration that contains no color additives and is available in three tablet strengths containing 500, 750, and 1000mg niacin. NIASPAN tablets also contain the inactive ingredients methylcellulose, povidone, and stearic acid.

CLINICAL PHARMACOLOGY

Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. Niacin (but not nicotinamide) in gram doses reduces total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and increases high-density lipoprotein cholesterol (HDL-C). The magnitude of the individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality. The increase in total HDL-C is associated with an increase in apolipoprotein A-I (Apo A-I) and a shift in the distribution of HDL subfractions. These shifts include an increase in the HDL_2:HDL_3 ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL particle containing only Apo A-I). Niacin treatment also decreases serum levels of apolipoprotein B-100 (Apo B), the major protein component of the very low-density lipoprotein (VLDL) and LDL fractions, and of Lp(a), a variant form of LDL independently associated with coronary risk.[1] In addition, preliminary reports suggest that niacin causes favorable LDL particle size transformations, although the clinical relevance of this effect requires further investigation. The effect of niacin-induced changes in lipids/lipoproteins on cardiovascular morbidity or mortality in individuals without pre-existing coronary disease has not been established.

A variety of clinical studies have demonstrated that elevated levels of TC, LDL-C, and Apo B promote human atherosclerosis. Similarly, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of TC and LDL-C, and inversely with the level of HDL-C.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Mechanism of Action

The mechanism by which niacin alters lipid profiles has not been well defined. It may involve several actions including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity, which may increase the rate of chylomicron triglyceride removal from plasma. Niacin decreases the rate of hepatic synthesis of VLDL and LDL, and does not appear to affect fecal excretion of fats, sterols, or bile acids.

Pharmacokinetics/Metabolism

Absorption

Niacin is rapidly and extensively absorbed (at least 60 to 76% of dose) when administered orally. To maximize bioavailability and reduce the risk of gastrointestinal (GI) upset, administration of NIASPAN with a low-fat meal or snack is recommended.

Single-dose bioavailability studies have demonstrated that NIASPAN tablet strengths are not interchangeable.

Distribution

Studies using radiolabeled niacin in mice show that niacin and its metabolites concentrate in the liver, kidney and adipose tissue.

Metabolism

The pharmacokinetic profile of niacin is complicated due to rapid and extensive first-pass metabolism, which is species and dose-rate specific. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted in the urine, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of nicotinamide adenine dinucleotide (NAD). It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans. At the doses used to treat hyperlipidemia, these metabolic pathways are saturable, which explains the nonlinear relationship between niacin dose and plasma concentrations following multiple-dose NIASPAN administration (Table 1).

Nicotinamide does not have hypolipidemic activity; the activity of the other metabolites is unknown.

Table 1. Mean Steady-State Pharmacokinetic Parameters for Plasma Niacin

NIASPAN dose/day	NIASPAN given as	Niacin Peak Concentration (µg/mL)	Niacin Time to Peak (hrs)
1000mg	2×500mg	0.6	5
1500mg	2×750mg	4.9	4
2000mg	2×1000mg	15.5	5

Elimination

Niacin and its metabolites are rapidly eliminated in the urine. Following single and multiple doses, approximately 60 to 76% of the niacin dose administered as NIASPAN was recovered in urine as niacin and metabolites; up to 12% was recovered as unchanged niacin after multiple dosing. The ratio of metabolites recovered in the urine was dependent on the dose administered.

Special Populations

Hepatic

No studies have been performed. NIASPAN should be used with caution in patients with a past history of liver disease, who consume substantial quantities of alcohol, or have unexplained transaminase elevations. NIASPAN is contraindicated in patients with active liver disease (see WARNINGS).

Renal

There are no data in this population. NIASPAN should be used with caution in patients with renal disease (see PRECAUTIONS).

Gender

Steady-state plasma concentrations of niacin and metabolites after administration of NIASPAN are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both genders. The gender differences observed in plasma levels of niacin and its metabolites may be due to gender-specific differences in metabolic rate or volume of distribution. Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of NIASPAN.

Niacin Clinical Studies

The role of LDL-C in atherogenesis is supported by pathological observations, clinical studies, and many animal experiments. Observational epidemiological studies have clearly established that high TC or LDL-C and low HDL-C are risk factors for CHD. Additionally, elevated levels of Lp(a) have been shown to be independently associated with CHD risk.[1] The efficacy of niacin in improving lipoprotein lipid profiles, either alone or in combination with other lipid-altering drugs, as an adjunct to diet therapy in the treatment of hyperlipoproteinemia has been well documented.

Niacin's ability to reduce mortality and the risk of definite, nonfatal myocardial infarction (MI) has also been assessed in long-term studies. The Coronary Drug Project,[2] completed in 1975, was designed to assess the safety and efficacy of niacin and other lipid-altering drugs in men 30 to 64 years old with a history of MI. Over an observation period of 5 years, niacin treatment was associated with a statistically significant reduction in nonfatal, recurrent MI. The incidence of definite, nonfatal MI was 8.9% for the 1,119 patients randomized to nicotinic acid versus 12.2% for the 2,789 patients who received placebo ($p<0.004$). Total mortality was similar in the two groups at 5 years (24.4% with nicotinic acid versus 25.4% with placebo; p=N.S.). At the time of a 15-year follow-up, there were 11% (69) fewer deaths in the niacin group compared to the placebo cohort (52.0% versus 58.2%; $p=0.0004$).[3] However, mortality at 15 years was not an original endpoint of the Coronary Drug Project. In addition, patients had not received niacin for approximately 9 years, and confounding variables such as concomitant medication use and medical or surgical treatments were not controlled.

Table 2. Lipid Response to NIASPAN Therapy

Treatment	n	Mean Percent Change from Baseline to Week 16* TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a)	Apo B	Apo A-1
NIASPAN 1000mg qhs	41	−3	−5	+18	−17	−21	−13	−6	+9
NIASPAN 2000mg qhs	41	−10	−14	+22	−25	−28	−27	−16	+8
Placebo	40	0	−1	+4	−3	0	0	+1	+3
NIASPAN 1500mg qhs	76	−8	−12	+20	−20	−13	−15	−12	+8
Placebo	73	+2	+1	+2	+1	+12	+2	+1	+2

n = number of patients at baseline;
* Mean percent change from baseline for all NIASPAN doses was significantly different ($p<0.05$) from placebo for all lipid parameters shown except Apo A-1 at 2000mg.

Table 3. Lipid Response in Dose-Escalation Study

Treatment	n	Mean Percent Change from Baseline* TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a)	Apo B	Apo A-1
Placebo‡	44	−2	−1	+5	−7	−6	−5	−2	+4
NIASPAN	87								
500mg qhs		−2	−3	+10	−10	−5	−3	−2	+5
1000mg qhs		−5	−9	+15	−17	−11	−12	−7	+8
1500mg qhs		−11	−14	+22	−26	−28	−20	−15	+10
2000mg qhs		−12	−17	+26	−29	−35	−24	−16	+12

n = number of patients enrolled;
‡ Placebo data shown are after 24 weeks of placebo treatment.
* For all NIASPAN doses except 500mg, mean percent change from baseline was significantly different ($p<0.05$) from placebo for all lipid parameters shown except Lp(a) and Apo A-1 which were significantly different from placebo starting with 1500mg and 2000mg, respectively.

The Cholesterol-Lowering Atherosclerosis Study (CLAS) was a randomized, placebo-controlled, angiographic trial testing combined colestipol and niacin therapy in 162 non-smoking males with previous coronary bypass surgery.[4] The primary, per-subject cardiac endpoint was global coronary artery change score. After 2 years, 61% of patients in the placebo cohort showed disease progression by global change score (n=82), compared with only 38.8% of drug-treated subjects (n=80), when both native arteries and grafts were considered ($p<0.005$); disease regression also occurred more frequently in the drug-treated group (16.2% versus 2.4%; $p=0.002$). In a follow-up to this trial in a subgroup of 103 patients treated for 4 years, again, significantly fewer patients in the drug-treated group demonstrated progression than in the placebo cohort (48% versus 85%, respectively; $p<0.0001$).[5]

The Familial Atherosclerosis Treatment Study (FATS) in 146 men ages 62 and younger with Apo B levels ≥125 mg/dL, established coronary artery disease, and family histories of vascular disease, assessed change in severity of disease in the proximal coronary arteries by quantitative arteriography.[6] Patients were given dietary counseling and randomized to treatment with either conventional therapy with double placebo (or placebo plus colestipol if the LDL-C was elevated); lovastatin plus colestipol; or niacin plus colestipol. In the conventional therapy group, 46% of patients had disease progression (and no regression) in at least one of nine proximal coronary segments; regression was the only change in 11%. In contrast, progression (as the only change) was seen in only 25% in the niacin plus colestipol group, while regression was observed in 39%. Though not an original endpoint of the trial, clinical events (death, MI, or revascularization for worsening angina) occurred in 10 of 52 patients who received conventional therapy, compared with 2 of 48 who received niacin plus colestipol.

The Harvard Atherosclerosis Reversibility Project (HARP) was a randomized placebo-controlled, 2.5-year study of the effect of a stepped-care antihyperlipidemic drug regimen on 91 patients (80 men and 11 women) with CHD and average baseline TC levels less than 250mg/dL and ratios of TC to HDL-C greater than 4.0.[7] Drug treatment consisted of an HMG-CoA reductase inhibitor administered alone as initial therapy followed by addition of varying dosages of either a slow-release nicotinic acid, cholestyramine, or gemfibrozil. Addition of nicotinic acid to the HMG-CoA reductase inhibitor resulted in further statistically significant mean reductions in TC, LDL-C, and TG, as well as a further increase in HDL-C in a majority of patients (40 of 44 patients). The ratios of TC to HDL-C and LDL-C to HDL-C were also significantly reduced by this combination drug regimen (see WARNINGS, *Skeletal Muscle*).

NIASPAN Clinical Studies

Placebo-controlled Clinical Studies in Patients with Primary Hypercholesterolemia and Mixed Dyslipidemia: In two randomized, double-blind, parallel, multi-center, placebo-controlled trials, NIASPAN dosed at 1000, 1500 or 2000mg daily at bedtime with a low-fat snack for 16 weeks (including 4 weeks of dose escalation) favorably altered lipid profiles compared to placebo (Table 2). Women appeared to have a greater response than men at each NIASPAN dose level (see *Gender Effect*, below).

[See table 2 at bottom of previous page]

In a double-blind, multi-center, forced dose-escalation study, monthly 500mg increases in NIASPAN dose resulted in incremental reductions of approximately 5% in LDL-C and Apo B levels in the daily dose range of 500mg through 2000mg (Table 3). Women again tended to have a greater response to NIASPAN than men (see *Gender Effect*, below).

[See table 3 at bottom of previous page]

Pooled results for major lipids from these three placebo-controlled studies are shown below (Table 4).

[See table 4 above]

Gender Effect: Combined data from the three placebo-controlled NIASPAN studies in patients with primary hypercholesterolemia and mixed dyslipidemia suggest that, at each NIASPAN dose level studied, changes in lipid concentrations are greater for women than for men (Table 5).

[See table 5 above]

Long-term Study: In a recently completed long-term open-label study, patients with primary hypercholesterolemia and mixed dyslipidemia received NIASPAN in doses titrated to individual response and tolerance. An HMG-CoA reductase inhibitor or a bile acid sequestrant (BAS) was added to NIASPAN therapy for patients whose response to NIASPAN alone (usually at 2000mg qhs) was insufficient, or who would not tolerate higher niacin doses. Interim data from 48 and 96 weeks of treatment (Table 6) suggest combination therapy enhanced TC and LDL-C response (see WARNINGS, *Skeletal Muscle*).

[See table 6 above]

Other Patient Populations: In a double-blind, multi-center, 19-week study the lipid-altering effects of NIASPAN (forced titration to 2000mg qhs) were compared to baseline in patients whose primary lipid abnormality was a low level of HDL-C (HDL-C≤40 mg/dL, TG ≤400 mg/dL, and LDL-C≤160, or <130 mg/dL in the presence of CHD). Results are shown below (Table 7).

[See table 7 above]

At NIASPAN 2000 mg/day, median changes from baseline (25^{th}, 75^{th} percentiles) for LDL-C, HDL-C, and TG were -3% (-14, +12%), +27% (+13, +38%), and −33% (−50, -19%), respectively.

Table 4. Selected Lipid Response to NIASPAN in Placebo-controlled Clinical Studies*

NIASPAN Dose	n	Mean Baseline and Median Percent Change from Baseline (25^{th}, 75^{th} Percentiles) LDL-C	HDL-C	TG
1000mg qhs	104			
Baseline (mg/dL)		218	45	172
Percent Change		−7 (−15, 0)	+14 (+7,+23)	−16 (−34,+3)
1500mg qhs	120			
Baseline (mg/dL)		212	46	171
Percent Change		−13 (−21,−4)	+19 (+9,+31)	−25 (−45,−2)
2000mg qhs	85			
Baseline (mg/dL)		220	44	160
Percent Change		−16 (−26,−7)	+22 (+15,+34)	−38 (−52,−14)

* Represents pooled analyses of results; minimum duration on therapy at each dose was 4 weeks.

Table 5. Effect of Gender on NIASPAN Dose Response

NIASPAN Dose	n (M/F)	Mean Percent Change from Baseline LDL-C M	LDL-C F	HDL-C M	HDL-C F	TG M	TG F	Apo B M	Apo B F
500mg qhs	50/37	−2	−5	+11	+8	−3	−9	−1	−5
1000mg qhs	76/52	−6*	−11*	+14	+20	−10	−20	−5*	−10*
1500mg qhs	104/59	−12	−16	+19	+24	−17	−28	−13	−15
2000mg qhs	75/53	−15	−18	+23	+26	−30	−36	−16	−16

n = Number of male/female patients enrolled.
* Percent change significantly different between genders ($p<0.05$).

Table 6. NIASPAN Efficacy with Combination Therapy

Treatment	Duration	n	Mean Percent Change from Baseline TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a)*	Apo B*
	Baseline	185	–	–	–	–	–	–	–
NIASPAN Alone	48 weeks	101	−11	−18	+29	−29	−24	−36	−15
	96 weeks	74	−10	−18	+32	−30	−27	na	na
	Baseline	53	–	–	–	–	–	–	–
NIASPAN & HMG-CoA	48 weeks	45	−23	−32	+26	−38	−30	−19	−26
	96 weeks	37	−24	−32	+25	−38	−32	na	na
	Baseline	16	–	–	–	–	–	–	–
NIASPAN & BAS	48 weeks	15	−11	−20	+36	−33	−13	−24	−19
	96 weeks	7	−15	−28	+31	−34	+5	na	na

Note: Median NIASPAN dose was 2000mg qhs in each dose group. Mean duration of HMG-CoA combination therapy was approximately 47 weeks. Mean duration of BAS combination therapy was approximately 40 weeks.
* number of patients (n) are up to 33% lower at baseline and at 48 weeks; na = data are not available.

Table 7. *Lipid Response to NIASPAN in Patients with Low HDL-C*

	n	Mean Baseline and Mean Percent Change from Baseline TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a)†	Apo B†	Apo A-I‡	Lp A-I‡
Baseline (mg/dL)	88	190	120	31	6	194	8	106	105	32
Week 19 (% Change)	71	−3	0	+26	−22	−30	−20	−9	+11	+20

n = number of patients enrolled
* Mean percent change from baseline was significantly different ($p<0.05$) for all lipid parameters shown except LDL-C.
†n=72 at baseline and 69 at week 19.
‡n=30 at baseline and week 19.

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Niacin therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate (see also the NCEP treatment guidelines[8]). Prior to initiating therapy with niacin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile obtained to measure TC, HDL-C, and TG.

1. NIASPAN is indicated as an adjunct to diet for reduction of elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb; Table 8), when the response to an appropriate diet has been inadequate.
2. In patients with a history of myocardial infarction and hypercholesterolemia, niacin is indicated to reduce the risk of recurrent nonfatal myocardial infarction.
3. In patients with a history of coronary artery disease (CAD) and hypercholesterolemia, niacin, in combination with a bile acid binding resin, is indicated to slow progression or promote regression of atherosclerotic disease.
4. NIASPAN in combination with a bile acid binding resin is indicated as an adjunct to diet for reduction of elevated TC and LDL-C levels in adult patients with primary hypercholesterolemia (Type IIa; Table 8), when the response to an appropriate diet, or diet plus monotherapy, has been inadequate.
5. Niacin is also indicated as adjunctive therapy for treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia; Table 8) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Such patients typically have serum TG levels over 2000 mg/dL and have elevations of VLDL-C as well as fasting chylomicrons (Type V hyperlipidemia; Table 8). Patients who consistently have total serum or plasma TG below 1000 mg/dL are unlikely to develop pancreatitis. Therapy with niacin may be considered for those patients with TG elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. Some Type IV patients with TG under 1000 mg/dL may, through dietary or alcohol indiscretion, convert to a Type V pattern with massive TG elevations accompanying fasting chylomicronemia, but the influence of niacin therapy on risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma TG, but who have normal levels of VLDL-C. Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia.[9]

Continued on next page

Niaspan—Cont.

Table 8. Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations Major	Minor
I (rare)	chylomicrons	TG	↑→TC
IIa	LDL	TC	-
IIb	LDL, VLDL	TC	TG
III (rare)	IDL	TC/TG	-
IV	VLDL	TG	↑→TC
V (rare)	chylomicrons, VLDL	TG	↑→TC

TC = total cholesterol; TG = triglycerides; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein
↑→ = increased or no change

CONTRAINDICATIONS

NIASPAN is contraindicated in patients with a known hypersensitivity to niacin or any component of this medication, significant or unexplained hepatic dysfunction, active peptic ulcer disease, or arterial bleeding.

WARNINGS

NIASPAN preparations should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to NIASPAN, therapy with NIASPAN should be initiated with low doses (i.e., 500 mg qhs) and the NIASPAN dose should then be titrated to the desired therapeutic response (see DOSAGE AND ADMINISTRATION).

Liver Dysfunction

Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses.

NIASPAN should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of NIASPAN.

Niacin preparations, like some other lipid-lowering therapies, have been associated with abnormal liver tests. In three placebo-controlled clinical trials involving titration to final daily NIASPAN doses ranging from 500 to 3000mg, 245 patients received NIASPAN for a mean duration of 17 weeks. No patient with normal serum transaminase levels (AST, ALT) at baseline experienced elevations to more than 3 times the upper limit of normal (ULN) during treatment with NIASPAN. In these studies, fewer than 1% (2/245) of NIASPAN patients discontinued due to transaminase elevations greater than 2 times the ULN.

Interim results from a recently completed, long-term extension study involving more than 700 patients (617 who were treated for a mean duration of 50 weeks) showed that less than 1% (4/717) of NIASPAN-treated patients with normal serum transaminase levels at baseline experienced elevations greater than 3 times ULN (one of the four was receiving concomitant HMG-CoA reductase inhibitor therapy).

In the placebo-controlled clinical trials and the long-term extension study, elevations in transaminases did not appear to be related to treatment duration; elevations in AST levels did appear to be dose related. Transaminase elevations were reversible upon discontinuation of NIASPAN.

Liver tests should be performed on all patients during therapy with NIASPAN. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be monitored before treatment begins, every 6 weeks to 12 weeks for the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued.

Skeletal Muscle

Rare cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥1 g/day) of niacin and HMG-CoA reductase inhibitors. However, no cases of rhabdomyolysis have been reported in 124 patients who were treated with NIASPAN in combination with various HMG-CoA reductase inhibitors. Physicians contemplating combined therapy with HMG-CoA reductase inhibitors and NIASPAN should carefully weigh the *potential benefits and risks and should carefully monitor* patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

PRECAUTIONS

General

Before instituting therapy with NIASPAN, an attempt should be made to control hyperlipidemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during NIASPAN therapy. Frequent monitoring of liver function tests and blood glucose should be performed to ascertain that the drug is producing no adverse effects on these organ systems. Diabetic patients may experience a dose-related rise in glucose tolerance, the clinical significance of which is unclear. Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycemic therapy may be necessary.

Caution should also be used when NIASPAN is used in patients with unstable angina or in the acute phase of MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout.

NIASPAN has been associated with small but statistically significant dose-related reductions in platelet count (mean of -11% with 2000mg). In addition, NIASPAN has been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%); accordingly, patients undergoing surgery should be carefully evaluated. Caution should be observed when NIASPAN is administered concomitantly with anticoagulants; prothrombin time and platelet counts should be monitored closely in such patients.

In placebo-controlled trials, NIASPAN has been associated with small but statistically significant, dose-related reductions in phosphorus levels (mean of −13% with 2000mg). Although these reductions were transient, phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia.

Niacin is rapidly metabolized by the liver, and excreted through the kidneys. NIASPAN is contraindicated in patients with significant or unexplained hepatic dysfunction (see CONTRAINDICATIONS and WARNINGS) and should be used with caution in patients with renal dysfunction.

Information for Patients

Patients should be advised:

— to take NIASPAN at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended;

— to carefully follow the prescribed dosing regimen, including the recommended titration schedule, in order to minimize side effects (see DOSAGE AND ADMINISTRATION);

— that flushing is a common side effect of niacin therapy that usually subsides after several weeks of consistent niacin use. Flushing may vary in severity, may last for several hours after dosing, and will, by taking NIASPAN® at bedtime, most likely occur during sleep; however, if awakened by flushing at night, to get up slowly, especially if feeling dizzy, feeling faint, or taking blood pressure medications;

— that taking aspirin (approximately 30 minutes before taking NIASPAN) or a non-steroidal anti-inflammatory drug (e.g., ibuprofen) may minimize flushing;

— to avoid ingestion of alcohol or hot drinks around the time of NIASPAN administration, to minimize flushing;

— that if NIASPAN therapy is discontinued for an extended length of time, their physician should be contacted prior to re-starting therapy; re-titration is recommended (see DOSAGE AND ADMINISTRATION; Table 10);

— to notify their physician if they are taking vitamins or other nutritional supplements containing niacin or related compounds such as nicotinamide (see Drug Interactions);

— to notify their physician if symptoms of dizziness occur;

— if diabetic, to notify their physician of changes in blood glucose;

— that NIASPAN tablets should not be broken, crushed or chewed, but should be swallowed whole.

Drug Interactions

HMG-CoA Reductase Inhibitors: See WARNINGS, *Skeletal Muscle.*

Antihypertensive Therapy: Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

Aspirin: Concomitant aspirin may decrease the metabolic clearance of nicotinic acid. The clinical relevance of this finding is unclear.

Bile Acid Sequestrants: An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding to cholestyramine. These results suggest that 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of NIASPAN.

Other: Concomitant alcohol or hot drinks may increase the side effects of flushing and pruritus and should be avoided around the time of NIASPAN ingestion. Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of NIASPAN.

Drug/Laboratory Test Interactions

Niacin may produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. Niacin may also give false-positive reactions with cupric sulfate solution (Benedict's reagent) in urine glucose tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Niacin administered to mice for a lifetime as a 1% solution in drinking water was not carcinogenic. The mice in this study received approximately 6 to 8 times a human dose of 3000 mg/day as determined on a mg/m^2 basis. Niacin was negative for mutagenicity in the Ames test. No studies on impairment of fertility have been performed. No studies have been conducted with NIASPAN regarding carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy

Pregnancy Category C.

Animal reproduction studies have not been conducted with niacin or with NIASPAN. It is also not known whether niacin at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving niacin for primary hypercholesterolemia (Types IIa or IIb) becomes pregnant, the drug should be discontinued. If a woman being treated with niacin for hypertriglyceridemia (Types IV or V) conceives, the benefits and risks of continued therapy should be assessed on an individual basis.

Nursing Mothers

Niacin has been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of nicotinic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. No studies have been conducted with NIASPAN in nursing mothers.

Pediatric Use

Safety and effectiveness of niacin therapy in pediatric patients (≤16 years) have not been established. No studies in

Table 9 Treatment-Emergent Adverse Events by Dose Level in ≥5% of Patients; Events Considered At Least Remotely Related to Study Medication

	Placebo-Controlled Studies NIASPAN Treatment†						
			Recommended Daily Maintenance Doses			Greater Than Recommended Daily Doses	
	Placebo (n=157) %	500mg‡ (n=87) %	1000mg (n=110) %	1500mg (n=136) %	2000mg (n=95) %	2500mg‡ (n=49) %	3000mg‡ (n=46) %
Headache	15	5*	9	11	8	4*	4
Pain	3	1	2	5	3	0	2
Pain, Abdominal	3	3	2	3	5	0	0
Diarrhea	8	6	7	6	8	10	11
Dyspepsia	8	2	4	5	5	6	0
Nausea	4	2	5	3	8	10	4
Vomiting	2	0	2	3	8*	8	2
Rhinitis	7	2	5	4	3	0	0
Pruritus	1	6	<1	3	1	0	0
Rash	<1	5	5	4	0	0	0

Note: Percentages are calculated from the total number of patients in each column. AEs are reported at the lowest dose where they occurred.
†Pooled results from placebo-controlled studies; for NIASPAN, n=245 and mean treatment duration = 17 weeks. Number of NIASPAN patients (n) are not additive across doses.
‡The 500mg, 2500mg and 3000mg/day doses are outside the recommended daily maintenance dosing range; see DOSAGE AND ADMINISTRATION.
* Significantly different from placebo at $p \leq 0.05$; Chi-square test (cell size>5), Fisher's Exact test (cell sizes≤5).
In general, the incidence of adverse events was higher in women compared to men.

Table 10. Recommended Dosing

TITRATION SCHEDULE	Week(s)	Daily dose	NIASPAN Dosage
INITIAL	1 to 4	500mg	1 NIASPAN 500mg tablet at bedtime
	5 to 8	1000mg	2 NIASPAN 500mg tablets at bedtime
	*	1500mg	2 NIASPAN 750mg tablets or 3 NIASPAN 500mg tablets at bedtime
	*	2000mg	2 NIASPAN 1000mg tablets or 4 NIASPAN 500mg tablets at bedtime

*After Week 8, titrate to patient response and tolerance. If response to 1000mg daily is inadequate, increase dose to 1500mg daily; may subsequently increase dose to 2000mg daily. Daily dose should not be increased more than 500mg in a 4-week period, and doses above 2000mg daily are not recommended. Women may respond at lower doses than men.

patients under 21 years of age have been conducted with NIASPAN.

ADVERSE REACTIONS

NIASPAN is generally well tolerated; adverse reactions have been mild and transient. In the placebo-controlled clinical trials, flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse events (reported by as many as 88% of patients) for NIASPAN. Spontaneous reports suggest that flushing may also be accompanied by symptoms of dizziness, tachycardia, palpitations, shortness of breath, sweating, chills, and/or edema, which in rare cases may lead to syncope. In pivotal studies, fewer that 6% (14/245) of NIASPAN patients discontinued due to flushing. In comparisons of immediate-release (IR) niacin and NIASPAN, although the proportion of patients who flushed was similar, fewer flushing episodes were reported by patients who received NIASPAN. Following 4 weeks of maintenance therapy at daily doses of 1500mg, the incidence of flushing over the 4-week period averaged 8.56 events per patient for IR niacin versus 1.88 following NIASPAN.

Other adverse events occurring in 5% or greater of patients treated with NIASPAN, at least remotely related to NIASPAN, are shown in Table 9 below.

[See table 9 at top of previous page]

The following adverse events have also been reported with niacin products, either during clinical trials or in routine patient management.

Body as a Whole: edema, asthenia, chills

Cardiovascular: atrial fibrillation, and other cardiac arrhythmias; tachycardia, palpitations; orthostasis; syncope; hypotension

Eye: toxic amblyopia, crystoid macular edema

Gastrointestinal: activation of peptic ulcers and peptic ulceration; jaundice

Metabolic: decreased glucose tolerance; gout

Musculoskeletal: myalgia

Nervous: dizziness, insomnia

Skin: hyper-pigmentation; maculopapular rash; acanthosis nigricans; urticaria; dry skin; sweating

Other: migraine

Clinical Laboratory Abnormalities

Chemistry: Elevations in serum transaminases (see WARNINGS - *Liver Dysfunction*), LDH, fasting glucose, uric acid, total bilirubin, and amylase; reductions in phosphorus

Hematology: Slight reductions in platelet counts and prolongation in prothrombin time (see WARNINGS)

DRUG ABUSE AND DEPENDENCE

Niacin is a non-narcotic drug. It has no known addiction potential in humans.

OVERDOSE

Supportive measures should be undertaken in the event of an overdosage.

DOSAGE AND ADMINISTRATION

NIASPAN should be taken at bedtime, after a low-fat snack, and doses should be individualized according to patient response. Therapy with NIASPAN must be initiated at 500 mg qhs in order to reduce the incidence and severity of side effects which may occur during early therapy. The recommended dose escalation is shown in Table 10 below.

[See table 10 above]

Maintenance Dose:

The daily dosage of NIASPAN should not be increased by more than 500mg in any 4-week period. The recommended maintenance dose is 1000mg (two 500mg tablets) to 2000mg (two 1000mg tablets or four 500mg tablets) once daily at bedtime. Doses greater than 2000mg daily are not recommended. Women may respond at lower NIASPAN doses than men (see CLINICAL PHARMACOLOGY, *Gender Effect*).

If lipid response to NIASPAN alone is insufficient, or if higher doses of NIASPAN are not well tolerated, some patients may benefit from combination therapy with a bile-acid binding resin or an HMG-CoA reductase inhibitor. (see WARNINGS, PRECAUTIONS, Drug Interactions, Concomitant Therapy below, and CLINICAL PHARMACOLOGY, NIASPAN Clinical Studies)

Flushing of the skin (see ADVERSE REACTIONS) may be reduced in frequency or severity by pretreatment with aspirin (taken 30 minutes prior to NIASPAN dose) or non-steroidal anti-inflammatory drugs. Tolerance to this flushing develops rapidly over the course of several weeks. Flushing, pruritus, and gastrointestinal distress are also greatly reduced by slowly increasing the dose of niacin and avoiding administration on an empty stomach.

Equivalent doses of NIASPAN should **not** be substituted for *sustained-release (modified-release, timed-release) niacin* preparations or immediate-release (crystalline) niacin (see WARNINGS). Patients previously receiving other niacin products should be started with the recommended NIASPAN titration schedule (see Table 10), and the dose should subsequently be individualized based on patient response. Single-dose bioavailability studies have demonstrated that NIASPAN tablet strengths are not interchangeable.

If NIASPAN therapy is discontinued for an extended period, reinstitution of therapy should include a titration phase (see Table 10).

NIASPAN tablets should be taken whole and should not be broken, crushed or chewed before swallowing.

Concomitant Therapy

Preliminary evidence suggests that the lipid-lowering effects of NIASPAN on TC and LDL-C are enhanced with an HMG-CoA reductase inhibitor, e.g., lovastatin, pravastatin, simvastatin, and fluvastatin. Additive effects on LDL-C are also seen when niacin is combined with bile acid binding resins. (see WARNINGS and PRECAUTIONS, Drug Interactions)

Dosage in Patients with Renal or Hepatic Insufficiency

Use of NIASPAN in patients with renal or hepatic insufficiency has not be studied. NIASPAN is contraindicated in patients with significant or unexplained hepatic dysfunction. NIASPAN should be used with caution in patients with renal insufficiency (see WARNINGS, PRECAUTIONS).

HOW SUPPLIED

NIASPAN is supplied as unscored, off-white capsule-shaped tablets containing 500, 750 or 1000mg of niacin in an extended-release formulation. Tablets are debossed KOS on one side and the tablet strength (500, 750 or 1000) on the other side. Tablets are supplied in bottles of 100 as shown below.

500mg tablets: bottles of 100 - *NDC# 60598-001-01*
750mg tablets: bottles of 100 - *NDC# 60598-002-01*
1000mg tablets: bottles of 100 - *NDC# 60598-003-01*
Store at room temperature, (20 to 25°C or 68 to 77°F).

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SEN-SEI-RO LIQUID GOLD™

***Kyowa's Agaricus blazei Murill* Mushroom Extract**
100 ml liquid
Dietary Supplement

DESCRIPTION

Sen-Sei-Ro Liquid Gold™, a dietary supplement containing an exclusive all-natural, standardized extract of the Kyowa's cultured *Agaricus blazei Murill* mushroom is primarily used to reduce symptoms of fatigue, to promote vitality, overall well-being, and to support immune functions.† Normal immune function can decline with age, and are necessary for maintenance of vitality, energy, good health, and quality of life. A few major biomarkers for decreased immune functions are decreased natural killer cell (NK) activity, and the number of lymphocytes and macrophage cells. These cells, primarily attack diseased cells and thereby, maintain body homeostasis, promote health and quality of life. For the past half a century in Brazil and other countries, *Agaricus blazei Murill* mushroom has been used to *restore vitality, and energy, and to serve as a potent tonic conducive* to general health and aging concerns.†

CLINICAL TRIALS

The effectiveness of ABMK22 in Sen-Sei-Ro Gold™ for health benefits were tested in several controlled pre- and clinical trials in animals and in humans.† Recent studies in Japan led researchers to report that in humans, ABMK22 in Sen-Sei-Ro Gold™ enhanced NK cell activity, promoted maturation and activation of dendritic cells indicated by increased cell kill, elevated expression of CD80 and *CD83* expressions (Biotherapy 15(4): 503–507, 2001), increased the number of macrophage (Anticancer Research 17(1A): 274–284, 1997; Japanese Association of Cancer Research, no. 2268, 1999) and tumor necrosis factor α (TNF-α)(Japanese Association of Cancer Research, no. 1406, 1999; Japanese J. Veterinary Clin. Medicine 17(2):31–42, 1998).† Further clinical studies with Sen-Sei-Ro Gold™ among 100 cancer patients undergoing chemotherapy in Korea have shown that NK cell activity were significantly enhanced, while NK cell activity in the placebo group was markedly diminished.† Earlier and recent both pre- and clinical studies in Japan, and Korea, led researchers to report that Kyowa's *Agaricus blazei Murill* mushroom extract can be part of an effective treatment for supporting the immune systems of cancer patients by stimulating host defense system (Biotherapy 15(4): 503–507, 2001; Carbohydrate Res. 186(2): 267–273, 1989; Japanese J. Pharmacology 662: 265–271, 1994; Agricultural and Biological Chemistry 54: 2889–2905, 1990).†

INGREDIENTS

Each 100ml heat-treated high pressure pack of all natural Kyowa's *Agaricus blazei Murill* water extract is scientifically standardized to contain 300mg% carbohydrate, 700mg% protein, 0mg% fat,; 1.4mg% sodium, 0% food quality cellulose, and 4 Kcal energy.

Molecular weights of polysaccharopeptides ranges between 600~8,000. Water: 99.2g%,; includes a variety of amino acids and vitamins (arginine 12mg%, lysine 6mg%, histidine 2mg%, phenylalanine 4mg%, tyrosine 4mg%, leucine 5mg%, isoleucine 3mg%, methionine 1mg%, valine 5mg%, alanine 13mg%, glycine 7mg%, proline 13mg%, glutamic acid 53mg%, serine 6mg%, threonine 5mg%, and asparagine 10mg%.

RECOMMENDED USE

As a dietary supplement, take 1~3 packs per day. Pour the liquid content into a cup or drink directly from the pack. Do not heat the pack either in a microwave oven or heating range or leave the pack open since the product does not contain any preservatives. If warming is necessary, place the pack in warm to mildly hot water for desired length of time. Once the pack is open, drink immediately.

ADVERSE REACTIONS

No subjects have reported any side effects since the dietary supplement was placed for consumers in Japan, and Korea for the past 9, and 4 years, respectively. The use of this dietary supplement is generally safe based on two-year chronic toxicity studies of the product carried out by the Good Laboratory Practice (GLP) and American Association of Accreditation of Laboratory Animal Certification (AAALAC) certified Toxicology Research Center. Toxicity evaluation of general, CNS, reproductive and developmental, cardiovascular, immunology, and the *two-year bioassay* for carcinogenicity was negative. Recent clinical studies with 100 cancer patients undergoing chemotherapy in Korea have shown no known side effects or contraindications.†

Continued on next page

Meruvax II—Cont.

Patients, parents or guardians should be instructed to report any serious adverse reactions to their health-care provider who in turn should report such events to the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.

Pregnancy should be avoided for three months following vaccination.

Laboratory Tests

See INDICATIONS AND USAGE, *Non-Pregnant Adolescents and Adult Females*, for Rubella Susceptibility Testing, and CLINICAL PHARMACOLOGY.

Immunosuppressive Therapy

The immune status of patients about to undergo immunosuppressive therapy should be evaluated so that the physician can consider whether vaccination prior to the initiation of treatment is indicated. (see CONTRAINDICATIONS and PRECAUTIONS).

The ACIP has stated that "patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive live-virus vaccines. Short-term (<2 weeks), low- to moderate-dose systemic corticosteroid therapy, topical steroid therapy (e.g., nasal, skin), long-term alternate-day treatment with low to moderate doses of short-acting systemic steroid, and intra-articular, bursal, or tendon injection of corticosteroids are not immunosuppressive in their usual doses and do not contraindicate the administration of rubella vaccine."

Immune Globulin

Administration of immune globulins concurrently with MERUVAX II may interfere with the expected immune response.

See also PRECAUTIONS, *General*.

Carcinogenesis, Mutagenesis, Impairment of Fertility

MERUVAX II has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with MERUVAX II. It is also not known whether MERUVAX II can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. There is evidence suggesting transmission of rubella vaccine viruses to products of conception. Therefore, rubella vaccine should not be administered to pregnant females (see CONTRAINDICATIONS).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: In a 10 year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception, (of whom 189 received the Wistar RA 27/3 strain) none of the newborns had abnormalities compatible with congenital rubella syndrome.

Nursing Mothers

Recent studies have shown that lactating postpartum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. In the infants with serological evidence of rubella infection, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. Caution should be exercised when MERUVAX II is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in infants below the age of 12 months have not been established (see INDICATIONS AND USAGE, *Recommended Vaccination Schedule*).

Geriatric Use

Clinical studies of MERUVAX II did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

ADVERSE REACTIONS

The following adverse reactions are listed in decreasing order of severity, without regard to causality, within each body system category and have been reported during clinical trials, with use of the marketed vaccine, or with use of polyvalent vaccine containing rubella:

Body as a Whole

Fever; syncope; headache; dizziness; malaise; irritability.

Cardiovascular System

Vasculitis.

Digestive System

Diarrhea; vomiting; nausea.

Hemic and Lymphatic System

Thrombocytopenia (see WARNINGS, *Thrombocytopenia*); purpura; regional lymphadenopathy; leukocytosis.

Immune System

Anaphylaxis and anaphylactoid reactions have been reported as well as related phenomena such as angioneurotic edema (including peripheral or facial edema) and bronchial spasm in individuals with or without an allergic history.

Musculoskeletal System

Arthritis; arthralgia; myalgia.

Chronic arthritis has been associated with natural rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Only rarely have vaccine recipients developed chronic joint symptoms.

Following vaccination in children, reactions in joints are uncommon and generally of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0–3%; women: 12–26%) and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in women older than 35 years, these reactions are generally well tolerated and rarely interfere with normal activities. Myalgia and paresthesia have been reported rarely after administration of MERUVAX II.

Nervous System

Encephalitis; Guillain-Barré Syndrome (GBS); polyneuritis; polyneuropathy; paresthesia.

Respiratory System

Sore throat; cough; rhinitis.

Skin

Stevens-Johnson Syndrome; erythema multiforme; urticaria; rash.

Local reactions including burning/stinging at injection site; wheal and flare; redness (erythema); pain; induration.

Special Senses–Ear

Nerve deafness; otitis media.

Special Senses–Eye

Optic neuritis; papillitis; retrobulbar neuritis; conjunctivitis.

Other

Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established. No deaths or permanent sequelae were reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982–1993.

Under the National Childhood Vaccine Injury Act of 1986, health-care providers and manufacturers are required to record and report certain suspected adverse events occurring within specific time periods after vaccination. However, the U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) which will accept all reports of suspected events. A VAERS report form as well as information regarding reporting requirements can be obtained by calling VAERS 1-800-822-7967.

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravenously

The dose for any age is 0.5 mL administered subcutaneously, preferably into the outer aspect of the upper arm.

The recommended age for primary vaccination is 12 to 15 months.

Revaccination with M-M-R II is recommended prior to elementary school entry. See also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*.

Immune Globulin (IG) is not to be given concurrently with MERUVAX II.

CAUTION: A sterile syringe free of perservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Single Dose Vial–First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. If the lyophilized vaccine cannot be dissolved, discard. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. MERUVAX II, when reconstituted, is clear yellow.

Use With Other Vaccines

MERUVAX II should not be given less than one month before or after administration of other live viral vaccines.

M-M-R II has been administered concurrently with VARIVAX* [Varicella Virus Vaccine Live (Oka/Merck)], and PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] using separate sites and syringes. No impairment of immune response to individual tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed in these studies with M-M-R II were similar to those seen when each vaccine was given alone.

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concurrently with measles, mumps and rubella vaccines is not recommended because there are limited data relating to the simultaneous administration of these antigens.

However, other schedules have been used. The ACIP has stated "Although data are limited concerning the simultaneous administration of the entire recommended vaccine series (i.e., DTP, OPV, MMR, and Hib vaccines, with or without hepatitis B vaccine), data from numerous studies have indicated no interference between routinely recommended childhood vaccines (either live, attenuated, or killed). These findings support the simultaneous use of all vaccines as recommended."

HOW SUPPLIED

No. 4747–MERUVAX II is supplied as a single-dose vial of lyophilized vaccine

NDC 0006-4747-00, and a vial of diluent.

No. 4673/4309–MERUVAX II is supplied as follows: (1) a box of 10 single-dose vials of lyophilized vaccine (package A) **NDC** 0006-4673-00; and (2) a box of 10 vials of diluent (package B). To conserve refrigerator space, the diluent may be stored separately at room temperature (Ten Pack).

Storage

During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of 10°C (50°F) or colder. Freezing during shipment will not affect potency.

Protect the vaccine from light at all times, since such exposure may inactivate the virus.

Before reconstitution, store the vial of lyophilized vaccine at 2–8°C (36–46°F) or colder. The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial in a dark place at 2–8°C (36–46°F) and discard if not used within 8 hours.

9243403 Issued August 2001

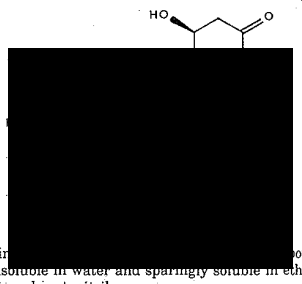
MEVACOR® Tablets
(Lovastatin)

℞

DESCRIPTION

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

Lovastatin is [1*S* -[1α(*R* *),3α,7β,8β(2*S* *,4*S* *),8aβ]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. The empirical formula of lovastatin is $C_{24}H_{36}O_5$ and its molecular weight is 404.55. Its structural formula is:



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

Tablets MEVACOR are supplied as 10 mg, 20 mg and 40 mg tablets for oral administration. In addition to the active ingredient lovastatin, each tablet contains the following inactive ingredients: cellulose, lactose, magnesium stearate, and starch. Butylated hydroxyanisole (BHA) is added as a preservative. Tablets MEVACOR 10 mg also contain red ferric oxide and yellow ferric oxide. Tablets MEVACOR 20 mg also contain FD&C Blue 2. Tablets MEVACOR 40 mg also contain D&C Yellow 10 and FD&C Blue 2.

*Registered trademark of MERCK & CO., INC.

CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological and clinical studies have established that high LDL-C and low high-density lipoprotein cholesterol (HDL-C) are both associated with coronary heart disease. However, the risk of developing coronary heart dis-

ease is continuous and graded over the range of cholesterol levels and many coronary events do occur in patients with total cholesterol (total-C) and LDL-C in the lower end of this range.

MEVACOR has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very low-density lipoprotein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of MEVACOR may involve both reduction of VLDL-C concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with MEVACOR. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that MEVACOR does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, MEVACOR can produce increases of variable magnitude in HDL-C, and modestly reduces VLDL-C and plasma triglycerides (TG) (see Tables I–III under *Clinical Studies*). The effects of MEVACOR on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

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

Pharmacokinetics

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

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

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

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

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

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

Lovastatin is a substrate for cytochrome P450 isoform 3A4 (CYP3A4) (see PRECAUTIONS, *Drug Interactions*.) Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study**, 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 80 mg lovastatin on the third day. This regimen of grapefruit juice resulted in a mean increase in the serum concentration of lovastatin and its β-hydroxyacid metabolite (as measured by the area under the concentration-time curve) of 15-fold and 5-fold, respectively [as measured using a chemical assay—high performance liquid chromatography.] In a second study, 15 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 40 mg lovastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity (using an enzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.34-fold and 1.36-fold, respectively, and of lovastatin and its β-hydroxyacid metabolite [measured using a chemical assay—liquid chromatography/tandem mass spectrometry—different from that used in the first** study] of 1.94-fold and 1.57-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies of lovastatin pharmacokinetics has not been studied.

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

Clinical Studies

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

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

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

[See table I above]

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

[See table II above]

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

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

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

[See table III above]

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

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

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

MEVACOR reduced the risk of a first acute major coronary event, the primary efficacy endpoint, by 37% (MEVACOR 3.5%, placebo 5.5%; p<0.001; Figure 1). A first acute major coronary event was defined as myocardial infarction (54 participants on MEVACOR, 94 on placebo) or unstable angina (54 vs. 80) or sudden cardiac death (8 vs. 9). Furthermore, among the secondary endpoints, MEVACOR reduced the risk of unstable angina by 32% (1.8 vs. 2.6%; p=0.023), of myocardial infarction by 40% (1.7 vs. 2.9%; p=0.002), and of undergoing coronary revascularization procedures (e.g.,

Continued on next page

TABLE I
MEVACOR vs Placebo
(Mean Percent Change from Baseline After 6 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL/C	TRIG.
Placebo	33	−2	−1	−1	0	+1	+9
MEVACOR							
10 mg q.p.m.	33	−16	−21	+5	−24	−19	−10
20 mg q.p.m.	33	−19	−27	+6	−30	−23	+9
10 mg b.i.d.	32	−19	−28	+8	−33	−25	−7
40 mg q.p.m.	33	−22	−31	+5	−33	−25	−8
20 mg b.i.d.	36	−24	−32	+2	−32	−24	−6

TABLE II
MEVACOR vs. Cholestyramine
(Percent Change from Baseline After 12 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TRIG. (median)
MEVACOR								
20 mg b.i.d.	85	−27	−32	+9	−36	−31	−34	−21
40 mg b.i.d.	88	−34	−42	+8	−44	−37	−31	−27
Cholestyramine								
12 g b.i.d.	88	−17	−23	+8	−27	−21	+2	+11

TABLE III
MEVACOR vs. Placebo
(Percent Change from Baseline—
Average Values Between Weeks 12 and 48)

DOSAGE	N**	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	TRIG. (median)
Placebo	1663	+0.7	+0.4	+2.0	+0.2	+0.6	+4
MEVACOR							
20 mg q.p.m.	1642	−17	−24	+6.6	−27	−21	−10
40 mg q.p.m.	1645	−22	−30	+7.2	−34	−26	−14
20 mg b.i.d.	1646	−24	−34	+8.6	−38	−29	−16
40 mg b.i.d.	1649	−29	−40	+9.5	−44	−34	−19

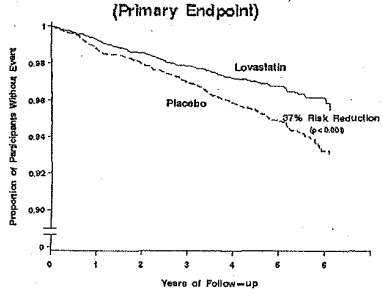
**Patients enrolled

Mevacor—Cont.

coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 33% (3.2 vs. 4.8%; p=0.001). Trends in risk reduction associated with treatment with MEVACOR were consistent across men and women, smokers and non-smokers, hypertensives and non-hypertensives, and older and younger participants. Participants with ≥2 risk factors had risk reductions (RR) in both acute major coronary events (RR 43%) and coronary revascularization procedures (RR 37%). Because there were too few events among those participants with age as their only risk factor in this study, the effect of MEVACOR on outcomes could not be adequately assessed in this subgroup.

Figure 1

Acute Major Coronary Events (Primary Endpoint)



Atherosclerosis

In the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT), the effect of therapy with lovastatin on coronary atherosclerosis was assessed by coronary angiography in hyperlipidemic patients. In this randomized, double-blind, controlled clinical trial, patients were treated with conventional measures (usually diet and 325 mg of aspirin every other day) and either lovastatin 20–80 mg daily or placebo. Angiograms were evaluated at baseline and at two years by computerized quantitative coronary angiography (QCA). Lovastatin significantly slowed the progression of lesions as measured by the mean change per-patient in minimum lumen diameter (the primary endpoint) and percent diameter stenosis, and decreased the proportions of patients categorized with disease progression (33% vs. 50%) and with new lesions (16% vs. 32%).

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

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

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

Eye

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

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

INDICATIONS AND USAGE

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

Primary Prevention of Coronary Heart Disease

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

— Myocardial infarction
— Unstable angina
— Coronary revascularization procedures

(See CLINICAL PHARMACOLOGY, *Clinical Studies*.)

Coronary Heart Disease

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

Hypercholesterolemia

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

General Recommendations

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

LDL-C = total-C − {0.2 × (TG) + HDL-C}

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

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

		LDL-Cholesterol mg/dL (mmol/L)	
Definite Atherosclerotic Disease†	Two or More Other Risk Factors††	Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES or NO	≥130††† (≥3.4)	≤100 (≤2.6)

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

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

††† In CHD patients with LDL-C levels 100–129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment.

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

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

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

***Classification of Hyperlipoproteinemias

Type	Lipoproteins elevated	Lipid Elevations: major	minor
I (rare)	chylomicrons	TG	→C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	→C
V (rare)	chylomicrons, VLDL	TG	→C

IDL = intermediate-density lipoprotein.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

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

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

WARNINGS

Skeletal Muscle

Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (>10× the upper limit of normal [ULN]). **Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time.** In the EXCEL study, there was one case of myopathy among 4933 patients randomized to lovastatin 20–40 mg daily for 48 weeks, and 4 among 1649 patients randomized to 80 mg daily. When drug treatment was interrupted or discontinued in these patients, muscle symptoms and creatine kinase (CK) increases promptly resolved. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the EXCEL study design.

Myopathy caused by drug interactions.

The incidence and severity of myopathy are increased by concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates, and lipid-lowering doses (≥ 1 g/day) of niacin (nicotonic acid).

In addition, the risk of myopathy may be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Lovastatin is metabolized by the cytochrome P450 isoform 3A4 (CYP3A4). Potent inhibitors of this metabolic pathway can raise the plasma levels of HMG-CoA reductase inhibitory activity and may increase the risk of myopathy. These include cyclosporine; the azole antifungals, itraconazole and ketoconazole; the macrolide antibiotics, erythromycin and clarithromycin; HIV protease inhibitors; the antidepressant nefazodone; and large quantities of grapefruit juice (> 1 quart daily) (see below; CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions*; and DOSAGE AND ADMINISTRATION).

Although the data are insufficient for lovastatin, the risk of myopathy appears to be increased when verapamil is used concomitantly with a closely related HMG-CoA reductase inhibitor (see PRECAUTIONS, *Drug Interactions*).

Reducing the risk of myopathy.

1. General measures. Patients starting therapy with lovastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness. A creatine kinase (CK) level above 10× ULN in a patient with unexplained muscle symptoms indicates myopathy. **Lovastatin therapy should be discontinued if myopathy is diagnosed or suspected.** In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved.

Of the patients with rhabdomyolysis, many had complicated medical histories. Some had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with lovastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

2. Measures to reduce the risk of myopathy caused by drug interactions (see above and PRECAUTIONS, *Drug Interactions*). Physicians contemplating combined therapy with lovastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain,

tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

The combined use of lovastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of lovastatin have been used without myopathy in small, short-term clinical trials with careful monitoring. Addition of these drugs to lovastatin typically provides little additional reduction in LDL cholesterol, but further reductions of triglycerides and further increases in HDL cholesterol may be obtained. If one of these drugs must be used with lovastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of lovastatin should generally not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION and DOSAGE AND ADMINISTRATION, *Concomitant Lipid-Lowering Therapy*), as the risk of myopathy increases substantially at higher doses. Concomitant use of lovastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (> 1 quart daily) is not recommended. If no alternative to a short course of treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is available, a brief suspension of lovastatin therapy during such treatment can be considered as there are no known adverse consequences to brief interruptions of long-term cholesterol-lowering therapy.

Liver Dysfunction

Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin, and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the incidence of persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

In AFCAPS/TexCAPS, the number of participants with consecutive elevations of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 times the upper limit of normal), over a median of 5.1 years of follow-up, was not significantly different between the MEVACOR and placebo groups (18 [0.6%] vs. 11 [0.3%]). The starting dose of MEVACOR was 20 mg/day; 50% of the MEVACOR treated participants were titrated to 40 mg/day at Week 18. Of the 18 participants on MEVACOR with consecutive elevations of either ALT or AST, 11 (0.7%) elevations occurred in participants taking 20 mg/day, while 7 (0.4%) elevations occurred in participants titrated to 40 mg/day. Elevated transaminases resulted in discontinuation of 6 (0.2%) participants from therapy in the MEVACOR group (n=3,304) and 4 (0.1%) in the placebo group (n=3,301).

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation of dose, and periodically thereafter (e.g., semiannually). Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of therapy with MEVACOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

PRECAUTIONS

General

Lovastatin may elevate creatine phosphokinase and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia

MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness (see WARNINGS, *Skeletal Muscle*).

Drug Interactions

Gemfibrozil and other fibrates, lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid): These drugs increase the risk of myopathy when given concomitantly with lovastatin, probably because they can produce myopathy when given alone (see WARNINGS, *Skeletal Muscle*). There is no evidence to suggest that these agents affect the pharmacokinetics of lovastatin.

CYP3A4 Interactions: Lovastatin has no CYP3A4 inhibitory activity; therefore, it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. However, lovastatin itself is a substrate for CYP3A4. Potent inhibitors of CYP3A4 may increase the risk of myopathy by increasing the plasma concentration of HMG-CoA reductase inhibitory activity during lovastatin therapy. These inhibitors include cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice (> 1 quart daily) (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Skeletal Muscle*).

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. Large quantities of grapefruit juice (> 1 quart daily) significantly increase the serum concentrations of lovastatin and its β-hydroxyacid metabolite during lovastatin therapy and should be avoided (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Skeletal Muscle*).

Although the data are insufficient for lovastatin, the risk of myopathy appears to be increased when verapamil is used concomitantly with a closely related HMG-CoA reductase inhibitor (see WARNINGS, *Skeletal Muscle*).

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two seconds increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Oral Hypoglycemic Agents: In pharmacokinetic studies of MEVACOR in hypercholesterolemic non-insulin dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity

Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose which produced plasma drug levels (C_{max}) which were about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Cataracts were seen in dogs treated for 11 and 28 weeks at 180 mg/kg/day and 1 year at 60 mg/kg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on a mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR.)

There was an increase in incidence of papilloma in the nonglandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males at drug exposures between 2–7 times that of human exposure at 80 mg/day (doses in rats were 5, 30 and 180 mg/kg/day).

An increased incidence of thyroid neoplasms in rats appears to be a response that has been seen with other HMG-CoA reductase inhibitors.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high dose females and mid- and high dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m^2 surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose).

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibi-

Continued on next page

Mevacor—Cont.

tors. In a review† of approximately 100 prospectively followed pregnancies in women exposed to MEVACOR or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3 to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with MEVACOR during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. MEVACOR 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 hazard.

Nursing Mothers

It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with lovastatin is not recommended at this time.

Geriatric Use

A pharmacokinetic study with lovastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70–78 years of age compared with patients between 18–30 years of age; however, clinical study experience in the elderly indicates that dosage adjustment based on this age-related pharmacokinetic difference is not needed. In the two large clinical studies conducted with lovastatin (EXCEL and AFCAPS/TexCAPS), 21% (3094/14850) of patients were ≥65 years of age. Lipid-lowering efficacy with lovastatin was at least as great in elderly patients compared with younger patients, and there were no overall differences in safety over the 20 to 80 mg/day dosage range (see CLINICAL PHARMACOLOGY).

†Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy. *Reproductive Toxicology.* 10(6):439-446. 1996.

ADVERSE REACTIONS

MEVACOR is generally well tolerated; adverse reactions usually have been mild and transient.

Phase III Clinical Studies

In Phase III controlled clinical studies involving 613 patients treated with MEVACOR, the adverse experience profile was similar to that shown below for the 8,245-patient EXCEL study (see *Expanded Clinical Evaluation of Lovastatin [EXCEL] Study*).

Persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 11% of patients had elevations of CK levels of at least twice the normal value on one or more occasions. The corresponding values for the control agent cholestyramine was 9 percent. This was attributable to the noncardiac fraction of CK. Large increases in CK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240–300 mg/dL [6.2–7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably or definitely drug-related in ≥1% in any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

[See table below]

Other clinical adverse experiences reported as possibly, probably or definitely drug-related in 0.5 to 1.0 percent of patients in any drug-treated group are listed below. In all these cases the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences which were rated by the investigator as possibly, probably or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

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

In AFCAPS/TexCAPS (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 6,605 participants treated with 20–40 mg/day of MEVACOR (n=3,304) or placebo (n=3,301), the safety and tolerability profile of the group treated with MEVACOR was comparable to that of the group treated with placebo during a median of 5.1 years of follow-up. The adverse experiences reported in AFCAPS/TexCAPS were similar to those reported in EXCEL (see ADVERSE REACTIONS, *Expanded Clinical Evaluation of Lovastatin (EXCEL) Study*).

Concomitant Therapy

In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggests that the addition of gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL-C than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with cyclosporine, gemfibrozil or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with lovastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

	Placebo (N=1668) %	MEVACOR 20 mg q.p.m. (N=1642) %	MEVACOR 40 mg q.p.m. (N=1645) %	MEVACOR 20 mg b.i.d. (N=1646) %	MEVACOR 40 mg b.i.d. (N=1649) %
Body As a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

OVERDOSAGE

After oral administration of MEVACOR to mice the median lethal dose observed was >15 g/m^2.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5–6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR (see NCEP Treatment Guidelines for details on dietary therapy). MEVACOR should be given with meals.

The usual recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 10–80 mg/day in single or two divided doses; the maximum recommended dose is 80 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Guidelines and CLINICAL PHARMACOLOGY). Patients requiring reductions in LDL-C of 20% or more to achieve their goal (see INDICATIONS AND USAGE) should be started on 20 mg/day of MEVACOR. A starting dose of 10 mg may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more.

In patients taking cyclosporine concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day. Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall significantly below the targeted range.

Concomitant Lipid-Lowering Therapy

MEVCOR is effective alone or when used concomitantly with bile-acid sequestrants. Use of MEVACOR with fibrates or niacin should generally be avoided. However, if MEVACOR is used in combination with fibrates or niacin, the dose of MEVACOR should generally not exceed 20 mg/day (see WARNINGS, *Skeletal Muscle* and PRECAUTIONS, *Drug Interations*).

Dosage in Patients with Renal Insufficiency

In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY and WARNINGS, *Skeletal Muscle*).

HOW SUPPLIED

No. 3560—Tablets MEVACOR 10 mg are peach, octagonal tablets, coded MSD 730 on one side and MEVACOR on the other. They are supplied as follows:

NDC 0006-0730-61 unit of use bottles of 60.

Shown in Product Identification Guide, page 323

No. 3561—Tablets MEVACOR 20 mg are light blue, octagonal tablets, coded MSD 731 on one side and MEVACOR on the other. They are supplied as follows:

NDC 0006-0731-61 unit of use bottles of 60
NDC 0006-0731-94 unit of use bottles of 90
NDC 0006-0731-28 unit dose packages of 100
NDC 0006-0731-82 bottles of 1,000
NDC 0006-0731-87 bottles of 10,000.

Shown in Product Identification Guide, page 323

No. 3562—Tablets MEVACOR 40 mg are green, octagonal tablets, coded MSD 732 on one side and MEVACOR on the other. They are supplied as follows:

NDC 0006-0732-61 unit of use bottles of 60
NDC 0006-0732-94 unit of use bottles of 90
NDC 0006-0732-82 bottles of 1,000
NDC 0006-0732-87 bottles of 10,000.

Shown in Product Identification Guide, page 323

Storage

Store between 5–30°C (41–86°F). Tablets MEVACOR must be protected from light and stored in a well-closed, light-resistant container.

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MIDAMOR® Tablets ℞
(Amiloride HCl)

DESCRIPTION

Amiloride HCl, an antikaliuretic-diuretic agent, is a pyrazine-carbonyl-guanidine that is unrelated chemically to other known antikaliuretic or diuretic agents. It is the salt of a moderately strong base (pKa 8.7). It is designated chemically as 3,5-diamino-6-chloro-*N* -(diaminomethylene) pyrazinecarboxamide monohydrochloride, dihydrate and has a molecular weight of 302.12. Its empirical formula is $C_6H_8ClN_7O \cdot HCl \cdot 2H_2O$ and its structural formula is:

MIDAMOR® (Amiloride HCl) is available for oral use as tablets containing 5 mg of anhydrous amiloride HCl. Each tablet contains the following inactive ingredients: calcium phosphate, D&C Yellow 10, iron oxide, lactose, magnesium stearate and starch.

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CLINICAL PHARMACOLOGY

MIDAMOR is a potassium-conserving (antikaliuretic) drug that possesses weak (compared with thiazide diuretics) natriuretic, diuretic, and antihypertensive activity. These effects have been partially additive to the effects of thiazide diuretics in some clinical studies. When administered with a thiazide or loop diuretic, MIDAMOR has been shown to decrease the enhanced urinary excretion of magnesium which occurs when a thiazide or loop diuretic is used alone. MIDAMOR has potassium-conserving activity in patients receiving kaliuretic-diuretic agents.

MIDAMOR is not an aldosterone antagonist and its effects are seen even in the absence of aldosterone.

MIDAMOR exerts its potassium sparing effect through the inhibition of sodium reabsorption at the distal convoluted tubule, cortical collecting tubule and collecting duct; this decreases the net negative potential of the tubular lumen and reduces both potassium and hydrogen secretion and their subsequent excretion. This mechanism accounts in large part for the potassium sparing action of amiloride.

MIDAMOR usually begins to act within 2 hours after an oral dose. Its effect on electrolyte excretion reaches a peak between 6 and 10 hours and lasts about 24 hours. Peak plasma levels are obtained in 3 to 4 hours and the plasma half-life varies from 6 to 9 hours. Effects on electrolytes increase with single doses of amiloride HCl up to approximately 15 mg.

Amiloride HCl is not metabolized by the liver but is excreted unchanged by the kidneys. About 50 percent of a 20 mg dose of MIDAMOR is excreted in the urine and 40 percent in the stool within 72 hours. MIDAMOR has little effect on glomerular filtration rate or renal blood flow. Because amiloride HCl is not metabolized by the liver, drug accumulation is not anticipated in patients with hepatic dysfunction, but accumulation can occur if the hepatorenal syndrome develops.

INDICATIONS AND USAGE

MIDAMOR is indicated as adjunctive treatment with thiazide diuretics or other kaliuretic-diuretic agents in congestive heart failure or hypertension to:

a. help restore normal serum potassium levels in patients who develop hypokalemia on the kaliuretic diuretic
b. prevent development of hypokalemia in patients who would be exposed to particular risk if hypokalemia were to develop, e.g., digitalized patients or patients with significant cardiac arrhythmias.

The use of potassium-conserving agents is often unnecessary in patients receiving diuretics for uncomplicated essential hypertension when such patients have a normal diet. MIDAMOR has little additive diuretic or antihypertensive effect when added to a thiazide diuretic.

MIDAMOR should rarely be used alone. It has weak (compared with thiazides) diuretic and antihypertensive effects. Used as single agents, potassium sparing diuretics, including MIDAMOR, result in an increased risk of hyperkalemia (approximately 10% with amiloride). MIDAMOR should be used alone only when persistent hypokalemia has been documented and only with careful titration of the dose and close monitoring of serum electrolytes.

CONTRAINDICATIONS

Hyperkalemia
MIDAMOR should not be used in the presence of elevated serum potassium levels (greater than 5.5 mEq per liter).
Antikaliuretic Therapy or Potassium Supplementation
MIDAMOR should not be given to patients receiving other potassium-conserving agents, such as spironolactone or triamterene. Potassium supplementation in the form of medication, potassium-containing salt substitutes or a potassium-rich diet should not be used with MIDAMOR except in severe and/or refractory cases of hypokalemia. Such concomitant therapy can be associated with rapid increases in serum potassium levels. If potassium supplementation is used, careful monitoring of the serum potassium level is necessary.
Impaired Renal Function
Anuria, acute or chronic renal insufficiency, and evidence of diabetic nephropathy are contraindications to the use of MIDAMOR. Patients with evidence of renal functional impairment (blood urea nitrogen [BUN] levels over 30 mg per 100 mL or serum creatinine levels over 1.5 mg per 100 mL) or diabetes mellitus should not receive the drug without careful, frequent and continuing monitoring of serum electrolytes, creatinine, and BUN levels. Potassium retention associated with the use of an antikaliuretic agent is accentuated in the presence of renal impairment and may result in the rapid development of hyperkalemia.
Hypersensitivity
MIDAMOR is contraindicated in patients who are hypersensitive to this product.

WARNINGS

Hyperkalemia

Like other potassium-conserving agents, amiloride may cause hyperkalemia (serum potassium levels greater than 5.5 mEq per liter) which, if uncorrected, is potentially fatal. Hyperkalemia occurs commonly (about 10%) when amiloride is used without a kaliuretic diuretic. This incidence is greater in patients with renal impairment, diabetes mellitus (with or without recognized renal insufficiency), and in the elderly. When MIDAMOR is used concomitantly with a thiazide diuretic in patients without these complications, the risk of hyperkalemia is reduced to about 1–2 percent. It is thus essential to monitor serum potassium levels carefully in any patient receiving amiloride, particularly when it is first introduced, at the time of diuretic dosage adjustments, and during any illness that could affect renal function.

The risk of hyperkalemia may be increased when potassium-conserving agents, including MIDAMOR, are administered concomitantly with an angiotensin-converting enzyme inhibitor, cyclosporine or tacrolimus. (See PRECAUTIONS, *Drug Interactions.*) Warning signs or symptoms of hyperkalemia include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and ECG abnormalities. Monitoring of the serum potassium level is essential because mild hyperkalemia is not usually associated with an abnormal ECG.

When abnormal, the ECG in hyperkalemia is characterized primarily by tall, peaked T waves or elevations from previous tracings. There may also be lowering of the R wave and increased depth of the S wave, widening and even disappearance of the P wave, progressive widening of the QRS complex, prolongation of the PR interval, and ST depression.

Treatment of hyperkalemia: If hyperkalemia occurs in patients taking MIDAMOR, the drug should be discontinued immediately. If the serum potassium level exceeds 6.5 mEq per liter, active measures should be taken to reduce it. Such measures include the intravenous administration of sodium bicarbonate solution or oral or parenteral glucose with a rapid-acting insulin preparation. If needed, a cation exchange resin such as sodium polystyrene sulfonate may be given orally or by enema. Patients with persistent hyperkalemia may require dialysis.

Diabetes Mellitus
In diabetic patients, hyperkalemia has been reported with the use of all potassium-conserving diuretics, including MIDAMOR, even in patients without evidence of diabetic nephropathy. Therefore, MIDAMOR should be avoided, if possible, in diabetic patients and, if it is used, serum electrolytes and renal function must be monitored frequently.
MIDAMOR should be discontinued at least three days before glucose tolerance testing.
Metabolic or Respiratory Acidosis
Antikaliuretic therapy should be instituted only with caution in severely ill patients in whom respiratory or metabolic acidosis may occur, such as patients with cardiopulmonary disease or poorly controlled diabetes. If MIDAMOR is given to these patients, frequent monitoring of acid-base balance is necessary. Shifts in acid-base balance alter the ratio of extracellular/intracellular potassium, and the development of acidosis may be associated with rapid increases in serum potassium levels.

PRECAUTIONS

General
Electrolyte Imbalance and BUN Increases
Hyponatremia and hypochloremia may occur when MIDAMOR is used with other diuretics and increases in BUN levels have been reported. These increases usually have accompanied vigorous fluid elimination, especially when diuretic therapy was used in seriously ill patients, such as those who had hepatic cirrhosis with ascites and metabolic alkalosis, or those with resistant edema. Therefore, when MIDAMOR is given with other diuretics to such patients, careful monitoring of serum electrolytes and BUN levels is important. In patients with pre-existing severe liver disease, hepatic encephalopathy, manifested by tremors, confusion, and coma, and increased jaundice, have been reported in association with diuretics, including amiloride HCl.
Drug Interactions
When amiloride HCl is administered concomitantly with an angiotensin-converting enzyme inhibitor, cyclosporine or tacrolimus, the risk of hyperkalemia may be increased. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. (See WARNINGS.)
Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.
In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when MIDAMOR and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. Since indomethacin and potassium-sparing diuretics, including MIDAMOR, may each be associated with increased serum potassium levels, the potential effects on potassium kinetics and renal function should be considered when these agents are administered concurrently.
Carcinogenicity, Mutagenicity, Impairment of Fertility
There was no evidence of a tumorigenic effect when amiloride HCl was administered for 92 weeks to mice at doses up to 10 mg/kg/day (25 times the maximum daily human dose). Amiloride HCl has also been administered for 104 weeks to male and female rats at doses up to 6 and 8 mg/kg/day (15 and 20 times the maximum daily dose for humans, respectively) and showed no evidence of carcinogenicity.
Amiloride HCl was devoid of mutagenic activity in various strains of *Salmonella typhimurium* with or without a mammalian liver microsomal activation system (Ames test).
Pregnancy
Pregnancy Category B. Teratogenicity studies with amiloride HCl in rabbits and mice given 20 and 25 times the maximum human dose, respectively, revealed no evidence of harm to the fetus, although studies showed that the drug crossed the placenta in modest amounts. Reproduction studies in rats at 20 times the expected maximum daily dose for humans showed no evidence of impaired fertility. At approximately 5 or more times the expected maximum daily dose for humans, some toxicity was seen in adult rats and rabbits and a decrease in rat pup growth and survival occurred.
There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Studies in rats have shown that amiloride is excreted in milk in concentrations higher than those found in blood, but it is not known whether MIDAMOR is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MIDAMOR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use
Safety and effectiveness in pediatric patients have not been established.
Geriatric Use
Clinical studies of MIDAMOR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CONTRAINDICATIONS, *Impaired Renal Function.*)

ADVERSE REACTIONS

MIDAMOR is usually well tolerated and, except for hyperkalemia (serum potassium levels greater than 5.5 mEq per liter—see WARNINGS), significant adverse effects have been reported infrequently. Minor adverse reactions were reported relatively frequently (about 20%) but the relationship of many of the reports to amiloride HCl is uncertain and the overall frequency was similar in hydrochlorothia-

Continued on next page

Vivactil—Cont.

larities among the tricyclic antidepressant drugs require that each of the reactions be considered when protriptyline is administered. VIVACTIL is more likely to aggravate agitation and anxiety and produce cardiovascular reactions such as tachycardia and hypotension.

Cardiovascular: Myocardial infarction; stroke; heart block; arrhythmias; hypotension, particularly orthostatic hypotension; hypertension; tachycardia; palpitation.

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation; hypomania; exacerbation of psychosis; insomnia, panic, and nightmares.

Neurological: Seizures; incoordination; ataxia; tremors; peripheral neuropathy; numbness, tingling, and paresthesias of extremities; extrapyramidal symptoms; drowsiness; dizziness; weakness and fatigue; headache; syndrome of inappropriate ADH (antidiuretic hormone) secretion; tinnitus; alteration in EEG patterns.

Anticholinergic: Paralytic ileus; hyperpyrexia; urinary retention, delayed micturition, dilatation of the urinary tract; constipation; blurred vision, disturbance of accommodation, increased intraocular pressure, mydriasis; dry mouth and rarely associated sublingual adenitis.

Allergic: Drug fever; petechiae, skin rash, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general, or of face and tongue).

Hematologic: Agranulocytosis; bone marrow depression; leukopenia; thrombocytopenia; purpura; eosinophilia.

Gastrointestinal: Nausea and vomiting; anorexia; epigastric distress; diarrhea; peculiar taste; stomatitis; abdominal cramps; black tongue.

Endocrine: Impotence, increased or decreased libido; gynecomastia in the male; breast enlargement and galactorrhea in the female; testicular swelling; elevation or depression of blood sugar levels.

Other: Jaundice (simulating obstructive); altered liver function; parotid swelling; alopecia; flushing; weight gain or loss, urinary frequency, nocturia; perspiration.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Usual Adult Dosage—Fifteen to 40 mg a day divided into 3 or 4 doses. If necessary, dosage may be increased to 60 mg a day. Dosages above this amount are not recommended. Increases should be made in the morning dose.

Adolescent and Elderly Patients—In general, lower dosages are recommended for these patients. Five mg 3 times a day may be given initially, and increased gradually if necessary. In elderly patients, the cardiovascular system must be monitored closely if the daily dose exceeds 20 mg.

When satisfactory improvement has been reached, dosage should be reduced to the smallest amount that will maintain relief of symptoms.

Minor adverse reactions require reduction in dosage. Major adverse reactions or evidence of hypersensitivity require prompt discontinuation of the drug.

The safety and effectiveness of VIVACTIL in pediatric patients have not been established.

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose, therefore, hospital monitoring is required as soon as possible.

MANIFESTATIONS

Critical manifestations of overdosage include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under ADVERSE REACTIONS.

MANAGEMENT

General

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose. These patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination

All patients suspected of a tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of ≥0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH >7.60 or a pCO_2 <20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide). In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center.

PSYCHIATRIC FOLLOW-UP

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

PEDIATRIC MANAGEMENT

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

HOW SUPPLIED

No. 3314—Tablets VIVACTIL, 10 mg, are yellow, oval, film coated tablets, coded MSD 47 on one side and VIVACTIL on the other. They are supplied as follows:

NDC 0006-0047-68 bottles of 100

Shown in Product Identification Guide, page 323

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

METABOLISM

Metabolic studies indicate that protriptyline is well absorbed from the gastrointestinal tract and is rapidly sequestered in tissues. Relatively low plasma levels are found after administration, and only a small amount of unchanged drug is excreted in the urine of dogs and rabbits. Preliminary studies indicate that demethylation of the secondary amine moiety occurs to a significant extent, and that metabolic transformation probably takes place in the liver. It penetrates the brain rapidly in mice and rats, and moreover that which is present in the brain is almost all unchanged drug.

Studies on the disposition of radioactive protriptyline in human test subjects showed significant plasma levels within 2 hours, peaking at 8 to 12 hours, then declining gradually. Urinary excretion studies in the same subjects showed significant amounts of radioactivity in 2 hours. The rate of excretion was slow. Cumulative urinary excretion during 16 days accounted for approximately 50% of the drug. The fecal route of excretion did not seem to be important.

7904026 Issued December 1999

Shown in Product Identification Guide, page 323

ZOCOR® Tablets (simvastatin) ℞

DESCRIPTION

ZOCOR* (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and other ingredients. Butylated hydroxyanisole is added as a preservative.

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CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that elevated plasma levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (Apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of high-density lipoprotein cholesterol (HDL-C) and its transport complex, Apo A-1, are associated with decreased cardiovascular risk. High plasma triglycerides (TG) and cholesterol-enriched TG-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C and small LDL particles, as well as in association with non-lipid metabolic risk factors for CHD. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

In the Scandinavian Simvastatin Survival Study (4S), the effect of improving lipoprotein levels with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol (total-C) 212–309 mg/dL (5.5–8.0 mmol/L). The patients were followed for a median of 5.4 years. In this multicenter, randomized, double-blind, placebo-controlled study, ZOCOR significantly reduced the risk of mortality by 30% (11.5% vs 8.2%, placebo vs ZOCOR); of CHD mortality by 42% (8.5% vs 5.0%); and of having a hospital-verified non-fatal myocardial infarction by 37% (19.6% vs 12.9%). Furthermore, ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (17.2% vs 11.4%) [see CLINICAL PHARMACOLOGY, *Clinical Studies*].

ZOCOR has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density lipoprotein (VLDL) and is catabolized predominantly by the high-affinity LDL receptor. The mechanism of the LDL-lowering effect of ZOCOR may involve both reduction of VLDL cholesterol concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. Apo B also falls substantially during treatment with ZOCOR. As each LDL particle contains one molecule of Apo B, and since in patients with predominant elevations in LDL-C (without accompanying elevation in VLDL) little Apo B is found in other lipoproteins, this strongly suggests that ZOCOR does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, ZOCOR reduces VLDL and TG and increases HDL-C. The effects of ZOCOR on Lp(a), fibrinogen, and certain other independent biochemical risk markers for CHD are unknown.

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

Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Absorption of simvastatin, estimated relative to an intravenous reference dose, in each of two animal species tested, averaged about 85% of an oral dose. In animal studies, after oral dosing, simvastatin achieved sub-

stantially higher concentrations in the liver than in non-target tissues. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be > 60% in man), the availability of drug to the general circulation is low. In a single-dose study in nine healthy subjects, it was estimated that less than 5% of an oral dose of simvastatin reaches the general circulation as active inhibitors. Following administration of simvastatin tablets, the coefficient of variation, based on between-subject variability, was approximately 48% for the area under the concentration-time curve (AUC) for total inhibitory activity in the general circulation.

Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Animal studies have not been performed to determine whether simvastatin crosses the blood-brain and placental barriers. However, when radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. While the recommended therapeutic dose range is 5 to 80 mg/day, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

In a study including 16 elderly patients between 70 and 78 years of age who received ZOCOR 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18–30 years of age. Clinical study experience in the elderly (n=1522), suggests that there were no overall differences in safety between elderly and younger patients (see PRECAUTIONS, *Geriatric Use*).

Kinetic studies with another reductase inhibitor, having a similar principal route of elimination, have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

In a study of 12 healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

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

Simvastatin is a substrate for CYP3A4 (see PRECAUTIONS, *Drug Interactions*). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study**, 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 60 mg simvastatin on the third day. This regimen of grapefruit juice resulted in mean increases in the concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [measured using a radioenzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 2.4-fold and 3.6-fold, respectively, and of simvastatin and its β-hydroxyacid metabolite [measured using a chemical assay—liquid chromatography/tandem mass spectrometry of 16-fold and 7-fold, respectively. In a second study, 16 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 20 mg simvastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using a validated enzyme inhibition assay different from that used in the first** study both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.13-fold and 1.18-fold, respectively, and of simvastatin and its β-hydroxyacid metabolite [measured using a chemical assay—liquid chromatography/tandem mass spectrometry] of 1.88-fold and 1.31-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.

**Lilja JJ, Kivisto KT, Neuvonen PJ, Clin Pharmacol Ther 1998;64(5):477–83.

Clinical Studies

Coronary Heart Disease

In 4S, the effect of therapy with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212–309 mg/dL (5.5–8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with standard care, including diet, and either ZOCOR 20–40 mg/day (n=2,221) or placebo (n=2,223) for a median duration of 5.4 years. After six weeks of treatment with ZOCOR the median (25th and 75th percentile) changes in LDL-C, TG, and HDL-C were −39% (−46, −31%), −19% (−31, 0%), and 6% (−3, 17%). Over the course of the study, treatment with ZOCOR led to mean reductions in total-C, LDL-C and TG of 25%, 35%, and 10%, respectively, and a mean increase in HDL-C of 8%. ZOCOR significantly reduced the risk of mortality (Figure 1) by 30%, (p=0.0003, 182 deaths in the ZOCOR group vs 256 deaths in the placebo group). The risk of CHD mortality was significantly reduced by 42%, (p=0.00001, 111 vs 189 deaths). There was no statistically significant difference between groups in non-cardiovascular mortality. ZOCOR also significantly decreased the risk of having major coronary events (CHD mortality plus hospital-verified and silent non-fatal myocardial infarction [MI]) (Figure 2) by 34%, (p<0.00001, 431 vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%, (p<0.00001, 252 vs 383 patients). Furthermore, ZOCOR significantly reduced the risk of fatal plus non-fatal cerebrovascular events (combined stroke and transient ischemic attacks) by 28% (p=0.033, 75 vs 102 patients). ZOCOR reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels. Because there were only 53 female deaths, the effect of ZOCOR on mortality in women could not be adequately assessed. However, ZOCOR significantly lessened the risk of having major coronary events by 34% (60 vs 91 women with one or more event). The randomization was stratified by angina alone (21% of each treatment group) or a previous MI. Because there were only 57 deaths among the patients with angina alone at baseline, the effect of ZOCOR on mortality in this subgroup could not be adequately assessed. However, trends in reduced coronary mortality, major coronary events and revascularization procedures were consistent between this group and the total study cohort. Additionally, in this study, 1,021 of the patients were 65 and older. Cholesterol reduction with simvastatin resulted in similar decreases in relative risk for total mortality, CHD mortality, and major coronary events in these elderly patients, compared with younger patients.

Figure 1

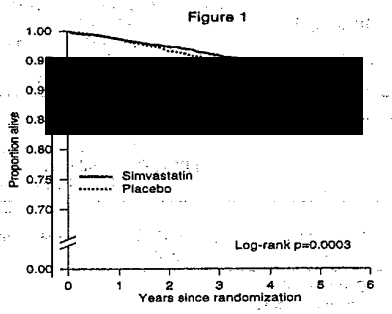
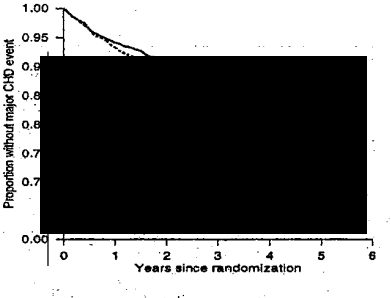


Figure 2



Angiographic Studies

In the Multicenter Anti-Atheroma Study, the effect of therapy with simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic men and women with coronary heart disease. In this randomized, double-blind, controlled study, patients with a mean baseline total-C value of 245 mg/dL (6.4 mmol/L) and a mean baseline LDL-C value of 170 mg/dL (4.4 mmol/L) were treated with conventional measures and with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. A total of 347 patients had a baseline angiogram and at least one follow-up angiogram. The co-primary endpoints of the study were mean change per-patient in minimum and mean lumen diameters, indicating focal and diffuse disease, respectively. Simvastatin significantly slowed the progression of lesions as measured in the final angiogram by both these parameters (mean changes in minimum lumen diameter: −0.04 mm with simvastatin vs −0.12 mm with placebo; mean changes in mean lumen diameter: −0.03 mm with simvastatin vs −0.08 mm with placebo), as well as by change from baseline in percent diameter stenosis (0.9% simvastatin vs 3.6% placebo). After four years, the groups also differed significantly in the proportions of patients categorized with disease progression (23% simvastatin vs 33% placebo) and disease regression (18% simvastatin vs 12% placebo). In addition, simvastatin significantly decreased the proportion of patients with new lesions (13% simvastatin vs 24% placebo) and with new total occlusions (5% vs 11%). The mean change per-patient in mean and minimum lumen diameters, calculated by comparing angiograms, in the subset of 274 patients who had matched angiographic projections at baseline, two and four years is presented below (Figures 3 and 4).

Figure 3

Mean Lumen Diameter
(Mean and Standard Error)

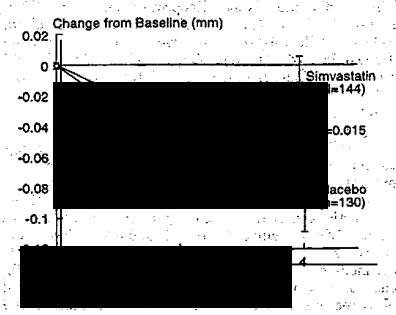
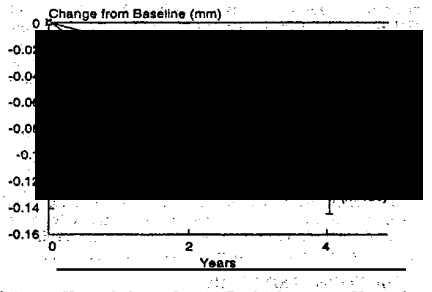


Figure 4

Minimum Lumen Diameter
(Mean and Standard Error)



Primary Hypercholesterolemia (Fredrickson type IIa and IIb)

ZOCOR has been shown to be highly effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4–6 weeks. The response was maintained during chronic therapy. Furthermore, improving lipoprotein levels with ZOCOR improved survival in patients with CHD and hypercholesterolemia treated with 20–40 mg/day for a median of 5.4 years.

In a multicenter, double-blind, placebo-controlled, dose-response study in patients with familial or non-familial hypercholesterolemia, ZOCOR given as a single dose in the evening (the recommended dosing) was similarly effective as when given on a twice-daily basis. ZOCOR consistently and significantly decreased total-C, LDL-C, total-C/HDL-C ratio, and LDL-C/HDL-C ratio. ZOCOR also decreased TG and increased HDL-C.

The results of studies depicting the mean response to simvastatin in patients with primary hypercholesterolemia and combined (mixed) hyperlipidemia are presented in Table 1.

[See table 1 at top of next page]

In the Upper Dose Comparative Study, the mean reduction in LDL-C was 47% at the 80-mg dose. Of the 664 patients randomized to 80 mg, 475 patients with plasma TG ≤ 200 mg/dL had a median reduction in TG of 21%, while in 189 patients with TG > 200 mg/dL, the median reduction in TG was 36%. In these studies, patients with TG > 350 mg/dL were excluded.

Continued on next page

Zocor—Cont.

In the Multi-Center Combined Hyperlipidemia Study, a randomized, 3-period crossover study, 130 patients with combined hyperlipidemia (LDL-C>130 mg/dL and TG: 300–700 mg/dL) were treated with placebo, ZOCOR 40, and 80 mg/day for 6 weeks. In a dose-dependent manner ZOCOR 40 and 80 mg/day, respectively, decreased mean LDL-C by 29 and 36% (placebo: +2%) and median TG levels by 28 and 33% (placebo: 4%), and increased mean HDL-C by 13 and 16% (placebo: 3%) and apolipoprotein A-1 by 8 and 11% (placebo: 4%).

Hypertriglyceridemia (Fredrickson type IV)

The results of a subgroup analysis in 74 patients with type IV hyperlipidemia from a 130-patient double-blind, placebo-controlled, 3-period crossover study are presented in Table 2. The median baseline values (mg/dL) for the patients in this study were: total-C = 254, LDL-C = 135, HDL-C = 36, TG = 404, VLDL-C = 83, and non-HDL-C = 215.

[See table 2 at right]

Dysbetalipoproteinemia (Fredrickson type III)

The results of a subgroup analysis in 7 patients with type III hyperlipidemia (dysbetalipoproteinemia) (apo E2/2) (VLDL-C/TG>0.25) from a 130-patient double-blind, placebo-controlled, 3-period crossover study are presented in Table 3. In this study the median baseline values (mg/dL) were: total-C = 324, LDL-C = 121, HDL-C = 31, TG = 417, VLDL-C = 170, and non-HDL-C = 291.

[See table 3 at right]

Homozygous Familial Hypercholesterolemia

In a controlled clinical study, 12 patients 15–39 years of age with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses or 80 mg/day in 3 divided doses. Eleven of the 12 patients had reductions in LDL-C. In those patients with reductions, the mean LDL-C changes for the 40- and 80-mg doses were 14% (range 8% to 23%, median 12%) and 30% (range 14% to 46%, median 29%), respectively. One patient had an increase of 15% in LDL-C. Another patient with absent LDL-C receptor function had an LDL-C reduction of 41% with the 80-mg dose.

Endocrine Function

In clinical studies, simvastatin did not impair adrenal reserve or significantly reduce basal plasma cortisol concentration. Small reductions from baseline in basal plasma testosterone in men were observed in clinical studies with simvastatin, an effect also observed with other inhibitors of HMG-CoA reductase and the bile acid sequestrant cholestyramine. There was no effect on plasma gonadotropin levels. In a placebo-controlled 12-week study there was no significant effect of simvastatin 80 mg on the plasma testosterone response to human chorionic gonadotropin (hCG). *In another 24-week study, simvastatin 20–40 mg had no detectable effect on spermatogenesis.* In 4S, in which 4,444 patients were randomized to simvastatin 20–40 mg/day or placebo for a median duration of 5.4 years, the incidence of male sexual adverse events in the two treatment groups was not significantly different. Because of these factors, the small changes in plasma testosterone are unlikely to be clinically significant. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown.

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be considered in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence of CHD, or other risk factors. Lipid-altering agents 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 National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Coronary Heart Disease

In patients with coronary heart disease and hypercholesterolemia, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing coronary death;
- Reduce the risk of non-fatal myocardial infarction;
- Reduce the risk for undergoing myocardial revascularization procedures;
- Reduce the risk of stroke or transient ischemic attack.

(For a discussion of efficacy results in the elderly and other pre-defined subgroups, see CLINICAL PHARMACOLOGY, *Clinical Studies*.)

Hyperlipidemia

- ZOCOR is indicated to reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb***).
- ZOCOR is indicated for the treatment of patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).
- ZOCOR is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).
- ZOCOR is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

General Recommendations

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

$$\text{LDL-C} = \text{total-C} - [(0.20 \times \text{TG}) + \text{HDL-C}]$$

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

Lipid determinations should be performed at intervals of no less than four weeks and dosage adjusted according to the patient's response to therapy.

The NCEP Treatment Guidelines are summarized in Table 4:

[See table 4 above]

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 Treatment 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.

ZOCOR is indicated to reduce elevated LDL-C and TG levels in patients with Type IIb hyperlipidemia (where hypercholesterolemia is the major abnormality). However, it has not been studied in conditions where the major abnormality *is elevation of chylomicrons* (i.e., *hyperlipidemia* Fredrickson types I and V).***

***Classification of Hyperlipoproteinemias

Type	Lipoproteins elevated	Lipid Elevations major	minor
I (rare)	chylomicrons	TG	↑→C
IIa	LDL	C	—

TABLE 1
Mean Response in Patients with Primary Hypercholesterolemia and Combined (mixed) Hyperlipidemia
(Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG*
Lower Dose Comparative Study (Mean % Change at Week 6)					
ZOCOR 5 mg q.p.m.	109	−19	−26	10	−12
ZOCOR 10 mg q.p.m.	110	−23	−30	12	−15
Scandinavian Simvastatin Survival Study (Mean % Change at Week 6)					
Placebo	2223	−1	−1	0	−2
ZOCOR 20 mg q.p.m.	2221	−28	−38	8	−19
Upper Dose Comparative Study (Mean % Change Averaged at Weeks 18 and 24)					
ZOCOR 40 mg q.p.m.	433	−31	−41	9	−18
ZOCOR 80 mg q.p.m.	664	−36	−47	8	−24
Multi-Center Combined Hyperlipidemia Study (Mean % Change at Week 6)					
Placebo	125	1	2	3	−4
ZOCOR 40 mg q.p.m.	123	−25	−29	13	−28
ZOCOR 80 mg q.p.m.	124	−31	−36	16	−33

*median percent change

TABLE 2
Six-week, Lipid-lowering Effects of Simvastatin in Type IV Hyperlipidemia
Median Percent Change (25th and 75th percentile) from Baseline

TREATMENT	N	Total-C	LDL-C	HDL-C	TG	VLDL-C	Non-HDL-C
Placebo	74	+2 (−7,+7)	+1 (−8, +14)	+3 (−3, +10)	−9 (−25, +13)	−7 (−25, +11)	+1 (−9, +8)
ZOCOR 40 mg/day	74	−25 (−34, −19)	−28 (−40, −17)	+11 (+5, +23)	−29 (−43, −16)	−37 (−54, −23)	−32 (−42, −23)
ZOCOR 80 mg/day	74	−32 (−38, −24)	−37 (−46, −26)	+15 +5, +23)	−34 (−45, −18)	−41 (−57, −28)	−38 (−49, −32)

TABLE 3
Six-week, Lipid-lowering Effects of Simvastatin in Type III Hyperlipidemia
Median Percent Change (min,max) from Baseline

TREATMENT	N	Total-C	LDL-C + IDL	HDL-C	TG	VLDL-C+IDL	Non-HDL-C
Placebo	7	−8 (−24,+34)	−8 (−27,+23)	−2 (−21,+16)	+4 (−22,+90)	−4 (−28,+78)	−8 (−26,−39)
ZOCOR 40 mg/day	7	−50 (−66,−39)	−50 (−60,−31)	+7 (−8,+23)	−41 (−74,−16)	−58 (−90,−37)	−57 (−72,−44)
ZOCOR 80 mg/day	7	−52 (−55,−41)	−51 (−57,−28)	+7 (−5,+29)	−38 (−58,+2)	−60 (−72,−39)	−59 (−61,−46)

TABLE 4
NCEP Treatment Guidelines:
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100–129: drug optional)††
2+ Risk factors (10 year risk ≤20%)	<130	≥130	10-year risk 10–20%: ≥130 10-year risk <10%: ≥ 160
0–1 Risk factor†††	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

† CHD, Coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

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

IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	↑→C
V (rare)	chylomicrons, VLDL	TG	↑→C

C = cholesterol, TG = triglycerides,
LDL = low-density lipoprotein,
VLDL = very-low-density lipoprotein,
IDL = intermediate-density lipoprotein.

CONTRAINDICATIONS

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

WARNINGS

Myopathy/Rhabdomyolysis

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally cause myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitor activity in plasma.

- **The risk of myopathy/rhabdomyolysis is increased by *concomitant use of simvastatin with the following:***

  Potent inhibitors of CYP3A4: Cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily), particularly with higher doses of simvastatin (see below; CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, CYP3A4 Interactions*).

  Lipid-lowering drugs that can cause myopathy when given alone: Gemfibrozil, other fibrates, or lipid-lowering doses (≥1 g/day) of niacin, particularly with higher doses of simvastatin (see below; CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone*).

  ***Other drugs*: Amiodarone or verapamil with higher doses of simvastatin** (see PRECAUTIONS, *Drug Interactions, Other drug interactions*). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone. In an analysis of clinical trials involving 25,248 patients treated with simvastatin 20 to 80 mg, the incidence of myopathy was higher in patients receiving verapamil and simvastatin (4/635; 0.63%) than in patients taking simvastatin without a calcium channel blocker (13/21,224; 0.061%).
- **The risk of myopathy/rhabdomyolysis is dose related.** The incidence in clinical trials, in which patients were carefully monitored and some interacting drugs were excluded, has been approximately 0.02% at 20 mg, 0.07% at 40 mg and 0.3% at 80 mg.

Consequently:

1. Use of simvastatin concomitantly with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided. If treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is unavoidable, therapy with simvastatin should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

2. The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine, gemfibrozil, other fibrates of lipid-lowering doses (≥1 g/day) of niacin. The combined use of simvastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Addition of these drugs to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained.

3. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of simvastatin at doses higher than 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.

4. All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and/or a CK level >10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

5. Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Liver Dysfunction

Persistent increases (to more than 3X the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In 4S (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the number of patients with more than one transaminase elevation to > 3X ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to > 3X ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1,105 patients, the 12-month incidence of persistent hepatic transaminase elevation without regard to drug relationship was 0.9% and 2.1% at the 40- and 80-mg dose, respectively. No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.

It is recommended that liver function tests be performed *before the initiation of treatment, and periodically thereafter (e.g., semiannually)* for the first year of treatment or until one year after the last elevation in dose. Patients titrated *to the 80-mg dose should receive an additional test at 3* months. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3X ULN or greater persist, withdrawal of therapy with ZOCOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

PRECAUTIONS

General

Simvastatin may cause elevation of CK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Information for Patients

Patients should be advised about substances they should not take concomitantly with simvastatin and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, *Myopathy/Rhabdomyolysis*). Patients should also be advised to inform other physicians prescribing a new medication that they are taking ZOCOR.

Drug Interactions

CYP3A4 Interactions

Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of simvastatin.

See WARNINGS, Myopathy/Rhabdomyolysis, and CLINICAL PHARMACOLOGY, Pharmacokinetics.

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
HIV protease inhibitors
Nefazodone
Cyclosporine
Large quantities of grapefruit juice (>1 quart daily)

Interactions with lipid-lowering drugs that can cause myopathy when given alone

The risk of myopathy is also increased by the following lipid-lowering drugs that are not potent CYP3A inhibitors, but which can cause myopathy when given alone.

See WARNINGS, *Myopathy/Rhabdomyolysis*.

Gemfibrozil
Other fibrates
Niacin (nicotinic acid) (>1 g/day)

Other drug interactions

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Propranolol: In healthy male volunteers there was a significant decrease in mean C_{max} but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20–40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of

Continued on next page

Zocor—Cont.

rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review† of approximately 100 prospectively followed pregnancies in women exposed to ZOCOR or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with ZOCOR during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. ZOCOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Nursing Mothers

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with simvastatin is not recommended at this time.

Geriatric Use

A pharmacokinetic study with simvastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70–78 years of age compared with patients between 18–30 years of age. In 4S and other large clinical studies conducted with simvastatin, 22% of patients were elderly (1,522 of 6,985 patients were ≥65 years). Simvastatin significantly reduced total mortality and CHD mortality in elderly patients with a history of CHD (see CLINICAL PHARMACOLOGY). Lipid-lowering efficacy was at least as great in elderly patients compared with younger patients, and there were no overall differences in safety over the 20 to 80 mg/day dosage range.

† Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology*, 10(6):439–446, 1996.

ADVERSE REACTIONS

In the pre-marketing controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR. Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well-tolerated.

Clinical Adverse Experiences

Adverse experiences occurring at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in Table 5.

TABLE 5
Adverse Experiences in Clinical Studies
Incidence 1 Percent or Greater, Regardless of Causality

	ZOCOR (N = 1,583) %	Placebo (N = 157) %	Cholestyramine (N = 179) %
Body as a Whole			
Abdominal pain	3.2	3.2	8.9
Asthenia	1.6	2.5	1.1
Gastrointestinal			
Constipation	2.3	1.3	29.1
Diarrhea	1.9	2.5	7.8
Dyspepsia	1.1	—	4.5
Flatulence	1.9	1.3	14.5
Nausea	1.3	1.9	10.1
Nervous System/ Psychiatric			
Headache	3.5	5.1	4.5
Respiratory			
Upper respiratory infection	2.1	1.9	3.4

Scandinavian Simvastatin Survival Study

Clinical Adverse Experiences

In 4S (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 4,444 patients treated with 20–40 mg/day of ZOCOR (n=2,221) or placebo (n=2,223), the safety and tolerability profiles were comparable between groups over the median 5.4 years of the study. The clinical adverse experiences reported as possibly, probably, or definitely drug-related in ≥ 0.5% in either treatment group are shown in Table 6.

TABLE 6
Drug-Related Clinical Adverse Experiences in 4S
Incidence 0.5 Percent or Greater

	ZOCOR (N = 2,221) %	Placebo (N = 2,223) %
Body as a Whole		
Abdominal pain	0.9	0.9
Gastrointestinal		
Diarrhea	0.5	0.3
Dyspepsia	0.6	0.5
Flatulence	0.9	0.7
Nausea	0.4	0.6
Musculoskeletal		
Myalgia	1.2	1.3
Skin		
Eczema	0.8	0.8
Pruritus	0.5	0.4
Rash	0.6	0.6
Special Senses		
Cataract	0.5	0.8

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with simvastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Concomitant Lipid-Lowering Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin at doses exceeding 10 mg/day with gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin should be avoided (see WARNINGS, *Myopathy/Rhabdomyolysis*).

OVERDOSAGE

Significant lethality was observed in mice after a single oral dose of 9 g/m^2. No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m^2, respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

A few cases of overdosage with ZOCOR have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 450 mg. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended. The dialyzability of simvastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ZOCOR and should continue on this diet during treatment with ZOCOR. The dosage should be individualized according to the baseline LDL-C level, the recommended goal of therapy (see NCEP Treatment Guidelines), and the patient's response. The dosage range is 5–80 mg/day (see below).

The recommended usual starting dose is 20 mg once a day in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg/day in the evening. Adjustments of dosage should be made at intervals of 4 weeks or more. See below for dosage recommendations for patients receiving concomitant therapy with cyclosporine, fibrates or niacin, and for those with renal insufficiency.

Dosage in Patients with Homozygous Familial Hypercholesterolemia

Based on the results of a controlled clinical study, the recommended dosage for patients with homozygous familial hypercholesterolemia is ZOCOR 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. ZOCOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Dosage in Patients taking Cyclosporine

In patients taking cyclosporine concomitantly with ZOCOR (see WARNINGS, *Myopathy/Rhabdomyolysis*), therapy should begin with 5 mg/day and should not exceed 10 mg/day.

Dosage in Patients taking Amiodarone or Verapamil

In patients taking amiodarone or verapamil concomitantly with ZOCOR, the dose should not exceed 20 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions, Other drug interactions*).

Concomitant Lipid-Lowering Therapy

ZOCOR is effective alone or when used concomitantly with bile-acid sequestrants. If ZOCOR is used in combination with gemfibrozil, other fibrates or lipid-lowering doses (≥ 1g/day) of niacin, the dose of ZOCOR should not exceed 10 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Dosage in Patients with Renal Insufficiency

Because ZOCOR does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However,

caution should be exercised when ZOCOR is administered to patients with severe renal insufficiency; such patients should be started at 5 mg/day and be closely monitored (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Myopathy/Rhabdomyolysis*).

HOW SUPPLIED

No. 3588 — Tablets ZOCOR 5 mg are buff, shield-shaped, film-coated tablets, coded MSD 726 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0726-31 unit of use bottles of 30
NDC 0006-0726-61 unit of use bottles of 60
NDC 0006-0726-54 unit of use bottles of 90
NDC 0006-0726-28 unit dose packages of 100
NDC 0006-0726-82 bottles of 1000.
Shown in Product Identification Guide, page 323

No. 3589 — Tablets ZOCOR 10 mg are peach, shield-shaped, film-coated tablets, coded MSD 735 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0735-31 unit of use bottles of 30
NDC 0006-0735-54 unit of use bottles of 90
NDC 0006-0735-28 unit dose packages of 100
NDC 0006-0735-82 bottles of 1000
NDC 0006-0735-87 bottles of 10,000.
Shown in Product Identification Guide, page 323

No. 3590 — Tablets ZOCOR 20 mg are tan, shield-shaped, film-coated tablets, coded MSD 740 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0740-31 unit of use bottles of 30
NDC 0006-0740-61 unit of use bottles of 60
NDC 0006-0740-54 unit of use bottles of 90
NDC 0006-0740-28 unit dose packages of 100
NDC 0006-0740-82 bottles of 1000
NDC 0006-0740-87 bottles of 10,000.
Shown in Product Identification Guide, page 323

No. 3591 — Tablets ZOCOR 40 mg are brick red, shield-shaped, film-coated tablets, coded MSD 749 on one side and ZOCOR on the other. They are supplied as follows:
NDC 0006-0749-31 unit of use bottles of 30
NDC 0006-0749-61 unit of use bottles of 60
NDC 0006-0749-54 unit of use bottles of 90
NDC 0006-0749-28 unit dose packages of 100
NDC 0006-0749-82 bottles of 1000.
Shown in Product Identification Guide, page 323

No. 6577 — Tablets ZOCOR 80 mg are brick red, capsule-shaped, film-coated tablets, coded 543 on one side and 80 on the other. They are supplied as follows:
NDC 0006-0543-31 unit of use bottles of 30
NDC 0006-0543-61 unit of use bottles of 60
NDC 0006-0543-54 unit of use bottles of 90
NDC 0006-0543-28 unit dose packages of 100
NDC 0006-0543-82 bottles of 1000.
Shown in Product Identification Guide, page 323

Storage
Store between 5–30°C (41–86°F).

Tablets ZOCOR (simvastatin) 5 mg, 10 mg, 20 mg, and 40 mg are manufactured by:
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
Tablets ZOCOR (simvastatin) 80 mg are manufactured for:
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
By:
MERCK SHARP & DOHME LTD,
Cramlington, Northumberland, UK NE23 3JU
7825442 Issued May 2002

Shown in Product Identification Guide, page 323

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BIOTIN OTC

[*'bī-ō-tĭn*]
biotin supplement–high potency

ACTIVE INGREDIENTS
Biotin 5 mg

DIRECTIONS
Take one capsule daily or as directed by your physician.

HOW SUPPLIED
Biotin is supplied as capsules in bottles of 120.
NDC 00394-0130-12

FLORICAL® OTC

[*flor ĭ cal*]
(fluoride and calcium supplement)

ACTIVE INGREDIENTS
Florical® contains 3.75 mg fluoride (as sodium fluoride), 145 mg calcium (as calcium carbonate)

DIRECTIONS
Take one tablet or capsule daily, or as recommended by physician.

HOW SUPPLIED
Florical® is supplied as tablets or capsules in bottles of 100 or 500.
NDC 00394-0102-02 (Capsules 100's)
NDC 00394-0102-05 (Capsules 500's)
NDC 00394-0100-02 (Tablets 100's)
NDC 00394-0100-05 (Tablets 500's)

MONOCAL® OTC

[*mon ō cal*]
(fluoride and calcium supplement)

ACTIVE INGREDIENTS
Monocal® contains 3 mg fluoride (as monofluorophosphate) and 250 mg calcium (as calcium carbonate)

DIRECTIONS
Take one tablet daily, or as recommended by physician.

HOW SUPPLIED
Monocal® is supplied as tablets in bottles of 100.
NDC 00394-0105-02

Merz Pharmaceuticals

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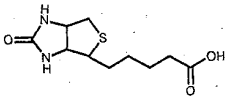
APPEAREX™ OTC

(biotin 2.5 mg)

DESCRIPTION AND MECHANISM OF ACTION

Appearex™ is a biotin preparation (2.5 mg) available for oral administration as a small, easy-to-swallow tablet. Each Appearex™ tablet contains as its active ingredient 2.5 mg of biotin, a dose clinically proven to improve nail strength and quality.[1–4] *Inactive ingredients include lactose monohydrate, cornstarch, povidone (K25), and magnesium stearate.* Biotin is a water-soluble vitamin component of the vitamin B complex. As an essential nutrient, biotin acts as a coenzyme for the body's carboxylation reactions and is a factor in maintaining healthy muscle, hair, nails, and skin. Its molecular formula is $C_{10}H_{16}N_2O_3S$, and its molecular weight is 244.308. The structural formula of biotin is shown in Figure 1.



The presumed mechanism of action by which Appearex™ affects brittle nails is via the pharmacologic effects of biotin on all keratin structures. Biotin stimulates the differentiation of epidermal cells and is involved in *keratinization. It is* also believed that biotin increases the quantity of keratin *matrix proteins in the nail, thereby improving* keratin structure.[3,5]

PHARMACOKINETICS
ABSORPTION AND TRANSPORT:
Biotin is efficiently absorbed in the small intestine sodium-mediated carrier transport.[6,7] Once absorbed, 80% of biotin is free, and the remaining 20% is bound to plasma proteins.[8] Cellular entry of biotin occurs by both diffusion and sodium-dependent transport.
DEGRADATION AND EXCRETION:
About 43% of biotin is excreted unchanged in the urine.[9] The remainder is excreted as degradation products including bisnorbiotin (30%), biotin sulfoxide (11%), and other small amounts of biotin sulfone, bisnorbiotin methylketone, and tetranorbiotin sulfoxide.[10]

ADVERSE REACTIONS
Adverse reactions associated with biotin supplementation are rare in the medical literature; however, urticaria and gastrointestinal upset have been reported. As with any oral treatment, if patients experience any adverse reactions or side effects, they should inform their physicians immediately and discontinue use.
DRUG INTERACTIONS
The anticonvulsants carbamazepine, phenytoin, Phenobarbital, and primidone may accelerate biotin metabolism, leading to a reduction in available biotin. Chronic use of these drugs has been associated with decreased plasma concentrations of biotin.[11,12]
The use of antibiotics may reduce the contribution of biotin made by bacteria within the large intestine.

PRECAUTIONS AND WARNINGS
Pregnant women and nursing mothers should consult their physicians before taking this product. Appearex™ should not be used in patients with known allergy or hypersensitivity to any of its ingredients.
TOXICITY
No toxic effects have been reported, even at higher doses.[13]

INDICATION AND USAGE
Appearex™ is recommended for first-line treatment of weak, brittle, splitting, or soft nails.
Appearex™ therapy should be taken regularly as directed to maintain strong, healthy nails. Clinical improvement is generally realized within 3 to 6 months.[1–3] Cessation of therapy may result in deterioration of nail health within 6 to 9 months.

CONTRAINDICATION
Appearex™ is contraindicated in patients allergic or hypersensitive to any of its ingredients.

DOSAGE AND ADMINISTRATION
Recommended treatment for adults is 1 tablet taken daily with water. For use in children under 12 years of age, consult a physician for guidance regarding proper dosing and administration.

HOW SUPPLIED
One Appearex™ package contains 30 tablets (1 month's supply) enclosed in blister packs.
SUMMARY
Appearex™, for the treatment of weak, brittle, splitting, or soft nails, is pharmaceutical grade oral biotin that restores nail quality by promoting keratinization. It has been clinically proven to increase nail plate thickness, smooth brittle nail ridges, and improve overall nail quality. As a water-soluble essential vitamin the biotin in Appearex™ is safe and well tolerated. For patients with brittle nails, one Appearex™ tablet taken daily provides the additional biotin needed to manage onychoschizia/onychorrhexis.

These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

REFERENCES

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Continued on next page

UROGENITAL SYSTEM	25.0	40.8
Breast Pain	5.3	8.1
Urinary Tract Infection	3.2	6.2
Vaginitis	4.9	5.4

The following adverse events have been reported with estrogen and/or progestin therapy:
Genitourinary system: changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine leiomyomata, vaginal candidiasis, changes in amount of cervical secretion, pre-menstrual-like syndrome, cystitis-like syndrome.
Breasts: tenderness, enlargement, fibrocystic disease of the breast.
Gastrointestinal: cholestatic jaundice, pancreatitis, flatulence, bloating, abdominal cramps.
Skin: chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, skin rash and pruritus.
CNS: headache, migraine, dizziness, chorea, insomnia.
Cardiovascular: changes in blood pressure, cerebrovascular accidents, deep venous thrombosis, and pulmonary embolism.
Eyes: intolerance to contact lenses, sudden partial or complete loss of vision, proptosis, diplopia, otosclerosis.
Miscellaneous: increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, changes in libido, fatigue, allergic or anaphylactoid reactions, leiomyoma, fibromyoma of the uterus, endometriosis.

OVERDOSAGE

ACUTE OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of progestin/estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur.

DOSAGE AND ADMINISTRATION

femhrt 1/5 therapy consists of a single tablet taken once daily.

1. For the Treatment of Vasomotor Symptoms

femhrt 1/5 should be given once daily for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary.

2. Prevention of Osteoporosis

femhrt 1/5 should be given once daily to prevent postmenopausal osteoporosis (see **Clinical Studies: Effect on Bone Mineral Density**). Response to therapy can be assessed by measurement of bone mineral density.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring vaginal bleeding. *Patients should be evaluated at least annually for breast abnormalities* and more often if there are any symptoms.

HOW SUPPLIED

femhrt 1/5 tablets are white and available in the following strength and package sizes:

N 0071-0144-23	Bottle of 90 D-shaped tablets with 1 **mg** norethindrone acetate and 5 **mcg** ethinyl estradiol
N 0071-0144-45	Blister card of 28 D-shaped tablets with 1 **mg** norethindrone acetate and 5 **mcg** ethinyl estradiol

Rx only

Keep this drug and all drugs out of the reach of children.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)[see USP Controlled Room Temperature].

INFORMATION FOR THE PATIENT

What is *femhrt*® 1/5?

Your healthcare provider has prescribed femhrt 1/5, a combination of two hormones, a progestin (1 mg norethindrone acetate) and an estrogen (5 mcg ethinyl estradiol) intended for use once a day. This insert describes the major benefits and risks of your treatment, as well as how and when treatment may be taken. If you have any questions, please contact your physician, nurse or pharmacist.

femhrt 1/5 is approved for use in the following ways:

- **To reduce moderate to severe menopausal symptoms.** *Estrogens are hormones produced by the ovaries of menstruating women. When a woman is between the ages of 45 and 55, the ovaries normally stop making estrogens. This drop in body estrogen levels causes the "change of life" or menopause, the end of monthly menstrual periods. When estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild; in others they can be severe. These symptoms may last only a few months or longer. Taking femhrt 1/5 can help reduce these symptoms. If you are not taking hormones for other reasons, such as the prevention of osteoporosis, you should take femhrt 1/5 only as long as you need it for relief from your menopausal symptoms.*
- **To prevent thinning bones (osteoporosis).** Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists, and hips may be affected by osteoporosis. *femhrt* 1/5 may be used as part of a program including weight-bearing exercise, such as walking or running, and calcium supplements.

  Women likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister or aunt. Women who have menopause at an earlier age, either naturally or because their ovaries were removed during an operation, are more likely to develop osteoporosis than women whose menopause happens later in life.

Who should not take *femhrt* 1/5?

femhrt 1/5 should not be taken in the following situations:

- **During pregnancy.** If you think you may be pregnant, do not take *femhrt* 1/5. Taking estrogens while you are pregnant may cause your unborn child to have birth defects. Do not take *femhrt* 1/5 to prevent miscarriage.
- **If you have unusual vaginal bleeding that has not been checked by your healthcare provider.** Unusual vaginal bleeding can be a warning sign of a serious condition, including cancer of the uterus, especially if bleeding happens after menopause. Your doctor must find out the cause of the bleeding to recommend the right treatment.
- **If you have had certain cancers.** Estrogens increase the risk of certain types of cancers, including cancer of the breast and uterus. If you have had cancer, talk with your doctor about whether you should take *femhrt* 1/5.
- **If you have any circulation problems.** Generally, estrogens should not be taken if you have ever had a blood-clotting condition or other circulatory problem. In special situations, some doctors may decide that estrogen therapy is so necessary that the risks of taking *femhrt* 1/5 are acceptable (see "What are the possible risks and side effects of *femhrt* 1/5?").
- **After childbirth or when breast-feeding a baby.** *femhrt* 1/5 should not be taken to try to stop the breasts from filling with milk after a baby is born. Taking *femhrt* 1/5 may increase your risk of developing blood clots (see "What are the possible risks and side effects of *femhrt* 1/5?").
- **If you have had a hysterectomy (uterus removed).** *femhrt* 1/5 contains a progestin to decrease the risk of developing endometrial hyperplasia (an overgrowth of the lining of the uterus that may lead to cancer). If you do not have a uterus, you do not need a progestin, and you should not take *femhrt* 1/5.

How should I take *femhrt* 1/5?

Take your *femhrt* 1/5 pill once a day at about the same time each day. If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take only your next regularly scheduled dose. Do not take two doses at the same time.

The length of treatment with estrogens varies from woman to woman. You and your healthcare provider should re-evaluate every 3 to 6 months whether or not you still need *femhrt* 1/5 to control your hot flashes.

What are the possible risks and side effects of *femhrt* 1/5?

- **Cancer of the uterus.** *femhrt* 1/5 has estrogen and progestin in it. If you take any drug that contains estrogen, including *femhrt*, you should see your doctor for regular check-ups and report any unusual vaginal bleeding right away. *Vaginal bleeding after menopause may be a warning sign of a serious condition, including cancer of the uterus.* Your doctor should identify the cause of any unusual vaginal bleeding.

  The risk of cancer of the uterus increases when estrogens are used without a progestin. The risk also increases the longer estrogens are taken and the larger the doses. You are more likely to get cancer of the uterus if you are overweight, diabetic, or have high blood pressure. *femhrt 1/5, which contains a progestin, reduces the estrogen-related* risk of getting a condition of the uterine lining called endometrial hyperplasia. This condition may lead to cancer of the uterus (see "Other Information").
- **Cancer of the breast.** Most studies have not shown a higher risk of breast cancer in women who have used estrogens. However, some studies report that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for longer time periods, *especially more than 10 years, or who used high doses for a* shorter time period. The effects of added progestin on the risk of breast cancer are unknown. You should have regular breast examinations by a health professional and examine your own breasts monthly. Ask your health care provider to show you how to do a breast exam yourself. If you are over 50 years of age, you should have a mammogram every year.
- **Gallbladder disease.** Women who use estrogens after menopause are more likely to develop gallbladder disease that leads to surgery than women who do not use estrogens.
- **Abnormal blood clotting.** Taking estrogens may cause changes in your blood clotting system that allow the blood to clot more easily. If blood clots form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting of blood to the heart), or a pulmonary embolus (by cutting off blood supply to the lungs). Any of these conditions may cause death or serious long-term disability.
- **Vaginal bleeding.** With *femhrt* 1/5, menstrual-like vaginal bleeding may occur. If bleeding occurs, it is frequently light spotting or bleeding, but it may be moderate or heavy. If you experience vaginal bleeding while taking *femhrt* 1/5, discuss your bleeding pattern with your healthcare provider.

In addition to the risks and side effects just listed, patients taking estrogen or progestin have reported the following side effects:

- nausea and vomiting
- breast tenderness or enlargement
- headache
- retention of extra fluid (edema), which may make some conditions worse, such as asthma, epilepsy, migraine, heart disease, or kidney disease
- runny nose
- abdominal pain
- enlargement of non-cancerous tumors (fibroids) of the uterus
- spotty darkening of the skin, particularly on the face; reddening of the skin; skin rashes

How can I reduce the risks associated with taking *femhrt* 1/5?

If you take *femhrt* 1/5, you can reduce your risks by carefully monitoring your treatment.

- **See your healthcare provider regularly.** While you take *femhrt* 1/5, see your doctor at least once a year for a checkup. If you develop vaginal bleeding while taking *femhrt 1/5, you might need further evaluation. If members* of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need more frequent breast examinations.
- **Reassess your need for treatment.** Every 3–6 months, you and your doctor should discuss whether or not you still need *femhrt* 1/5 for control of your hot flashes.
- **Be alert for signs of trouble.** If any of the following warning signs (or any other unusual symptoms) happen while you are taking *femhrt* 1/5, call your doctor right away:
  - pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clots in the legs, heart, or lungs)
  - severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg (possible clots in the brain or eye)
  - breast lumps (possible breast cancer)
  - yellowing of the skin or whites of the eyes (possible liver problem)
  - pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

Other Information

- Discuss carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.
- If you take calcium supplements as part of your treatment to help prevent osteoporosis, ask your doctor about the amounts recommended. A daily intake of 1500 mg of calcium is often recommended for postmenopausal women. Vitamin D (400 IU daily) may help your body use more of the calcium.
- Taking estrogens with progestins may have unhealthy effects on blood sugar, which might make a diabetic condition worse.
- Your doctor has prescribed this drug for you and you alone. Do not give your *femhrt* 1/5 to anyone else. Do not take *femhrt* 1/5 for conditions for which it was not prescribed.
- Keep all drugs out of the reach of children. In case of overdose, call your doctor, hospital, or poison control center right away.

This leaflet provides the most important information about *femhrt* 1/5. If you want more information, ask your doctor or pharmacist for the professional labeling. The professional labeling is published in a book called "The Physicians' Desk Reference" or PDR, available in bookstores and public libraries.

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Manufactured by:
DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA
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Morris Plains, NJ 07950 USA
0132G032

Shown in Product Identification Guide, page 328

LIPITOR®

(Atorvastatin Calcium) Tablets

℞

DESCRIPTION

Lipitor® (atorvastatin calcium) is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methyl-

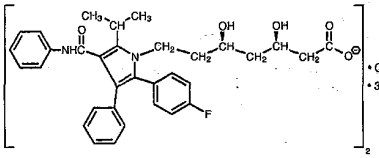
Continued on next page

This product information was prepared in August 2002. On these and other Parke-Davis Products, information may be obtained by addressing PARKE-DAVIS, a Warner-Lambert Division, a Pfizer Company, Morris Plains, New Jersey 07950.

Lipitor—Cont.

glutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Lipitor tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hydroxypropylmethylcellulose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

CLINICAL PHARMACOLOGY

Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (*intermediate-density lipoprotein*), LDL (*low-density lipoprotein*), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, Lipitor lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; Lipitor also reduces LDL production and the number of LDL particles. Lipitor reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo 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.

Lipitor reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Lipitor also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Lipitor reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Lipitor reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia. The effect of Lipitor on cardiovascular morbidity and mortality has not been determined.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Pharmacodynamics

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response (see DOSAGE AND ADMINISTRATION).

TABLE 1. Dose-Response in Patients With Primary Hypercholesterolemia (Adjusted Mean % Change From Baseline)[a]

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

[a]Results are pooled from 2 dose-response studies

TABLE 2. Mean Percent Change From Baseline at End Point (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff[1]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[1] A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.
[a] Significantly different from lovastatin, ANCOVA, $p \leq 0.05$
[b] Significantly different from pravastatin, ANCOVA, $p \leq 0.05$
[c] Significantly different from simvastatin, ANCOVA, $p \leq 0.05$

Pharmacokinetics and Drug Metabolism

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see DOSAGE AND ADMINISTRATION).

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk (see CONTRAINDICATIONS, Pregnancy and Lactation, and PRECAUTIONS, Nursing Mothers).

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme (see PRECAUTIONS, Drug Interactions). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but *the half-life of inhibitory activity for HMG-CoA reductase is* 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering *at any dose of drug in the elderly patient population* compared to younger adults (see PRECAUTIONS section; Geriatric Use subsection).

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with Lipitor between men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is *not necessary* (see DOSAGE AND ADMINISTRATION).

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Insufficiency: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are *approximately 16-fold and 11-fold increased, respectively,* in patients with Childs-Pugh B disease (see CONTRAINDICATIONS).

Clinical Studies

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (*Fredrickson* Types IIa and IIb)

Lipitor reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Lipitor is effective in a wide variety of patient populations with hypercholesterolemia, with and without hypertriglyceridemia, in men and women, and in the elderly. Experience in pediatric patients has been limited to patients with homozygous FH.

In two multicenter, placebo-controlled, dose-response studies in patients with hypercholesterolemia, Lipitor given as a single dose over 6 weeks significantly reduced total-C, LDL-C, apo B, and TG (Pooled results are provided in Table 1).

[See table 1 above]

In patients with Fredrickson Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25^{th} and 75^{th} percentile) percent changes from baseline in HDL-C for atorvastatin 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7(0, 17), 7.8(0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decrease in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with *hypercholesterolemia, Lipitor was compared to other HMG-CoA* reductase inhibitors. After randomization, patients were treated for 16 weeks with either Lipitor 10 mg per day or a fixed dose of the comparative agent (Table 2).

[See table 2 above]

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 2 is not known. Table 2 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, *and simvastatin. The drugs compared in the studies* summarized in the table are not necessarily interchangeable.

Hypertriglyceridemia (*Fredrickson* Type IV)

The response to Lipitor in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below. For the atorvastatin-treated patients, median (min, max) baseline TG level was 565 (267-1502).

[See table 3 at top of next page]

Dysbetalipoproteinemia (*Fredrickson* Type III)
The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia (*Fredrickson* Type III) are shown in the table below.
[See table 4 at right]

Homozygous Familial Hypercholesterolemia
In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of Lipitor. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

INDICATIONS AND USAGE

Lipitor is indicated:
1. as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb);
2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV);
3. for the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet;
4. to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable.

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate (see *National Cholesterol Education Program (NCEP) Guidelines*, summarized in Table 5).
[See table 5 at right]
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.
Prior to initiating therapy with Lipitor, secondary causes for hypercholesterolemia (eg, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 × [TG] + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.
Lipitor has not been studied in conditions where the major *lipoprotein abnormality is elevation of chylomicrons (Fredrickson* Types I and V).

CONTRAINDICATIONS

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

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 pregnant women. Therefore, *HMG-CoA reductase inhibitors are contraindicated* during pregnancy and in nursing mothers. ATORVASTATIN 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 drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Dysfunction
HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The *incidence* of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**
One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.
It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.
Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS).

Skeletal Muscle
Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.
Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.
The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.
Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General
Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Information for Patients
Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions
The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle).
Antacid: When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.
Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs

Continued on next page

TABLE 3. Combined Patients With Isolated Elevated TG; Median (min, max) Percent Changes From Baseline

	Placebo (N=12)	Atorvastatin 10 mg (N=37)	Atorvastatin 20 mg (N=13)	Atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

TABLE 4. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max)	
		Atorvastatin 10 mg	Atorvastatin 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

TABLE 5: 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
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 judgement 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.

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Lipitor—Cont.

metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of *cimetidine.*

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma *digoxin* concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, *Skeletal Muscle).*

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased *AUC values for* norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and *theoretically might blunt adrenal and/or gonadal* steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied *in adequate numbers of patients.* The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. *Caution should be exercised if an* HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 *months* at 120 *mg/kg/day.* Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed *in moribund condition after* 11 *weeks of escalating* doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or *in rats at doses up to 100 mg/kg/day. These doses* were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human *dose of* 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration *of retinogeniculate fibers) in clinically normal dogs* in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the *mean drug level* in humans taking the highest recommended dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity *study in mice given* 100, 200, *or* 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli,* the HGPRT *forward mutation assay in Chinese* hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 *rats treated with* 100 *mg/kg/day of atorvastatin* for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two *years.*

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS

Safety in pregnant women has not been established. *Atorvastatin crosses the rat placenta and reaches a level in* fetal liver equivalent to that of maternal plasma. Atorvastatin was not *teratogenic in rats at doses up to* 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2).

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there *was decreased pup survival at birth, neonate,* weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) *the human* AUC at 80 mg/day.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. Lipitor 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 Lipitor, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers

Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the *potential for adverse reactions in nursing* infants, women taking Lipitor should not breast-feed (see CONTRAINDICATIONS).

TABLE 6. Adverse Events in Placebo-Controlled Studies (% of Patients)

BODY SYSTEM/ Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Pediatric Use

Treatment experience in a pediatric population is limited to doses of Lipitor up to 80 mg/day for 1 year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients. None of these patients was below 9 years of age.

Geriatric Use

The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥65 years of age) was evaluated in the ACCESS study. In this 54-week open-label *trial* 1,958 patients initiated therapy with atorvastatin 10 mg. Of these, 835 were elderly (≥65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was −38.2% in the elderly patients versus −34.6% in the non-elderly group. The rates of discontinuation due to adverse events were *similar between the two age groups.* There were no differences in clinically relevant laboratory abnormalities between the age groups.

ADVERSE REACTIONS

Lipitor is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain.

Clinical Adverse Experiences

Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 6.

[See table below]

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of *patients and the events in plain type occurred in* <2% of patients.

Body as a Whole: *Chest pain,* face edema, *fever,* neck rigidity, malaise, photosensitivity reaction, generalized edema.

Digestive System: *Nausea,* gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, *pancreatitis, cholestatic jaundice.*

Respiratory System: *Bronchitis, rhinitis,* pneumonia, dyspnea, asthma, epistaxis.

Nervous System: *Insomnia, dizziness,* paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

Musculoskeletal System: *Arthritis,* leg cramps, bursitis, *tenosynovitis, myasthenia,* tendinous contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, *urticaria, eczema, seborrhea,* skin ulcer.

Urogenital System: *Urinary tract infection,* urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, *urinary urgency, abnormal* ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, *glaucoma, parosmia,* taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: *Peripheral edema,* hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, *thrombocytopenia, petechia.*

Postintroduction Reports

Adverse events associated with Lipitor therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic *epidermal necrolysis),* and rhabdomyolysis.

OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. *In the event of an overdose,* the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug *binding to plasma proteins,* hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Lipitor and should continue on this diet during treatment with Lipitor.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (*Fredrickson* Types IIa and IIb)

The recommended *starting dose of Lipitor* is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once *daily.* The dosage range of Lipitor is 10 to 80 mg once daily. Lipitor can be administered as a single dose at any time of the day, with

or without food. The starting dose and maintenance doses of Lipitor should be individualized according to patient characteristics such as goal of therapy and response (see *NCEP Guidelines*, summarized in Table 5). After initiation and/or upon titration of Lipitor, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.
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 total-C be used to monitor therapy.
Homozygous Familial Hypercholesterolemia
The dosage of Lipitor in patients with homozygous FH is 10 to 80 mg daily. Lipitor should be used as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) in these patients or if such treatments are unavailable.
Concomitant Therapy
Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS, Skeletal Muscle, and PRECAUTIONS, Drug Interactions for other drug-drug interactions).
Dosage in Patients With Renal Insufficiency
Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HOW SUPPLIED

Lipitor is supplied as white, elliptical, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin.
10 mg tablets: coded "PD 155" on one side and "10" on the other.
N0071-0155-23 bottles of 90
N0071-0155-34 bottles of 5000
N0071-0155-40 10 × 10 unit dose blisters
20 mg tablets: coded "PD 156" on one side and "20" on the other.
N0071-0156-23 bottles of 90
N0071-0156-40 10 × 10 unit dose blisters
40 mg tablets: coded "PD 157" on one side and "40" on the other.
N0071-0157-23 bottles of 90
80 mg tablets: coded "PD 158" on one side and "80" on the other.
N0071-0158-23 bottles of 90
Storage
Store at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP].
Rx only

Manufactured by:
Pfizer Ireland Pharmaceuticals
Dublin, Ireland
Distributed by:
PFIZER PARKE-DAVIS
Division of Pfizer Inc, NY, NY 10017
MADE IN PUERTO RICO
69-5884-00-1 Revised April 2002
Shown in Product Identification Guide, page 328

LOESTRIN® 21 ℞
(Norethindrone Acetate and Ethinyl Estradiol Tablets, USP)

LOESTRIN® 21 1/20 ℞
(Each white tablet contains 1 mg norethindrone acetate and 20 mcg ethinyl estradiol.)

LOESTRIN® 21 1.5/30 ℞
(Each green tablet contains 1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol.)

LOESTRIN® Fe ℞
(Norethindrone Acetate and Ethinyl Estradiol Tablets, USP and Ferrous Fumarate Tablets*)
***Ferrous fumarate tablets are not USP for dissolution and assay**

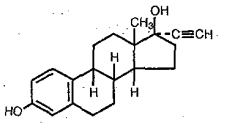
LOESTRIN® Fe 1/20 ℞
(Each white tablet contains 1 mg norethindrone acetate and 20 mcg ethinyl estradiol.
Each brown tablet contains 75 mg ferrous fumarate.)

LOESTRIN® Fe 1.5/30 ℞
(Each green tablet contains 1 mg norethindrone acetate and 30 mcg ethinyl estradiol.
Each brown tablet contains 75 mg ferrous fumarate.)

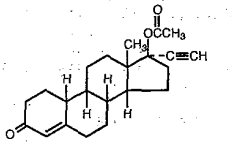
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

Loestrin **21** and Loestrin **Fe** are progestogen-estrogen combinations.
Loestrin **Fe** *1/20 and 1.5/30: Each provides a continuous dosage regimen consisting of 21 oral contraceptive tablets and seven ferrous fumarate tablets. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen, are non-hormonal, and do not serve any therapeutic purpose.*
Each white tablet contains norethindrone acetate (17 alpha-ethinyl-19-nortestosterone acetate), 1 mg; ethinyl estradiol (17 alpha-ethinyl-1,3,5(10)-estratriene-3, 17 beta-diol), 20 mcg. Also contains acacia, NF; lactose, NF; magnesium stearate, NF; starch, NF; confectioner's sugar, NF; talc, USP.
Each *green tablet contains* norethindrone acetate (17 alpha-ethinyl-19-nortestosterone acetate), 1.5 mg; ethinyl estradiol (17 alpha-ethinyl-1,3,5(10)-estratriene-3, 17 *beta-diol),* 30 mcg. Also contains acacia, NF; lactose, NF; magnesium stearate, NF; starch, NF; confectioner's sugar, NF; talc, USP; D&C yellow No. 10; FD&C yellow No. 6; FD&C blue No. 1.
The structural formulas are as follows:



Ethinyl Estradiol



Norethindrone Acetate

Each brown tablet contains microcrystalline cellulose, NF; ferrous fumarate, USP; magnesium stearate, NF; povidone, USP; sodium starch glycolate, NF; sucrose with modified dextrins.

CLINICAL PHARMACOLOGY

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is *inhibition of ovulation, other alterations include changes in* the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).
Pharmacokinetics
The pharmacokinetics of Loestrin have not been characterized; however, the following pharmacokinetic information regarding norethindrone acetate and ethinyl estradiol is taken from the literature.
Absorption
Norethindrone acetate appears to be completely and rapidly deacetylated *to norethindrone after oral administration,* since the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone (1). Norethindrone acetate and ethinyl estradiol are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 43% for ethinyl estradiol (1–3).
Distribution
Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 *L/kg* (1–3). Plasma protein *binding of* both steroids is extensive (>95%); norethindrone binds to both albumin and sex hormone binding globulin, whereas ethinyl estradiol binds only to albumin (4).
Metabolism
Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the *urinary metabolites (5). A small amount of norethindrone* acetate is metabolically converted to ethinyl estradiol. Ethinyl estradiol is also extensively metabolized, *both by oxidation* and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in *gastrointestinal mucosa. Ethinyl estradiol may under* enterohepatic circulation (6).
Excretion
Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites (5,6). Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg) (1–3).
Special Population
Race:
The effect of race on the disposition of Loestrin has not been evaluated.
Renal Insufficiency
The effect of renal disease on the disposition of Loestrin has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged *compared to concentrations in premenopausal* women with normal renal function.
Hepatic Insufficiency
The effect of hepatic disease on the disposition of Loestrin has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function.
Drug-Drug Interactions
Numerous drug-drug interactions have been reported for oral contraceptives. A summary of these is found under PRECAUTIONS, Drug Interactions.

INDICATIONS AND USAGE

Loestrin **21** and Loestrin **Fe** are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.
Oral contraceptives are highly effective. Table 1 lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.
[See table I at top of next page]

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:
- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebral vascular or coronary artery disease
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- *Hepatic adenomas or carcinomas*
- Known or suspected pregnancy

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity, and diabetes.
Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.
The information contained in this package insert is principally based on studies carried out in patients who used oral *contraceptives with higher formulations of estrogens and* progestogens than those in common use today. The effect of *long-term use of the oral contraceptives with lower formu*lations of both estrogens and progestogens remains to be determined.
Throughout this labeling, epidemiological studies reported are of two types: retrospective or *case control studies and* prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, *a ratio of* the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does not provide information about the actual occurrence of a disease in the population (adapted from References 8 and 9 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.
1. Thromboembolic Disorders and Other Vascular Problems
a. Myocardial infarction
An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six (10–16). The risk is very low *under the age of 30.*
Smoking in combination with oral contraceptive use has *been shown to contribute substantially to the incidence of* myocardial infarctions in women in their mid-thirties or *older with smoking accounting for the majority of excess* cases (17). Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 (Table II) among women who use oral contraceptives.
[See table II at top of next page]
Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity (19). In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism (20–24). Oral contraceptives have

Continued on next page

This product information was prepared in August 2002. On these and other Parke-Davis Products, information may be obtained by addressing PARKE-DAVIS, a Warner-Lambert Division, a Pfizer Company, Morris Plains, New Jersey 07950.

CONTRAINDICATIONS

CLEOCIN T Topical Solution, CLEOCIN T Topical Gel and CLEOCIN T Topical Lotion are contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

WARNINGS

Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin.

Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea.

Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 milligrams to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been *observed to begin up to several weeks following cessation* of oral and parenteral therapy with clindamycin.

PRECAUTIONS

General

CLEOCIN T Topical Solution contains an alcohol base which will cause burning and irritation of the eye. In the event of accidental contact with sensitive surfaces (eye, abraded skin, mucous membranes), bathe with copious amounts of cool tap water. The solution has an unpleasant taste and caution should be exercised when applying medication around the mouth.

CLEOCIN T should be prescribed with caution in atopic individuals.

Drug Interactions

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore it should be used with caution in patients receiving such agents.

Pregnancy: Teratogenic effects—Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin ranging from 100 to 600 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to clindamycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of CLEOCIN T. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients under the age of 12 have not been established.

ADVERSE REACTIONS

In 18 clinical studies of various formulations of CLEOCIN T using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events [see table below].

Number of Patients Reporting Events

Treatment Emergent Adverse Event	Solution n=553 (%)	Gel n=148 (%)	Lotion n=160 (%)
Burning	62 (11)	15 (10)	17 (11)
Itching	36 (7)	15 (10)	17 (11)
Burning/Itching	60 (11)	# (–)	# (–)
Dryness	105 (19)	34 (23)	29 (18)
Erythema	86 (16)	10 (7)	22 (14)
Oiliness/Oily Skin	8 (1)	26 (18)	12* (10)
Peeling	61 (11)	# (–)	11 (7)

not recorded
* of 126 subjects

Orally and parenterally administered clindamycin has been associated with severe colitis which may end fatally.

Cases of diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulations of clindamycin and rarely with topical clindamycin (see WARNINGS).

Abdominal pain and gastrointestinal disturbances as well as gram-negative folliculitis have also been reported in association with the use of topical formulations of clindamycin.

OVERDOSAGE

Topically applied CLEOCIN T can be absorbed in sufficient amounts to produce systemic effects. (See WARNINGS.)

DOSAGE AND ADMINISTRATION

Apply a thin film of CLEOCIN T Topical Solution, CLEOCIN T Topical Lotion, CLEOCIN T Topical Gel, or use a CLEOCIN T Topical Solution pledget for the application of CLEOCIN T twice daily to affected area. More than one pledget may be used. Each pledget should be used only once and then be discarded.

Lotion: Shake well immediately before using.

Pledget: Remove pledget from foil just before use. Do not use if the seal is broken. Discard after single use.

Keep all liquid dosage forms in containers tightly closed.

HOW SUPPLIED

CLEOCIN T Topical Solution containing clindamycin phosphate equivalent to 10 mg clindamycin per milliliter is available in the following sizes:

30 mL applicator bottle—NDC 0009-3116-01
60 mL applicator bottle—NDC 0009-3116-02
Carton of 60 single-use pledget applicators—NDC 0009-3116-14

CLEOCIN T Topical Gel containing clindamycin phosphate equivalent to 10 mg clindamycin per gram is available in the following sizes:

60 gram tube—NDC 0009-3331-01
30 gram tube—NDC 0009-3331-02

CLEOCIN T Topical Lotion containing clindamycin phosphate equivalent to 10 mg clindamycin per milliliter is available in the following size:

60 mL plastic squeeze bottle—NDC 0009-3329-01

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Protect from freezing.

℞ only

Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA

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COLESTID® ℞

micronized colestipol hydrochloride tablets

DESCRIPTION

The active ingredient in COLESTID Tablets is micronized colestipol hydrochloride, which is a lipid lowering agent for oral use. Colestipol is an insoluble, high molecular weight basic anion-exchange copolymer of diethylenetriamine and 1-chloro-2, 3-epoxypropane, with approximately 1 out of 5 amine nitrogens protonated (chloride form). It is a light yellow water-insoluble resin which is hygroscopic and swells when suspended in water or aqueous fluids.

Each COLESTID Tablet contains one gram of micronized colestipol hydrochloride. COLESTID Tablets are light yellow in color and are tasteless and odorless. Inactive ingredients: cellulose acetate phthalate, glyceryl triacetate, carnauba wax, hydroxypropyl methylcellulose, magnesium stearate, povidone, silicon dioxide. COLESTID Tablets contain no calories.

CLINICAL PHARMACOLOGY

Cholesterol is the major, and probably the sole precursor of bile acids. During normal digestion, bile acids are secreted via the bile from the liver and gall bladder into the intestines. Bile acids emulsify the fat and lipid materials present in food, thus facilitating absorption. A major portion of the bile acids secreted is reabsorbed from the intestines and returned via the portal circulation to the liver, thus completing the enterohepatic cycle. Only very small amounts of bile acids are found in normal serum.

Colestipol hydrochloride binds bile acids in the intestine forming a complex that is excreted in the feces. This nonsystemic action results in a partial removal of the bile acids from the enterohepatic circulation, preventing their reabsorption. Since colestipol hydrochloride is an anion exchange resin, the chloride anions of the resin can be replaced by other anions, usually those with a greater affinity for the resin than the chloride ion.

Colestipol hydrochloride is hydrophilic, but it is virtually water insoluble (99.75%) and it is not hydrolyzed by digestive enzymes. The high molecular weight polymer in colestipol hydrochloride apparently is not absorbed. In humans, less than 0.17% of a single ^{14}C-labeled colestipol hydrochloride dose is excreted in the urine when given following 60 days of dosing of 20 grams of colestipol hydrochloride per day.

The increased fecal loss of bile acids due to colestipol hydrochloride administration leads to an increased oxidation of cholesterol to bile acids. This results in an increase in the number of low-density lipoprotein (LDL) receptors, increased hepatic uptake of LDL and a decrease in beta lipoprotein or LDL serum levels, and a decrease in serum cholesterol levels. Although colestipol hydrochloride produces an increase in the hepatic synthesis of cholesterol in man, serum cholesterol levels fall.

There is evidence to show that this fall in cholesterol is secondary to an increased rate of clearance of cholesterol-rich lipoproteins (beta or low-density lipoproteins) from the plasma. Serum triglyceride levels may increase or remain unchanged in colestipol hydrochloride treated patients.

The decline in serum cholesterol levels with colestipol hydrochloride treatment is usually evident by one month. When colestipol hydrochloride is discontinued, serum cholesterol levels usually return to baseline levels within one month. Periodic determinations of serum cholesterol levels as outlined in the National Cholesterol Education Program (NCEP) guidelines, should be done to confirm a favorable *initial and long-term response.*[1]

In a large, placebo-controlled, multiclinic study, the LRC-CPPT[2], hypercholesterolemic subjects treated with cholestyramine, a bile-acid sequestrant with a mechanism of action and an effect on serum cholesterol similar to that of colestipol hydrochloride, had reductions in total and LDL-C. Over the 7-year study period the cholestyramine group experienced a 19% reduction (relative to the incidence in the placebo group) in the combined rate of coronary heart disease (CHD) death plus nonfatal myocardial infarction (cumulative incidences of 7% cholestyramine and 8.6% placebo). The subjects included in the study were middle-aged men (aged 35–59) with serum cholesterol levels above 265 mg/dL, *LDL-C above 175 mg/dL on a moderate cholesterol-lowering diet,* and no history of heart disease. It is not clear to what extent these findings can be extrapolated to other segments of the hypercholesterolemic population not studied.

Treatment with colestipol results in a significant increase in lipoprotein LpAI. Lipoprotein LpAI is one of the two major lipoprotein particles within the high-density lipoprotein (HDL) density range[3], and has been shown in cell culture to *promote cholesterol efflux or removal from cells*[4]. *Although* the significance of this finding has not been established in clinical studies, the elevation of the lipoprotein LpAI particle within the HDL fraction is consistent with an antiatherogenic effect of colestipol hydrochloride, even though little change is observed in HDL cholesterol (HDL-C).

In patients with heterozygous familial hypercholesterolemia who have not obtained an optimal response to colestipol hydrochloride alone in maximal doses, the combination of *colestipol hydrochloride and nicotinic acid has been shown* to further lower serum cholesterol, triglyceride, and LDL-cholesterol (LDL-C) values. Simultaneously, HDL-C values increased significantly. In many such patients it is possible to normalize serum lipid values.[5–7]

Preliminary evidence suggests that the cholesterol-lowering effects of lovastatin and the bile acid sequestrant, colestipol hydrochloride, are additive.

The effect of intensive lipid-lowering therapy on coronary atherosclerosis has been assessed by arteriography in hyperlipidemic patients. In these randomized, controlled clinical trials, patients were treated for two to four years by either conventional measures (diet, placebo, or in some cases low-dose resin), or with intensive combination therapy using diet and COLESTID Granules plus either nicotinic acid or lovastatin. When compared to conventional measures, intensive lipid-lowering combination therapy significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions in patients with or at risk for coronary artery disease.[8–11]

INDICATIONS AND USAGE

Since no drug is innocuous, strict attention should be paid to the indications and contraindications, particularly when selecting drugs for chronic long-term use.

COLESTID Tablets are indicated as adjunctive therapy to diet for the reduction of elevated serum total and LDL-C in patients with primary hypercholesterolemia (elevated LDL-C) who do not respond adequately to diet. Generally, COLESTID Tablets have no clinically significant effect on serum triglycerides, but with their use, triglyceride levels may be raised in some patients.

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Treatment should begin and continue with dietary therapy (see NCEP guidelines). A minimum of six months of intensive dietary therapy and counseling should be carried out prior to initiation of drug therapy. Shorter periods may be considered in patients with severe elevations of LDL-C or with definite CHD.

According to the NCEP guidelines, the goal of treatment is to lower LDL-C, and LDL-C is to 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. The NCEP treatment guidelines are shown below.

Continued on next page

Colestid Tablets—Cont.

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

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

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

CONTRAINDICATIONS

COLESTID Tablets are contraindicated in those individuals who have shown hypersensitivity to any of their components.

PRECAUTIONS

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

LDL-C = Total cholesterol − [(Triglycerides/5) + HDL-C]

For TG levels >400 mg/dL, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases COLESTID Tablets may not be indicated.

Because it sequesters bile acids, colestipol hydrochloride may interfere with normal fat absorption and, thus, may reduce absorption of folic acid and fat soluble vitamins such as A, D, and K.

Chronic use of colestipol hydrochloride may be associated with an increased bleeding tendency due to hypoprothrombinemia from vitamin K deficiency. This will usually respond promptly to parenteral vitamin K_1 and recurrences can be prevented by oral administration of vitamin K_1.

Serum cholesterol and triglyceride levels should be determined periodically based on NCEP guidelines to confirm a favorable initial and adequate long-term response.

COLESTID Tablets may produce or severely worsen pre-existing constipation. The dosage should be increased gradually in patients to minimize the risk of developing fecal impaction. In patients with pre-existing constipation, the starting dose should be 2 grams once or twice a day. Increased fluid and fiber intake should be encouraged to alleviate constipation and a stool softener may occasionally be indicated. If the initial dose is well tolerated, the dose may be increased as needed by a further 2 to 4 grams/day (at monthly intervals) with periodic monitoring of serum lipoproteins. If constipation worsens or the desired therapeutic response is not achieved at 2 to 16 grams/day, combination therapy or alternate therapy should be considered. Particular effort should be made to avoid constipation in patients with symptomatic coronary artery disease. Constipation associated with COLESTID may aggravate hemorrhoids.

While there have been no reports of hypothyroidism induced in individuals with normal thyroid function, the theoretical possibility exists, particularly in patients with limited thyroid reserve.

Since colestipol hydrochloride is a chloride form of an anion exchange resin, there is a possibility that prolonged use may lead to the development of hyperchloremia acidosis.

Carcinogenesis, Mutagenesis and Impairment of Fertility

In studies conducted in rats in which cholestyramine resin (a bile acid sequestering agent similar to colestipol hydrochloride) was used as a tool to investigate the role of various intestinal factors, such as fat, bile salts, and microbial flora, in the development of intestinal tumors induced by potent carcinogens, the incidence of such tumors was observed to be greater in cholestyramine resin treated rats than in control rats.

The relevance of this laboratory observation from studies in rats with cholestyramine resin to the clinical use of COLESTID Tablets is not known. In the LRC-CPPT study referred to above, the total incidence of fatal and nonfatal neoplasms was similar in both treatment groups. When the many different categories of tumors are examined, various alimentary system cancers were somewhat more prevalent in the cholestyramine group. The small numbers and the multiple categories prevent conclusions from being drawn. Further follow-up of the LRC-CPPT participants by the sponsors of that study is planned for cause-specific mortality and cancer morbidity. When colestipol hydrochloride was administered in the diet to rats for 18 months, there was no evidence of any drug related intestinal tumor formation. In the Ames assay, colestipol hydrochloride was not mutagenic.

Use in Pregnancy

Since colestipol hydrochloride is essentially not absorbed systemically (less than 0.17% of the dose), it is not expected to cause fetal harm when administered during pregnancy in recommended dosages. There are no adequate and well-controlled studies in pregnant women, and the known interference with absorption of fat-soluble vitamins may be detrimental even in the presence of supplementation.

Nursing Mothers: Caution should be exercised when COLESTID Tablets are administered to a nursing mother. The possible lack of proper vitamin absorption described in the "Pregnancy" section may have an effect on nursing infants.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Information for Patients

COLESTID Tablets may be larger than pills you have taken before. If you have had swallowing problems or choking with food, liquids or other tablets or capsules in the past, you should discuss this with your doctor before taking COLESTID Tablets.

It is important that you take COLESTID Tablets correctly:

1. Always take one tablet at a time and swallow promptly.
2. Swallow each tablet whole. Do not cut, crush, or chew the tablets.
3. COLESTID Tablets must be taken with water or another liquid that you prefer. Swallowing the tablets will be easier if you drink plenty of liquid as you swallow each tablet.

Difficulty swallowing and temporary obstruction of the esophagus (the tube between your mouth and stomach) have been rarely reported in patients taking COLESTID Tablets. If a tablet does get stuck after you swallow it, you may notice pressure or discomfort. If this happens to you, you should contact your doctor. Do not take COLESTID Tablets again without your doctor's advice.

If you are taking other medications, you should take them at least one hour before or four hours after taking COLESTID Tablets.

DRUG INTERACTIONS

Since colestipol hydrochloride is an anion exchange resin, it may have a strong affinity for anions other than the bile acids. *In vitro* studies have indicated that colestipol hydrochloride binds a number of drugs. Therefore, COLESTID Tablets may delay or reduce the absorption of concomitant oral medication. The interval between the administration of COLESTID Tablets and any other medication should be as long as possible. Patients should take other drugs at least one hour before or four hours after COLESTID Tablets to avoid impeding their absorption.

Repeated doses of colestipol hydrochloride given prior to a single dose of propranolol in human trials have been reported to decrease propranolol absorption. However, in a follow-up study in normal subjects, single-dose administration of colestipol hydrochloride and propranolol and twice-a-day administration for 5 days of both agents did not affect the extent of propranolol absorption, but had a small yet statistically significant effect on its rate of absorption; the time to reach maximum concentration was delayed approximately 30 minutes. Effects on the absorption of other beta-blockers have not been determined. Therefore, patients on propranolol should be observed when COLESTID Tablets are either added or deleted from a therapeutic regimen.

Studies in humans show that the absorption of chlorothiazide as reflected in urinary excretion is markedly decreased even when administered one hour before colestipol hydrochloride. The absorption of tetracycline, furosemide, penicillin G, hydrochlorothiazide, and gemfibrozil was significantly decreased when given simultaneously with colestipol hydrochloride; these drugs were not tested to determine the effect of administration one hour before colestipol hydrochloride.

No depressant effect on blood levels in humans was noted when colestipol hydrochloride was administered with any of the following drugs: aspirin, clindamycin, clofibrate, methyldopa, nicotinic acid (niacin), tolbutamide, phenytoin or warfarin. Particular caution should be observed with digitalis preparations since there are conflicting results for the effect of colestipol hydrochloride on the availability of digoxin and digitoxin. The potential for binding of these drugs if given concomitantly is present. Discontinuing colestipol hydrochloride could pose a hazard to health if a potentially toxic drug that is significantly bound to the resin has been titrated to a maintenance level while the patient was taking colestipol hydrochloride.

Bile acid binding resins may also interfere with the absorption of oral phosphate supplements and hydrocortisone.

ADVERSE REACTIONS

Gastrointestinal

The most common adverse reactions are confined to the gastrointestinal tract. To achieve minimal GI disturbance with an optimal LDL-C lowering effect, a gradual increase of dosage starting with 2 grams, once or twice daily is recommended. Constipation is the major single complaint and at times is severe. Most instances of constipation are mild, transient, and controlled with standard treatment. Increased fluid intake and inclusion of additional dietary fiber should be the first step; a stool softener may be added if needed. Some patients require decreased dosage or discontinuation of therapy. Hemorrhoids may be aggravated.

Other, less frequent gastrointestinal complaints consist of abdominal discomfort (abdominal pain and cramping), intestinal gas (bloating and flatulence), indigestion and heartburn, diarrhea and loose stools, and nausea and vomiting. Bleeding hemorrhoids and blood in the stool have been infrequently reported. Peptic ulceration, cholecystitis, and cholelithiasis have been rarely reported in patients receiving colestipol hydrochloride granules, and are not necessarily drug related.

Difficulty swallowing and transient esophageal obstruction have been rarely reported in patients taking COLESTID Tablets.

Transient and modest elevations of aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT) and alkaline phosphatase were observed on one or more occasions in various patients treated with colestipol hydrochloride.

The following nongastrointestinal adverse reactions have been reported with generally equal frequency in patients receiving COLESTID Tablets, colestipol granules, or placebo in clinical studies:

Cardiovascular

Chest pain, angina, and tachycardia have been infrequently reported.

Hypersensitivity

Rash has been infrequently reported. Urticaria and dermatitis have been rarely noted in patients receiving colestipol hydrochloride granules.

Musculoskeletal

Musculoskeletal pain, aches and pains in the extremities, joint pain and arthritis, and backache have been reported.

Neurologic

Headache, migraine headache, and sinus headache have been reported. Other infrequently reported complaints include dizziness, light-headedness, and insomnia.

Miscellaneous

Anorexia, fatigue, weakness, shortness of breath, and swelling of the hands or feet, have been infrequently reported.

OVERDOSAGE

Overdosage of COLESTID Tablets has not been reported. Should overdosage occur, however, the chief potential harm would be obstruction of the gastrointestinal tract. The location of such potential obstruction, the degree of obstruction and the presence or absence of normal gut motility would determine treatment.

DOSAGE AND ADMINISTRATION

For adults, COLESTID Tablets are recommended in doses of 2 to 16 grams/day given once or in divided doses. The starting dose should be 2 grams once or twice daily. Dosage increases of 2 grams, once or twice daily should occur at 1- or 2-month intervals. Appropriate use of lipid profiles as per NCEP guidelines including LDL-C and triglycerides, is advised so that optimal but not excessive doses are used to obtain the desired therapeutic effect on LDL-C level. If the desired therapeutic effect is not obtained at a dose of 2 to 16 grams/day with good compliance and acceptable side effects, combined therapy or alternate treatment should be considered.

COLESTID Tablets must be taken one at a time and be promptly swallowed whole, using plenty of water or other appropriate liquid. Do not cut, crush, or chew the tablets. Patients should take other drugs at least one hour before or four hours after COLESTID Tablets to minimize possible interference with their absorption. (See DRUG INTERACTIONS.)

Before Administration of COLESTID Tablets

1. Define the type of hyperlipoproteinemia, as described in NCEP guidelines.
2. Institute a trial of diet and weight reduction.
3. Establish baseline serum total and LDL-C and triglyceride levels.

During Administration of COLESTID Tablets

1. The patient should be carefully monitored clinically, including serum cholesterol and triglyceride levels. Periodic determinations of serum cholesterol levels as outlined in the NCEP guidelines should be done to confirm a favorable initial and long-term response.
2. Failure of total or LDL-C to fall within the desired range should lead one to first examine dietary and drug compliance. If these are deemed acceptable, combined therapy or alternate treatment should be considered.
3. Significant rise in triglyceride level should be considered as indication for dose reduction, drug discontinuation, or combined or alternate therapy.

HOW SUPPLIED

COLESTID Tablets are yellow, elliptical, imprinted U, and are supplied as follows:

Bottles of 120 NDC 0009-0450-03
Bottles of 500 NDC 0009-0450-04

Each tablet contains 1 gram of colestipol hydrochloride.

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

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Manufactured for:
Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA
By:
International Processing Corporation
Winchester, KY 40391, USA
Revised June 2002 815 838 307
692851

CORVERT®

℞

[cör-vĕrt]

ibutilide fumarate injection

For intravenous infusion only

DESCRIPTION

CORVERT Injection (ibutilide fumarate injection) is an antiarrhythmic drug with predominantly class III (cardiac action potential prolongation) properties according to the Vaughan Williams Classification. Each milliliter of CORVERT Injection contains 0.1 mg of ibutilide fumarate (equivalent to 0.087 mg ibutilide free base), 0.189 mg sodium acetate trihydrate, 8.90 mg sodium chloride, hydrochloric acid to adjust pH to approximately 4.6, and Water for Injection.

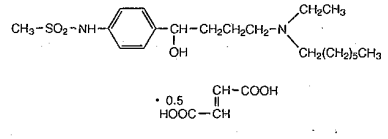
CORVERT Injection is an isotonic, clear, colorless, sterile aqueous solution.

Ibutilide fumarate has one chiral center, and exists as a racemate of the (+) and (−) enantiomers.

The chemical name for ibutilide fumarate is Methanesulfonamide, N-[4-[4-(ethylheptyl-amino)-1-hydroxybutyl] phenyl], (+) (−), (E)-2-butenedioate (1:0.5) (hemifumarate salt). Its molecular formula is $C_{22}H_{38}N_2O_5S$, and its molecular weight is 442.62.

Ibutilide fumarate is a white to off-white powder with an aqueous solubility of over 100 mg/mL at pH 7 or lower.

The structural formula is represented below:



Ibutilide Fumarate

CLINICAL PHARMACOLOGY

Mechanism of Action: CORVERT injection prolongs action potential duration in isolated adult cardiac myocytes and increases both atrial and ventricular refractoriness *in vivo*, ie, class III electrophysiologic effects. Voltage clamp studies indicate that CORVERT, at nanomolar concentrations, delays repolarization by activation of a slow, inward current (predominantly sodium), rather than by blocking outward potassium currents, which is the mechanism by which other class III antiarrhythmics act. These effects lead to prolongation of atrial and ventricular action potential duration and refractoriness, the predominant electrophysiologic properties of CORVERT in humans that are thought to be the basis for its antiarrhythmic effect.

Electrophysiologic Effects: CORVERT produces mild slowing of the sinus rate and atrioventricular conduction. CORVERT produces no clinically significant effect on QRS duration at intravenous doses up to 0.03 mg/kg administered over a 10-minute period. Although there is no established relationship between plasma concentration and antiarrhythmic effect, CORVERT produces dose-related prolongation of the QT inverval, which is thought to be associated with its antiarrhythmic activity. (See WARNINGS for relationship between QTc prolongation and torsades de pointes-type arrhythmias.) In a study in healthy volunteers, intravenous infusions of CORVERT resulted in prolongation of the QT interval that was directly correlated with ibutilide plasma concentration during and after 10-minute and 8-hour infusions. A steep ibutilide concentration/response (QT prolongation) relationship was shown. The maximum effect was a function of both the dose of CORVERT and the infusion rate.

Hemodynamic Effects: A study of hemodynamic function in patients with ejection fractions both above and below 35% showed no clinically significant effects on cardiac output, mean pulmonary arterial pressure, or pulmonary capillary wedge pressure at doses of CORVERT up to 0.03 mg/kg.

Pharmacokinetics: After intravenous infusion, ibutilide plasma concentrations rapidly decrease in a multiexponential fashion. The pharmacokinetics of ibutilide are highly variable among subjects. Ibutilide has a high systemic plasma clearance that approximates liver blood flow (about 29 mL/min/kg), a large steady-state volume of distribution (about 11 L/kg) in healthy volunteers, and minimal (about 40%) protein binding. Ibutilide is also cleared rapidly and highly distributed in patients being treated for atrial flutter or atrial fibrillation. The elimination half-life averages about 6 hours (range from 2 to 12 hours). The pharmacokinetics of ibutilide are linear with respect to the dose of CORVERT over the dose range of 0.01 mg/kg to 0.10 mg/kg. The enantiomers of ibutilide fumarate have pharmacokinetic properties similar to each other and to ibutilide fumarate.

The pharmacokinetics of CORVERT Injection in patients with atrial flutter or atrial fibrillation are similar regardless of the type of arrhythmia, patient age, sex, or the concomitant use of digoxin, calcium channel blockers, or beta blockers.

Metabolism and elimination: In healthy male volunteers, about 82% of a 0.01 mg/kg dose of [^{14}C] ibutilide fumarate was excreted in the urine (about 7% of the dose as unchanged ibutilide) and the remainder (about 19%) was recovered in the feces.

Eight metabolites of ibutilide were detected in metabolic profiling of urine. These metabolites are thought to be formed primarily by ω-oxidation followed by sequential β-oxidation of the heptyl side chain of ibutilide. Of the eight metabolites, only the ω-hydroxy metabolite possesses class III electrophysiologic properties similar to that of ibutilide in an *in vitro* isolated rabbit myocardium model. The plasma concentrations of this active metabolite, however, are less than 10% of that of ibutilide.

Clinical Studies: Treatment with intravenous ibutilide fumarate for acute termination of recent onset atrial flutter/fibrillation was evaluated in 466 patients participating in two randomized, double-blind, placebo-controlled clinical trials. Patients had had their arrhythmias for 3 hours to 90 days, were anticoagulated for at least 2 weeks if atrial fibrillation was present more than 3 days, had serum potassium of at least 4.0 mEq/L and QTc below 440 msec, and were monitored by telemetry for at least 24 hours. Patients could not be on class I or other class III antiarrhythmics (these had to be discontinued at least 5 half-lives prior to infusion) but could be on calcium channel blockers, beta blockers, or digoxin. In one trial, single 10-minute infusions of 0.005 to 0.025 mg/kg were tested in parallel groups (0.3 to 1.5 mg in a 60 kg person). In the second trial, up to two infusions of ibutilide fumarate were evaluated—the first 1.0 mg, the second given 10 minutes after completion of the first infusion, either 0.5 or 1.0 mg. In a third double-blind study, 319 patients with atrial fibrillation or atrial flutter of 3 hours to 45 days duration were randomized to receive single, 10-minute intravenous infusions of either sotalol (1.5 mg/kg) or CORVERT (1 mg or 2 mg). Among patients with atrial flutter, 53% receiving 1 mg ibutilide fumarate and 70% receiving 2 mg ibutilide fumarate converted, compared to 18% of those receiving sotalol. In patients with atrial fibrillation, 22% receiving 1 mg ibutilide fumarate and 43% receiving 2 mg ibutilide fumarate converted compared to 10% of patients receiving sotalol.

Patients in registration trials were hemodynamically stable. Patients with specific cardiovascular conditions such as symptomatic heart failure, recent acute myocardial infarction, and angina were excluded. About two thirds had cardiovascular symptoms, and the majority of patients had left atrial enlargement, decreased left ventricular ejection fraction, a history of valvular disease, or previous history of atrial fibrillation or flutter. Electrical cardioversion was allowed 90 minutes after the infusion was complete. Patients could be given other antiarrhythmic drugs 4 hours postinfusion.

Results of the first two studies are shown in the tables below. Conversion of atrial flutter/fibrillation usually (70% of those who converted) occurred within 30 minutes of the start of infusion and was dose related. The latest conversion seen was at 90 minutes after the start of the infusion. Most converted patients remained in normal sinus rhythm for 24 hours. Overall responses in these patients, defined as termination of arrhythmias for any length of time during or within 1 hour following completed infusion of randomized dose, were in the range of 43% to 48% at doses above 0.0125 mg/kg (vs 2% for placebo). Twenty-four hour responses were similar. For these atrial arrhythmias, ibutilide was more effective in patients with flutter than fibrillation (≥48% vs ≤40%).

[See first table above]

[See second table above]

PERCENT OF PATIENTS WHO CONVERTED (First Trial)

			Ibutilide			
		Placebo	0.005 mg/kg	0.01 mg/kg	0.015 mg/kg	0.025 mg/kg
	n	41	41	40	38	40
Both	Initially*	2	12	33	45	48
	At 24 hours†	2	12	28	42	43
Atrial flutter	Initially*	0	14	30	58	55
	At 24 hours†	0	14	30	58	50
Atrial fibrillation	Initially*	5	10	35	32	40
	At 24 hours†	5	10	25	26	35

* Percent of patients who converted within 70 minutes after the start of infusion.
† Percent of patients who remained in sinus rhythm 24 hours after dosing.

PERCENT OF PATIENTS WHO CONVERTED (Second Trial)

			Ibutilide	
		Placebo	1.0 mg/0.5 mg	1.0 mg/1.0 mg
	n	86	86	94
Both	Initially*	2	43	44
	At 24 hours†	2	34	37
Atrial flutter	Initially*	2	48	63
	At 24 hours†	2	45	59
Atrial fibrillation	Initially*	2	38	25
	At 24 hours†	2	21	17

* Percent of patients who converted within 90 minutes after the start of infusion.
† Percent of patients who remained in sinus rhythm 24 hours after dosing.

Continued on next page

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LESCOL® Rx
(fluvastatin sodium)
Capsules
LESCOL® XL
(fluvastatin sodium)
Extended-Release Tablets
Rx only

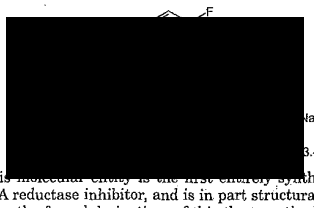
The following prescribing information is based on official labeling if effect July 2002.

Prescribing Information

DESCRIPTION

Lescol® (fluvastatin sodium), is a water-soluble cholesterol lowering agent which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

Fluvastatin sodium is [*R*, S*-(E)*]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt. The empirical formula of fluvastatin sodium is $C_{24}H_{25}FNO_4$•Na, its molecular weight is 433.46 and its structural formula is:



This molecular entity is the first entirely synthetic HMG-CoA reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class.

Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. Lescol is supplied as capsules containing fluvastatin sodium, equivalent to 20 mg or 40 mg of fluvastatin, for oral administration. Lescol® XL (fluvastatin sodium) is supplied as extended-release tablets containing fluvastatin sodium, equivalent to 80 mg of fluvastatin, for oral administration.

Active Ingredient: fluvastatin sodium

Inactive Ingredients in capsules: gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, yellow iron oxide, and other ingredients.

Capsules may also include: benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide and sodium propionate.

Inactive Ingredients in extended-release tablets: microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, potassium bicarbonate, povidone, magnesium stearate, iron oxide yellow, titanium dioxide and polyethylene glycol 8000.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), triglycerides (TG) and apolipoprotein B (a membrane transport complex for LDL-C) 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.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

In patients with hypercholesterolemia and mixed dyslipidemia, treatment with Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium) reduced Total-C, LDL-C, apolipoprotein B, and triglycerides while producing an increase in HDL-C. Increases in HDL-C are greater in patients with low HDL-C (<35 mg/dL). Neither agent had a consistent effect on either Lp(a) or fibrinogen. The effect of Lescol or Lescol XL induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been determined.

Mechanism of Action

Lescol is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The end result of these biochemical processes is a reduction of the plasma cholesterol concentration.

Pharmacokinetics/Metabolism

Oral Absorption

Fluvastatin is absorbed rapidly and completely following oral administration of the capsule, with peak concentrations reached in less than 1 hour. Following administration of a 10 mg dose, the absolute bioavailability is 24% (range 9%–50%). Administration with food reduces the rate but not the extent of absorption. At steady-state, administration of fluvastatin with the evening meal results in a two-fold decrease in C_{max} and more than two-fold increase in t_{max} as compared to administration 4 hours after the evening meal. No significant differences in extent of absorption or in the lipid-lowering effects were observed between the two administrations. After single or multiple doses above 20 mg, fluvastatin exhibits saturable first-pass metabolism resulting in higher-than-expected plasma fluvastatin concentrations.

Fluvastatin has two optical enantiomers, an active 3R, 5S and an inactive 3S,5R form. In vivo studies showed that stereo-selective hepatic binding of the active form occurs during the first pass resulting in a difference in the peak levels of the two enantiomers, with the active to inactive peak concentration ratio being about 0.7. The approximate ratio of the active to inactive approaches unity after the peak is seen and thereafter the two enantiomers decline with the same half-life. After an intravenous administration, bypassing the first-pass metabolism, the ratios of the enantiomers in plasma were similar throughout the concentration-time profiles.

Fluvastatin administered as Lescol XL 80 mg tablets reaches peak concentration in approximately 3 hours under fasting conditions, after a low-fat meal, or 2.5 hours after a low-fat meal. The mean relative bioavailability of the XL tablet is approximately 29% (range: 9%–66%) compared to that of the Lescol immediate release capsule administered under fasting conditions. Administration of a high fat meal delayed the absorption (T_{max}: 6H) and increased the bioavailability of the XL tablet by approximately 50%. Once Lescol XL begins to be absorbed, fluvastatin concentrations rise rapidly. The maximum concentration seen after a high fat meal is much less than the peak concentration following a single dose or twice daily dose of the 40 mg Lescol capsule. Overall variability in the pharmacokinetics of Lescol XL is large (42%–64% CV for C_{max} and AUC), and especially so after a high fat meal (63%–89% for C_{max} and AUC). Intra-subject variability in the pharmacokinetics of Lescol XL under fasting conditions (about 25% for C_{max} and AUC) tends to be much smaller as compared to the overall variability. Multiple peaks in plasma fluvastatin concentrations have been observed after Lescol XL administration.

Distribution

Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution (VD_{ss}) is estimated at 0.35 L/kg. The parent drug is targeted to the liver and no active metabolites are present systemically. At therapeutic concentrations, the protein binding of fluvastatin is not affected by warfarin, salicylic acid and glyburide.

Metabolism

Fluvastatin is metabolized in the liver, primarily via hydroxylation of the indole ring at the 5- and 6-positions. N-dealkylation and beta-oxidation of the side-chain also occurs. The hydroxy metabolites have some pharmacologic activity, but do not circulate in the blood. Both enantiomers of fluvastatin are metabolized in a similar manner.

In vitro studies demonstrated that fluvastatin undergoes oxidative metabolism, predominantly via 2C9 isozyme systems (75%). Other isozymes that contribute to fluvastatin metabolism are 2C8 (~5%) and 3A4 (~20%). *(See PRECAUTIONS: Drug Interactions Section).*

Elimination

Fluvastatin is primarily (about 90%) eliminated in the feces as metabolites, with less than 2% present as unchanged drug. Urinary recovery is about 5%. After a radiolabeled dose of fluvastatin, the clearance was 0.8 L/h/kg. Following multiple oral doses of radiolabeled compound, there was no accumulation of fluvastatin; however, there was a 2.3 fold accumulation of total radioactivity.

Steady-state plasma concentrations show no evidence of accumulation of fluvastatin following immediate release capsule administration of up to 80 mg daily, as evidenced by a beta-elimination half-life of less than 3 hours. However, under conditions of maximum rate of absorption (i.e., fasting) systemic exposure to fluvastatin is increased 33% to 53% compared to a single 20 mg or 40 mg dose of the immediate release capsule. Accumulation following once daily administration of the 80 mg Lescol XL tablet has not been studied. Single-dose and steady-state pharmacokinetic parameters in 33 subjects with hypercholesterolemia for the capsules and single dose data in 24 healthy subjects for the extended-release tablets are summarized below:

[See table above]

Table 1
Single-dose and steady-state pharmacokinetic parameters

	C_{max} (ng/mL) mean±SD (range)	AUC (ng·h/mL) mean±SD (range)	t_{max} (hr) mean±SD (range)	CL/F (L/hr) mean±SD (range)	$t_{1/2}$ (hr) mean±SD (range)
Capsules					
20 mg single dose (n=17)	166±106 (48.9–517)	207±65 (111–288)	0.9±0.4 (0.5–2.0)	107±38.1 (69.5–181)	2.5±1.7 (0.5–6.6)
20 mg twice daily (n=17)	200±86 (71.8–366)	275±111 (91.6–467)	1.2±0.9 (0.5–4.0)	87.8±45 (42.8–218)	2.8±1.7 (0.9–6.0)
40 mg single dose (n=16)	273±189 (72.8–812)	456±259 (207–1221)	1.2±0.7 (0.75–3.0)	108±44.7 (32.8–193)	2.7±1.3 (0.8–5.9)
40 mg twice daily (n=16)	432±236 (119–990)	697±275 (359–1559)	1.2±0.6 (0.5–2.5)	64.2±21.1 (25.7–111)	2.7±1.3 (0.7–5.0)
Extended-Release Tablets 80 mg single dose (n=24)					
Fasting	126±53 (37–242)	579±341 (144–1760)	3.2±2.6 (1–12)		
Fed State- High Fat Meal	183±163 (21–733)	861±632 (199–3132)	6 (2–24)		

Special Populations

Renal Insufficiency: No significant (<6%) renal excretion of fluvastatin occurs in humans.

Hepatic Insufficiency: Fluvastatin is subject to saturable first-pass metabolism/sequestration by the liver and is eliminated primarily via the biliary route. Therefore, the potential exists for drug accumulation in patients with hepatic insufficiency. Caution should therefore be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion *(see WARNINGS).*

Fluvastatin AUC and C_{max} values increased by about 2.5 fold in hepatic insufficiency patients. This result was attributed to the decreased presystemic metabolism due to hepatic dysfunction. The enantiomer ratios of the two isomers of fluvastatin in hepatic insufficiency patients were comparable to those observed in healthy subjects.

Age: Plasma levels of fluvastatin are not affected by age.

Gender: Women tend to have slightly higher (but statistically insignificant) fluvastatin concentrations than men for the immediate release capsule. This is most likely due to body weight differences, as adjusting for body weight decreases the magnitude of the differences seen. For Lescol XL, there are 67% and 77% increases in systemic availability for women over men under fasted and high fat meal conditions.

Pediatric: No data are available. Fluvastatin is not indicated for use in the pediatric population.

CLINICAL STUDIES

Hypercholesterolemia (heterozygous familial and non familial) and Mixed Dyslipidemia

In 12 placebo-controlled studies in patients with Type IIa or IIb hyperlipoproteinemia, Lescol® (fluvastatin sodium) alone was administered to 1621 patients in daily dose regimens of 20 mg, 40 mg, and 80 mg (40 mg twice daily) for at least 6 weeks duration. After 24 weeks of treatment, daily doses of 20 mg, 40 mg, and 80 mg (40 mg twice daily) resulted in median LDL-C reductions of 22% (n=747), 25% (n=748) and 36% (n=257), respectively. Lescol treatment produced dose-related reductions in Apo B and in triglycerides and increases in HDL-C. The median (25^{th}, 75^{th} percentile) percent changes from baseline in HDL-C after 12 weeks of treatment with Lescol at daily doses of 20 mg, 40 mg and 80 mg (40 mg twice daily) were +2 (−4,+10), +5 (−2,+12), and +4 (−3,+12), respectively. In a subgroup of patients with primary mixed dyslipidemia, defined as baseline TG levels ≥200 mg/dL, treatment with Lescol also produced significant decreases in Total-C, LDL-C, TG and Apo B and variable increases in HDL-C. The median (25^{th}, 75^{th} percentile) percent changes from baseline in HDL-C after 12 weeks of treatment with Lescol at daily doses of 20 mg, 40 mg and 80 mg (40 mg twice daily) in this population were +4 (−2,+12), +8 (+1,+15), and +4 (−3,+13), respectively.

In a long-term open-label free titration study, after 96 weeks LDL-C decreases of 25% (20 mg, n=68), 31% (40 mg, n=298) and 34% (80 mg, n=209) were seen. No consistent effect on Lp(a) was observed.

Continued on next page

Lescol—Cont.

Lescol® XL (fluvastatin sodium) Extended-Release Tablets have been studied in five controlled studies of patients with Type IIa or IIb hyperlipoproteinemia. Lescol XL was administered to over 900 patients in trials from 4 to 26 weeks in duration. In the three largest of these studies, Lescol XL given as a single daily dose of 80 mg significantly reduced Total-C, LDL-C, TG and Apo B. Therapeutic response is well established within two weeks, and a maximum response is achieved within four weeks. After four weeks of therapy, the median decrease in LDL-C was 38% and at week 24 endpoint the median LDL-C decrease was 35%. Significant increases in HDL-C were also observed. The median (25^{th} and 75^{th} percentile) percent changes from baseline in HDL-C for Lescol XL were +7(+0,+15) after 24 weeks of treatment.
[See table 2 at right]
In patients with primary mixed dyslipidemia (Fredrickson Type IIb) as defined by baseline plasma triglycerides levels ≥200 mg/dL, Lescol XL 80 mg produced a median reduction in triglycerides of 25%. In these patients, Lescol XL 80 mg produced median (25^{th} and 75^{th} percentile) percent change from baseline in HDL-C of +11(+3,+20). Significant decreases in Total-C, LDL-C, and Apo B were also achieved. In these studies, patients with triglycerides >400 mg/dL were excluded.

Atherosclerosis

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of Lescol therapy on coronary atherosclerosis was assessed by quantitative coronary angiography (QCA) in patients with coronary artery disease and mild to moderate hypercholesterolemia (baseline LDL-C range 115–190 mg/dL). In this randomized double-blind, placebo controlled trial, 429 patients were treated with conventional measures (Step 1 AHA Diet) and either Lescol 40 mg/day or placebo. In order to provide treatment to patients receiving placebo with LDL-C levels ≥160 mg/dL at baseline, adjunctive therapy with cholestyramine was added after week 12 to all patients in the study with baseline LDL-C values of ≥160 mg/dL. These baseline levels were present in 25% of the study population. Quantitative coronary angiograms were evaluated at baseline and 2.5 years in 340 (79%) angiographic evaluable patients.
Lescol significantly slowed the progression of coronary atherosclerosis. Compared to placebo, Lescol significantly slowed the progression of lesions as measured by within-patient per-lesion change in minimum lumen diameter (MLD), the primary endpoint (see Figure 1 below), percent diameter stenosis (Figure 2), and the formation of new lesions (13% of all fluvastatin patients versus 22% of all placebo patients). Additionally, a significant difference in favor of Lescol was found between all fluvastatin and all placebo patients in the distribution among the three categories of definite progression, definite regression, and mixed or no change. Beneficial angiographic results (change in MLD) were independent of patients' gender and consistent across a range of baseline LDL-C levels.

Figure 1
Change in Minimum Lumen Diameter (mm)

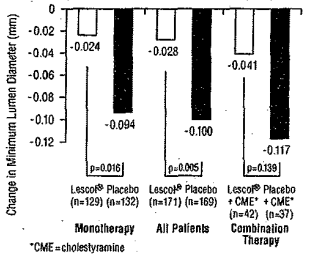
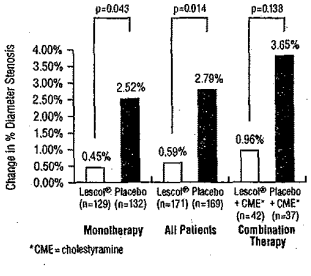


Figure 2
Change in % Diameter Stenosis



INDICATIONS AND USAGE

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerosis vascular disease due to hypercholesterolemia.

Table 2
Median Percent Change in Lipid Parameters from Baseline to Week 24 Endpoint
All Placebo-Controlled Studies (Lescol) and Active Controlled Trials (Lescol XL)

Dose	Total Chol. N	Total Chol. % Δ	TG N	TG % Δ	LDL N	LDL % Δ	Apo B N	Apo B % Δ	HDL N	HDL % Δ
All Patients										
Lescol 20 mg[1]	747	−17	747	−12	747	−22	114	−19	747	+3
Lescol 40 mg[1]	748	−19	748	−14	748	−25	125	−18	748	+4
Lescol 40 mg twice daily[1]	257	−27	257	−18	257	−36	232	−28	257	+6
Lescol XL 80 mg[2]	750	−25	750	−19	748	−35	745	−27	750	+7
Baseline TG ≥200 mg/dL										
Lescol 20 mg[1]	148	−16	148	−17	148	−22	23	−19	148	+6
Lescol 40 mg[1]	179	−18	179	−20	179	−24	47	−18	179	+7
Lescol 40 mg twice daily[1]	76	−27	76	−23	76	−35	69	−28	76	+9
Lescol XL 80 mg[2]	239	−25	239	−25	237	−33	235	−27	239	+11

[1] Data for Lescol from 12 placebo controlled trials
[2] Data for Lescol XL 80 mg tablet from three 24 week controlled trials

Table 3
NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100–129: drug optional)††
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%–20%: ≥130 10-year risk <10%: ≥160
0–1 Risk factor†††	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

†CHD, coronary heart disease
††Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100mg/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 judgement also may call for deferring drug therapy in this subcategory.
†††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.

Table 4
Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations: Major	Lipid Elevations: Minor
I (rare)	Chylomicrons	TG	↑ → C
IIa	LDL	C	–
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	–
IV	VLDL	TG	↑ → C
V (rare)	Chylomicrons, VLDL	TG	↑ → C

C = cholesterol, TG = triglycerides, LDL = low density lipoprotein, VLDL = very low density lipoprotein, IDL = intermediate density lipoprotein

Hypercholesterolemia (heterozygous familial and non familial) and Mixed Dyslipidemia

Lescol® (fluvastatin sodium) and Lescol® XL (fluvastatin sodium) are indicated as an adjunct to diet to reduce elevated total cholesterol (Total-C), LDL-C, TG and Apo B levels, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate.

Atherosclerosis

Lescol and Lescol XL are also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels.
Therapy with lipid-altering agents should be considered only after secondary causes for hyperlipidemia such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other medication, or alcoholism, have been excluded. Prior to initiation of fluvastatin sodium, a lipid profile should be performed to measure Total-C, HDL-C and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

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

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients LDL-C may be low or normal despite elevated Total-C. In such cases, Lescol is not indicated.
Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy.
The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:
[See table 3 above]
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 level is ≥130 mg/dL (NCEP-ATP II).
Since the goal of treatment is to lower LDL-C, the NCEP recommends that the 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.
[See table 4 above]
Neither Lescol nor Lescol XL have been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e., hyperlipoproteinemia Types I, III, IV, or V).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication. Lescol® (fluvastatin sodium) and Lescol® XL (fluvastatin sodium) are contraindicated in patients with active liver disease or unexplained, persistent elevations in serum transaminases *(see WARNINGS)*.

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 pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers.

Fluvastatin sodium 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 apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Approximately 1.1% of patients treated with Lescol® (fluvastatin sodium) capsules in worldwide trials developed dose-related, persistent elevations of transaminase levels to more than 3 times the upper limit of normal. Fourteen of these patients (0.6%) were discontinued from therapy. In all clinical trials, a total of 33/2969 patients (1.1%) had persistent transaminase elevations with an average fluvastatin exposure of approximately 71.2 weeks; 19 of these patients (0.6%) were discontinued. The majority of patients with these abnormal biochemical findings were asymptomatic.

In a pooled analysis of all placebo-controlled studies in which Lescol capsules were used, persistent transaminase elevations (>3 times the upper limit of normal [ULN] on two consecutive weekly measurements) occurred in 0.2%, 1.5%, and 2.7% of patients treated with 20, 40, and 80 mg (titrated to 40 mg twice daily) Lescol capsules, respectively. Ninety-one percent of the cases of persistent liver function test abnormalities (20 of 22 patients) occurred within 12 weeks of therapy and in all patients with persistent liver function test abnormalities there was an abnormal liver function test present at baseline or by week 8.

In the pooled analysis of the 24-week controlled trials, persistent transaminase elevation occurred in 1.9%, 1.8% and 4.9% of patients treated with Lescol® XL (fluvastatin sodium) 80 mg, Lescol 40 mg and Lescol 40 mg twice daily, respectively. In 13 of 16 patients treated with Lescol XL the abnormality occurred within 12 weeks of initiation of treatment with Lescol XL 80 mg.

It is recommended that liver function tests be performed before the initiation of therapy and at 12 weeks following initiation of treatment or elevation in dose. Patients who develop transaminase elevations or signs and symptoms of liver disease should be monitored to confirm the finding and should be followed thereafter with frequent liver function tests until the levels return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist (found on two consecutive occasions) withdrawal of fluvastatin sodium therapy is recommended.

Active liver disease or unexplained transaminase elevations are contraindications to the use of Lescol and Lescol XL *(see CONTRAINDICATIONS)*. Caution should be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion *(see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism)*. Such patients should be closely monitored.

Skeletal Muscle

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with fluvastatin and with other drugs in this class. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal, has been reported.

Myopathy should be considered in any patients with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Fluvastatin sodium therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Fluvastatin sodium therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy and or rhabdomyolysis during treatment with HMG-CoA reductase inhibitors has been reported to be increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. Myopathy was not observed in a clinical trial in 74 patients involving patients who were treated with fluvastatin sodium together with niacin.

Uncomplicated myalgia has been observed infrequently in patients treated with Lescol at rates indistinguishable from placebo.

The use of fibrates alone may occasionally be associated with myopathy. The combined use of HMG-CoA reductase inhibitors and fibrates should generally be avoided.

PRECAUTIONS

General

Before instituting therapy with Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems *(see INDICATIONS AND USAGE)*.

The HMG-CoA reductase inhibitors may cause elevation of creatine phosphokinase and transaminase levels *(see WARNINGS and ADVERSE REACTIONS)*. This should be considered in the differential diagnosis of chest pain in a patient on therapy with fluvastatin sodium.

Homozygous Familial Hypercholesterolemia

HMG-CoA reductase inhibitors are reported to be less effective in patients with rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Women should be informed that if they become pregnant while receiving Lescol or Lescol XL the drug should be discontinued immediately to avoid possible harmful effects on a developing fetus from a relative deficit of cholesterol and biological products derived from cholesterol. In addition, Lescol or Lescol XL should not be taken during nursing. *(See CONTRAINDICATIONS.)*

Drug Interactions

The below listed drug interaction information is derived from studies using immediate release fluvastatin. Similar studies have not been conducted using the Lescol XL tablet.

Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin *(See WARNINGS: Skeletal Muscle).*

In vitro data indicate that fluvastatin metabolism involves multiple Cytochrome P450 (CYP) isozymes. CYP2C9 isoenzyme is primarily involved in the metabolism of fluvastatin (~75%), while CYP2C8 and CYP3A4 isoenzymes are involved to a much less extent, i.e. ~5% and ~20%, respectively. If one pathway is inhibited in the elimination process of fluvastatin other pathways may compensate.

In vivo drug interaction studies with CYP3A4 inhibitors/substrates such as cyclosporine, erythromycin, and itraconazle result in minimal changes in the pharmacokinetics of fluvastatin, confirming less involvement of CYP3A4 isozyme. Concomitant administration of fluvastatin and phenytoin increased the levels of phenytoin and fluvastatin, suggesting predominant involvement of CYP2C9 in fluvastatin metabolism.

Niacin/Propranolol: Concomitant administration of immediate release fluvastatin sodium with niacin or propranolol has no effect on the bioavailability of fluvastatin sodium.

Cholestyramine: Administration of immediate release fluvastatin sodium concomitantly with, or up to 4 hours after cholestyramine, results in fluvastatin decreases of more than 50% for AUC and 50%–80% for C_{max}. However, administration of immediate release fluvastatin sodium 4 hours after cholestyramine resulted in a clinically significant additive effect compared with that achieved with either component drug.

Cyclosporine: Plasma cyclosporine levels remain unchanged when fluvastatin (20 mg daily) was administered concurrently in renal transplant recipients on stable cyclosporine regimens. Fluvastatin AUC increased 1.9 fold, and C_{max} increased 1.3 fold compared to historical controls.

Digoxin: In a crossover study involving 18 patients chronically receiving digoxin, a single 40 mg dose of immediate release fluvastatin had no effect on digoxin AUC, but had an 11% increase in digoxin C_{max} and small increase in digoxin urinary clearance.

Erythromycin: Erythromycin (500 mg, single dose) did not affect steady-state plasma levels of fluvastatin (40 mg daily).

Itraconazole: Concomitant administration of fluvastatin (40 mg) and itraconazole (100 mg daily × 4 days) does not affect plasma itraconazole or fluvastatin levels.

Gemfibrozil: There is no change in either fluvastatin (20 mg twice daily) or gemfibrozil (600 mg twice daily) plasma levels when these drugs are co-administered.

Phenytoin: Single morning dose administration of phenytoin (300 mg extended release) increased mean steady-state fluvastatin (40 mg) C_{max} by 27% and AUC by 40% whereas fluvastatin increased the mean phenytoin C_{max} by 5% and AUC by 20%. Patients on phenytoin should continue to be monitored appropriately when fluvastatin therapy is initiated or when the fluvastatin dosage is changed.

Diclofenac: Concurrent administration of fluvastatin (40 mg) increased the mean C_{max} and AUC of diclofenac by 60% and 25% respectively.

Tolbutamide: In healthy volunteers, concurrent administration of either single or multiple daily doses of fluvastatin sodium (40 mg) with tolbutamide (1 g) did not affect the plasma levels of either drug to a clinically significant extent.

Glibenclamide (Glyburide): In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean C_{max}, AUC, and $t_{1/2}$ of glibenclamide approximately 50%, 69% and 121%, respectively. Glibenclamide (5–20 mg daily) increased the mean C_{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin and C-peptide levels. However, patients on concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 40 mg twice daily.

Losartan: Concomitant administration of fluvastatin with losartan has no effect on the bioavailability of either losartan or its active metabolite.

Cimetidine/Ranitidine/Omeprazole: Concomitant administration of immediate release fluvastatin sodium with cimetidine, ranitidine and omeprazole results in a significant increase in the fluvastatin C_{max} (43%, 70% and 50%, respectively) and AUC (24%–33%), with an 18%–23% decrease in plasma clearance.

Rifampicin: Administration of immediate release fluvastatin sodium to subjects pretreated with rifampicin results in significant reduction in C_{max} (59%) and AUC (51%), with a large increase (95%) in plasma clearance.

Warfarin: In vitro protein binding studies demonstrated no interaction at therapeutic concentrations. Concomitant administration of a single dose of warfarin (30 mg) in young healthy males receiving immediate release fluvastatin sodium (40 mg/day × 8 days) resulted in no elevation of racemic warfarin concentration. There was also no effect on prothrombin complex activity when compared to concomitant administration of placebo and warfarin. However, bleeding and/or increased prothrombin times have been reported in patients taking coumarin anticoagulants concomitantly with other HMG-CoA reductase inhibitors. Therefore, patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when fluvastatin sodium is initiated or the dosage of fluvastatin sodium is changed.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production.

Fluvastatin exhibited no effect upon non-stimulated cortisol levels and demonstrated no effect upon thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treated groups, but no commensurate elevation in LH occurred, suggesting that the observation was not due to a direct effect upon testosterone production. No effect upon FSH in males was noted. Due to the limited number of premenopausal females studied to date, no conclusions regarding the effect of fluvastatin upon female sex hormones may be made.

Two clinical studies in patients receiving fluvastatin at doses up to 80 mg daily for periods of 24 to 28 weeks demonstrated no effect of treatment upon the adrenal response to ACTH stimulation. A clinical study evaluated the effect of fluvastatin at doses up to 80 mg daily for 28 weeks upon the gonadal response to HCG stimulation. Although the mean total testosterone response was significantly reduced ($p<0.05$) relative to baseline in the 80 mg group, it was not significant in comparison to the changes noted in groups receiving either 40 mg of fluvastatin or placebo.

Patients treated with fluvastatin sodium 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.

CNS Toxicity

CNS effects, as evidenced by decreased activity, ataxia, loss of righting reflex, and ptosis were seen in the following animal studies: the 18-month mouse carcinogenicity study at 50 mg/kg/day, the 6-month dog study at 36 mg/kg/day, the 6-month hamster study at 40 mg/kg/day, and in acute, high-dose studies in rats and hamsters (50 mg/kg), rabbits (300 mg/kg) and mice (1500 mg/kg). CNS toxicity in the acute high-dose studies was characterized (in mice) by conspicuous vacuolation in the ventral white columns of the spinal cord at a dose of 5000 mg/kg and (in rat) by edema with separation of myelinated fibers of the ventral spinal tracts and sciatic nerve at a dose of 1500 mg/kg. CNS toxicity, characterized by periaxonal vacuolation, was observed in the medulla of dogs that died after treatment for 5 weeks with 48 mg/kg/day; this finding was not observed in the remaining dogs when the dose level was lowered to 36 mg/kg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. No CNS lesions have been observed after chronic treatment for up to 2 years with fluvastatin in the mouse (at doses up to 350 mg/kg/day), rat (up to 24 mg/kg/day), or dog (up to 16 mg/kg/day).

Prominent bilateral posterior Y suture lines in the ocular lens were seen in dogs after treatment with 1, 8, and 16 mg/kg/day for 2 years.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year study was performed in rats at dose levels of 6, 9, and 18–24 (escalated after 1 year) mg/kg/day. These treatment levels represented plasma drug levels of approximately 9, 13, and 26–35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and 1 carcinoma of the forestomach at the 24 mg/kg/day dose level was considered to reflect the prolonged hyperplasia induced by direct contact exposure to fluvastatin sodium rather than to a systemic effect of the drug. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded for males treated with 18–24 mg/kg/day. The increased incidence of thyroid follicular cell neoplasm in male rats with fluvastatin sodium appears to be consistent with findings from other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg/day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg/day and in females at 15 mg/kg/day. These treatment levels represented plasma drug levels of approximately 0.05, 2, and 7 times the mean human plasma drug concentration after a 40 mg oral dose.

Continued on next page

Lescol—Cont.

No evidence of mutagenicity was observed in vitro, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of *Salmonella typhimurium* or *Escherichia coli;* malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese Hamster cells; HGPRT V79 Chinese Hamster cells. In addition, there was no evidence of mutagenicity in vivo in either a rat or mouse micronucleus test.
In a study in rats at dose levels for females of 0.6, 2 and 6 mg/kg/day and at dose levels for males of 2, 10 and 20 mg/kg/day, fluvastatin sodium had no adverse effects on the fertility or reproductive performance.
Seminal vesicles and testes were small in hamsters treated for 3 months at 20 mg/kg/day (approximately three times the 40 milligram human daily dose based on surface area, mg/m^2). There was tubular degeneration and aspermatogenesis in testes as well as vesiculitis of seminal vesicles. Vesiculitis of seminal vesicles and edema of the testes were also seen in rats treated for 2 years at 18 mg/kg/day (approximately 4 times the human C_{max} achieved with a 40 milligram daily dose).

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Fluvastatin sodium produced delays in skeletal development in rats at doses of 12 mg/kg/day and in rabbits at doses of 10 mg/kg/day. Malaligned thoracic vertebrae were seen in rats at 36 mg/kg, a dose that produced maternal toxicity. These doses resulted in 2 times (rat at 12 mg/kg) or 5 times (rabbit at 10 mg/kg) the 40 mg human exposure based on mg/m^2 surface area. A study in which female rats were dosed during the third trimester at 12 and 24 mg/kg/day resulted in maternal mortality at or near term and postpartum. In addition, fetal and neonatal lethality were apparent. No effects on the dam or fetus occurred at 2 mg/kg/day. A second study at levels of 2, 6, 12 and 24 mg/kg/day confirmed the findings in the first study with neonatal mortality beginning at 6 mg/kg. A modified Segment III study was performed at dose levels of 12 or 24 mg/kg/day with or without the presence of concurrent supplementation with mevalonic acid, a product of HMG-CoA reductase which is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the maternal and neonatal mortality but did not prevent low body weights in pups at 24 mg/kg on days 0 and 7 postpartum. Therefore, the maternal and neonatal lethality observed with fluvastatin sodium reflect its exaggerated pharmacologic effect during pregnancy. There are no data with fluvastatin sodium in pregnant women. However, rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. **Lescol or Lescol XL should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If a woman becomes pregnant while taking Lescol or Lescol XL, the drug should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers

Based on preclinical data, drug is present in breast milk in a 2:1 ratio (milk:plasma). Because of the potential for serious adverse reactions in nursing infants, nursing women should not take Lescol or Lescol XL *(see CONTRAINDICATIONS).*

Pediatric Use

Safety and effectiveness in individuals less than 18 years old have not been established. Treatment in patients less than 18 years of age is not recommended at this time.

Geriatric Use

The effect of age on the pharmacokinetics of immediate release fluvastatin sodium was evaluated. Results indicate that for the general patient population plasma concentrations of fluvastatin sodium do not vary as a function of age. *(See also CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism.)* Elderly patients (≥65 years of age) demonstrated a greater treatment response in respect to LDL-C, Total-C and LDL/HDL ratio than patients <65 years of age.

ADVERSE REACTIONS

In all clinical studies of Lescol® (fluvastatin sodium), 1.0% (32/2969) of fluvastatin-treated patients were discontinued due to adverse experiences attributed to study drug (mean exposure approximately 16 months ranging in duration from 1 to >36 months). This results in an exposure adjusted rate of 0.8% (32/4051) per patient year in fluvastatin patients in controlled studies compared to an incidence of 1.1% (4/355) in placebo patients. Adverse reactions have usually been of mild to moderate severity.
In controlled clinical studies, 3.9% (36/912) of patients treated with Lescol® XL (fluvastatin sodium) 80 mg discontinued due to adverse events (causality not determined).
Adverse experiences occurring in the Lescol and Lescol XL controlled studies with a frequency >2%, regardless of causality, include the following:

Table 5
Adverse experiences occurring in >2% patients in Lescol and Lescol XL controlled studies

Adverse Event	Lescol[1] (%) (N=2326)	Placebo[1] (%) (N=960)	Lescol XL[2] (%) (N=912)
Integumentary			
Rash	2.3	2.4	1.6
Musculoskeletal			
Back Pain	5.7	6.6	4.7
Myalgia	5.0	4.5	3.8
Arthralgia	4.0	4.1	1.3
Arthritis	2.1	2.0	1.3
Arthropathy	NA	NA	3.2
Respiratory			
Upper Respiratory Tract Infection	16.2	16.5	12.5
Pharyngitis	3.8	3.8	2.4
Rhinitis	4.7	4.9	1.5
Sinusitis	2.6	1.9	3.5
Coughing	2.4	2.9	1.9
Bronchitis	1.8	1.0	2.6
Gastrointestinal			
Dyspepsia	7.9	3.2	3.5
Diarrhea	4.9	4.2	3.3
Abdominal Pain	4.9	3.8	3.7
Nausea	3.2	2.0	2.5
Constipation	3.1	3.3	2.3
Flatulence	2.6	2.5	1.4
Misc. Tooth Disorder	2.1	1.7	1.4
Central Nervous System			
Dizziness	2.2	2.5	1.9
Psychiatric Disorders			
Insomnia	2.7	1.4	0.8
Genitourinary			
Urinary Tract Infection	1.6	1.1	2.7
Miscellaneous			
Headache	8.9	7.8	4.7
Influenza-Like Symptoms	5.1	5.7	7.1
Accidental Trauma	5.1	4.8	4.2
Fatigue	2.7	2.3	1.6
Allergy	2.3	2.2	1.0

[1] Controlled trials with Lescol Capsules (20 and 40 mg daily and 40 mg twice daily)
[2] Controlled trials with Lescol XL 80 mg Tablets

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with fluvastatin sodium therapy.
Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.
Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.
Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.
Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.
Reproductive: gynecomastia, loss of libido, erectile dysfunction.
Eye: progression of cataracts (lens opacities), ophthalmoplegia.
Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Concomitant Therapy

Fluvastatin sodium has been administered concurrently with cholestyramine and nicotinic acid. No adverse reactions unique to the combination or in addition to those previously reported for this class of drugs alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. *(See WARNINGS: Skeletal Muscle.)*

OVERDOSAGE

The approximate oral LD_{50} is greater than 2 g/kg in mice and greater than 0.7 g/kg in rats.
The maximum single oral dose of Lescol® (fluvastatin sodium) capsules received by healthy volunteers was 80 mg. No clinically significant adverse experiences were seen at this dose. The maximum dose administered with an extended-release formulation was 640 mg for two weeks. This dose was not well tolerated and produced a variety of GI complaints and an increase in transaminase values (i.e., SGOT and SGPT).
There has been a single report of 2 children, one 2 years old and the other 3 years of age, either of whom may have possibly ingested fluvastatin sodium. The maximum amount of fluvastatin sodium that could have been ingested was 80 mg (4 × 20 mg capsules). Vomiting was induced by ipecac in both children and no capsules were noted in their emesis. Neither child experienced any adverse symptoms and both recovered from the incident without problems.
Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. The dialyzability of fluvastatin sodium and of its metabolites in humans is not known at present.
Information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®.*

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium) and should continue on this diet during treatment with Lescol or Lescol XL. (See NCEP Treatment Guidelines for details on dietary therapy.)
For patients requiring LDL-C reduction to a goal of ≥25%, the recommended starting dose is 40 mg as one capsule, 80 mg as one Lescol XL tablet administered as a single dose in the evening or 80 mg in divided doses of the 40 mg capsule given twice daily. For patients requiring LDL-C reduction to a goal of <25% a starting dose of 20 mg may be used. The recommended dosing range is 20–80 mg/day. Lescol or Lescol XL may be taken without regard to meals, since there are no apparent differences in the lipid-lowering effects of fluvastatin sodium administered with the evening meal or 4 hours after the evening meal. Since the maximal reductions in LDL-C of a given dose are seen within 4 weeks, periodic lipid determinations should be performed and dosage adjustment made according to the patient's response to therapy and established treatment guidelines. *The therapeutic effect of Lescol or Lescol XL is maintained* with prolonged administration.

Concomitant Therapy

Lipid-lowering effects on total cholesterol and LDL cholesterol are additive when immediate release Lescol is combined with a bile-acid binding resin or niacin. When administering a bile-acid resin (e.g., cholestyramine) and fluvastatin sodium, Lescol should be administered at bedtime, at least 2 hours following the resin to avoid a significant interaction due to drug binding to resin. *(See also ADVERSE REACTIONS: Concomitant Therapy.)*

Dosage in Patients with Renal Insufficiency

Since fluvastatin sodium is cleared hepatically with less than 6% of the administered dose excreted into the urine, dose adjustments for mild to moderate renal impairment are not necessary. Fluvastatin has not been studied at doses greater than 40 mg in patients with severe renal impairment; therefore caution should be exercised when treating such patients at higher doses.

HOW SUPPLIED

Lescol® (fluvastatin sodium) Capsules

20 mg

Brown and light brown imprinted twice with "S" and "20" on one half and "LESCOL" and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.
Bottles of 30 capsules ..... (NDC 0078-0176-15)
Bottles of 100 capsules ..... (NDC 0078-0176-05)

40 mg

Brown and gold imprinted twice with "S" and "40" on one half and "LESCOL" and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.
Bottles of 30 capsules ..... (NDC 0078-0234-15)
Bottles of 100 capsules ..... (NDC 0078-0234-05)

Lescol® XL (fluvastatin sodium) Extended-Release Tablets

80 mg

Yellow, round, slightly biconvex film-coated tablet with beveled edges debossed with "Lescol XL" on one side and "80" on the other.
Bottles of 30 tablets ..... (NDC 0078-0354-15)
Bottle of 100 tablets ..... (NDC 0078-0354-05)

Store and Dispense

Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F). [See USP Controlled Room Temperature]. Dispense in a tight container. Protect from light.

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