PRESCRIBING INFORMATION

[Pr]Lescol*

(fluvastatin sodium) 20 and 40 mg capsules

[Pr]Lescol* XL

(fluvastatin sodium) 80 mg extended release tablets

THERAPEUTIC CLASSIFICATION

Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

LESCOL (fluvastatin sodium) is a fully synthetic HMG-CoA reductase inhibitor and is hydrophilic. Fluvastatin sodium is a racemate of two erythro enantiomers of which one exerts the pharmacological activity.

Mechanism of Action

Fluvastatin sodium 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 ultimate result of these mechanisms is a reduction of the plasma total cholesterol (Total-C) and low density lipoprotein cholesterol (LDL-C) concentrations.

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

of human atherosclerosis and of its complications. Effective treatment of hypercholesterolemia/dyslipidemia in long-term clinical trials has consistently been associated with a reduced risk of CAD.

Pharmacokinetics/Metabolism

Oral Absorption

LESCOL (fluvastatin sodium) 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}: 6 hours) 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). Intrasubject 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 (VDss) 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. Following once daily administration of the 80 mg Lescol XL tablet for 7 days, systemic exposure to fluvastatin is increased (20%-30%) compared to a single dose of the 80 mg LESCOL XL tablet. Terminal half-life of LESCOL XL was about 9 hours as a result of the slow-release formulation.

INDICATIONS AND CLINICAL USE

Therapy with lipid-altering agents should be considered a component of multiple risk factor intervention in those individuals at increased risk for atherosclerosis vascular disease due to hypercholesterolemia. LESCOL/LESCOL XL (fluvastatin sodium) should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other non-pharmacological measures alone has been inadequate.

Hypercholesterolemia and Mixed Hyperlipemia

LESCOL/LESCOL XL (fluvastatin sodium) are indicated as an adjunct to diet (at least equivalent to the Adult Treatment Panel III (ATP III TLC diet)) in the treatment of elevated total cholesterol (Total-C), LDL-C and triglycerides (TG) and Apo B levels in patients with primary hypercholesterolemia and mixed hyperlipidemia (Fredrickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate.

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 < 4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

$$\text{LDL-C (mmol/L)} = \text{Total-C} - \text{HDL-C} - 0.37\ \text{TG}$$

For TG levels > 4.52 mmol/L (>400 mg/dL), 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, as with other HMG-CoA reductase inhibitors, LESCOL is not indicated.

Since the goal of treatment is to lower LDL-C, LDL-C levels should 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.

LESCOL/LESCOL XL have 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).

Secondary Prevention of Cardiovascular Events

In patients with coronary heart diseases who had undergone a percutaneous intervention (PCI) procedures, LESCOL has been shown to delay the occurrence of major adverse cardiac events (MACE), defined as the first occurrence of cardiac death, nonfatal myocardial infarction or re-intervention procedures (see **PHARMACOLOGY-CLINICAL STUDIES**).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication. LESCOL/LESCOL XL (fluvastatin sodium) are contraindicated in patients with active liver disease or unexplained, persistent clinically relevant elevations in serum transaminases (see WARNINGS).

As with other drugs of this class, LESCOL/LESCOL XL are contraindicated during pregnancy and in nursing mothers (see PRECAUTIONS).

WARNINGS

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the same cytochrome P-450 isoenzyme system particularly the CYP3A4. The various HMG-CoA reductase inhibitors differ with respect to the P450 isoenzyme involved in their metabolism. LESCOL/LESCOL XL are predominantly metabolized by the CYP2C9 subclass of the P450 cytochromes and therefore is not expected to interact with drugs known to be CYP 3A4 substrates, such as immunosuppressants, macrolide antibiotics, selective serotonine reuptake inhibitors, azole antifungal agents, or grapefruit juice. It may interact, however, with CYP 2C9

substrates, e.g. nonsteroidal antiinflammatory drugs or oral anticoagulants. These potential interactions may be less clinically relevant due to the overlap between the different CYP 2C isoenzymes. (see WARNINGS - Skeletal Muscle Effects and PRECAUTIONS - Drug Interactions).

For more information, please refer to SELECTED-BIBLIOGRAPHY - Drug Interactions.

Hepatic Effects

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents.

Overall, 25 of 2373 patients (1.1%) treated with LESCOL capsules in worldwide controlled clinical trials developed marked persistent elevations (to more than 3 times the upper limit of normal) in transaminase levels requiring discontinuation of treatment in 14 (0.6%) patients. The incidence of such elevations varied from 0.9% at 20 mg/day to 1.9 % at 80 mg/day.

In all clinical trials (controlled and uncontrolled) with LESCOL capsules, ranging from 28 to 71.2 weeks of exposure, 33 of 2969 (1.1%) patients had persistent transaminase elevations requiring discontinuation of treatment in 19 (0.6%) patients. In the majority of patients, these abnormal biochemical findings were asymptomatic.

In a retrospective pooled analysis of all placebo-controlled studies of at least 6 weeks and up to 130 weeks with LESCOL capsules, all patients with transaminase elevations >3 times the upper limit of normal were evaluated. A total of 1814 patients received daily either 20 mg, 40 mg or 80 mg (40 mg b.i.d.) fluvastatin sodium.

All patients with persistent (two consecutive occasions) transaminase elevations > 3 times the upper limit of normal had abnormal transaminase elevations at either baseline (before initiation of therapy) and/or by 8 weeks after the start of therapy or dose increase.

In a pooled analysis of three 24-week controlled trials in 854 patients, persistent transaminase elevation occurred in 1.9% of patients treated with LESCOL XL 80 mg, and in 13 of 16 patients the abnormality occurred within 12 weeks of initiation of treatment with LESCOL XL 80 mg.

It is recommended that liver function tests be performed at baseline and 8 weeks after initiation of treatment as well as after an increase in the dose. Particular attention should be paid to patients who develop abnormal serum transaminase levels or signs and symptoms of liver disease. In these patients, measurements should be repeated promptly to confirm the finding and then performed more frequently until the abnormality(ies) return to normal .

If the transaminase levels show evidence of progression, particularly if they rise to three times the upper limit of normal and are persistent, the drug should be discontinued.

LESCOL/LESCOL XL should be used with caution in patients who consume substantial quantities of alcohol (> 14 drinks/week) and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LESCOL/LESCOL XL; if such condition develops during therapy, the drug should be discontinued.

Skeletal Muscle Effects

With fluvastatin, myopathy has rarely been reported whereas myositis and rhabdomyolysis have been reported very rarely. Patients should be advised to promptly report unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever. In patients with

unexplained diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of creatine kinase (CK) values, myopathy, myositis or rhabdomyolysis should be considered.

Creatine kinase measurement:

There is no current evidence to require routine monitoring of plasma total creatine kinase levels in asymptomatic patients on statins. If creatine kinase has to be measured it should not be done following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes interpretation difficult.

Before the treatment:

As with all other statins physicians should prescribe fluvastatin with caution in patients with pre-disposing factors for rhabdomyolysis and its complications. A creatine kinase level should be measured before starting fluvastatin treatment in the following situations:

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse
- The necessity of such measurement should be considered in elderly patients (age > 70 years), because they are more susceptible to muscle reactions.

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (> 5 x Upper Levels of Normal [ULN]), levels should be re-measured within 5 to 7 days later to confirm the results. If CK levels are still significantly elevated (> 5 x ULN) at baseline, treatment should not be started.

Whilst on treatment:

If muscular symptoms like pain, weakness or cramps occur in patients receiving fluvastatin, their CK levels should be measured. Treatment should be stopped, if these levels are found to be significantly elevated (> 5 x ULN).

LESCOL/LESCOL XL withdrawal should be considered if muscular symptoms are severe and cause daily discomfort, even if CK levels are not significantly elevated (i.e. 5 x ULN).

Should the symptoms resolve and CK levels return to normal, then reintroduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

An increased risk of myopathy has been reported with HMG CoA reductase inhibitors which are predominantly CYP 3A4 substrates when administered concomitantly with other drugs metabolized by the CYP 3A4 isoenzymes such as immunosuppressive drugs, including cyclosporine, fibrates, macrolide antibiotics, azole antifungal agents, selective serotonine reuptake inhibitors, or niacin at lipid lowering doses.

Since LESCOL/LESCOL XL is predominantly metabolized by the CYP2C9 subclass of the P450 cytochromes and not metabolized to a significant extent by other cytochrome subclasses, including CYP3A4, it is not expected to increase the risks of myopathy when co-administered with other drugs metabolized by the P450 isoenzyme system. The benefits and risks of using HMG-CoA reductase inhibitors concomitantly with immunosuppressive drugs, erythromycin, or other drugs metabolized by the P450 enzyme system, fibrates or lipid-lowering doses of niacin should nevertheless be carefully considered. (See WARNINGS - Pharmacokinetic Interactions and PRECAUTIONS - DRUG INTERACTIONS- Cytochrome P450).

Experience to date with the use of fluvastatin together with cyclosporine consists of 3 pharmacokinetics studies (fluvastatin doses of 20 mg, 40 mg), 17 clinical trials of small-medium size and short-, medium-term duration (fluvastatin doses of 20 mg, 40 mg, 40 mg BID) in renal and heart transplant recipients, and one large prospective placebo-controlled trial in 2,102 renal transplant recipients followed up for 5 to 6 years

(fluvastatin doses of 40 mg and 40 mg BID). In a pharmacokinetic study conducted in 19 stable renal transplant patients receiving cyclosporine A concomitantly with fluvastatin 20 mg/day, the AUC for fluvastatin was increased by 1.9 times. Similarly, in a pharmacokinetic study conducted in 19 stable renal transplant patients on stable cyclosporine A regimen who received fluvastatin extended release 80 mg/day for 1 week, both the AUC and Cmax for fluvastatin were increased by two fold as compared with data from historical controls treated with the same fluvastatin regimen. Published data indicate that the trough concentration of cyclosporine A was not changed (see PHARMACOLOGY, Pharmacokinetics and SELECTED BIBLIOGRAPHY). In heart transplant patients treated with fluvastatin 40 mg/day and cyclosporine A for four weeks, AUC for fluvastatin was increased 3.5 times and 3.1 times in patients than in the age-matched healthy controls on study days 1 and 28, respectively. No correlation between systemic fluvastatin levels and musculoskeletal adverse events or biochemical markers of musculoskeletal damage or renal function impairment have been observed in clinical trials conducted to date.

Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with LESCOL together with niacin at lipid lowering doses.

The use of fibrates alone or in combination with HMG CoA reductase inhibitors has been occasionally associated with myopathy. In short-term studies involving a small number of patients, myopathy was not reported during administration of bezafibrate and LESCOL at doses of 40 mg/day and 60 mg/day. To date, the 80 mg/day dose has not been evaluated with bezafibrate.

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

PRECAUTIONS

GENERAL

Before instituting therapy with LESCOL/LESCOL XL (fluvastatin sodium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight and obese patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). The patient should be advised to inform subsequent physicians of the prior use of LESCOL/LESCOL XL or any other lipid metabolism regulator.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

LESCOL/LESCOL XL (fluvastatin sodium) has not been evaluated in patients with rare homozygous familial hypercholesterolemia. Most HMG-CoA reductase inhibitors are less or not effective in this subgroup of hypercholesterolemic patients (see SELECTED BIBLIOGRAPHY). For heterozygous familial hypercholesterolemia (FH) see PHARMACOLOGY - Clinical studies.

EFFECT ON LIPOPROTEIN(A) [Lp(a)]

In some patients the beneficial effect of lowered total cholesterol and LDL cholesterol levels may be partly blunted by a concomitant increase in the Lp(a) levels. Until further experience is obtained from controlled clinical trials, it is suggested, where feasible, that Lp(a) measurements be carried out in patients placed on therapy with LESCOL/LESCOL XL (see SELECTED BIBLIOGRAPHY).

EFFECT ON CoQ_{10} LEVELS (UBIQUINONE)

A significant decrease in plasma CoQ_{10} levels in patients treated with fluvastatin sodium and other statins has been observed in short-term clinical trials. The clinical significance of a potential long-term statin-induced deficiency of CoQ_{10} has not yet been established. It has been reported that a decrease in myocardial

ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY).

RENAL IMPAIRMENT

Because fluvastatin sodium does not undergo significant renal excretion modification of dosage should not be necessary in patients with mild to moderate renal impairment (creatinine clearance > 30 mL/min).

As there is no experience with LESCOL/LESCOL XL in patients with severe renal insufficiency (creatinine > 260 μmol/L, i.e. creatinine clearance < 30 mL/min), its use cannot be recommended in this patient population.

ENDOCRINE FUNCTION

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

Fluvastatin sodium exhibited no effect upon non-stimulated cortisol levels, FSH (males only) or thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treated groups, but no commensurate elevation in LH occurred. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in an adequate number of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

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.

EFFECT ON LENS

Current data from long-term clinical trials do not indicate an adverse effect of LESCOL/LESCOL XL on the human lens.

PREGNANCY

LESCOL/LESCOL XL are contraindicated during pregnancy (see CONTRAINDICATIONS). Data on the use of LESCOL/LESCOL XL in pregnant women is limited. A few reports have been received of congenital anomalies in infants whose mothers were treated during a critical period of pregnancy with other HMG-CoA reductase inhibitors. During the clinical program, a total of 5 women who were receiving LESCOL capsules became pregnant and were discontinued from the studies. Of these 5 women, 3 gave birth to healthy babies, one experienced an ectopic pregnancy which was attributed to a severely scarred fallopian tube and one spontaneously aborted.

Atherosclerosis is a chronic process and discontinuation of lipid metabolism regulators 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.

LESCOL/LESCOL XL 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 (see CONTRAINDICATIONS).

NURSING MOTHERS

It is not known whether fluvastatin sodium 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 fluvastatin sodium, women receiving LESCOL/LESCOL XL should not breast-feed (see CONTRAINDICATIONS).

PEDIATRIC USE

Limited experience with the use of other HMG-CoA reductase inhibitors is available in children. Safety and effectiveness of LESCOL/LESCOL XL in children have not been established.

GERIATRIC USE

The effect of age on the pharmacokinetics of immediate release fluvastatin sodium capsules was evaluated. Results indicate that for the general patient population plasma concentrations of fluvastatin sodium do not vary either as a function of age or gender. (See also PHARMACOLOGY: Pharmacokinetics/Metabolism.)

HYPERSENSITIVITY REACTION

Rare cases of hypersensitivity reactions, such as rash, urticaria, eczema and other skin reactions (e.g.dermatitis, bullous exanthema), thrombocytopenia, angioedema, face edema, vasculitis and lupus erythematosus syndrome have been reported during post-marketing experience with LESCOL capsules. If hypersensitivity is suspected, LESCOL/LESCOL XL should be discontinued. Patients should be advised to report to their doctors promptly any signs of hypersensitivity such as rash, angioedema, urticaria, photosensitivity, polyarthralgia, fever and malaise.

DRUG INTERACTIONS

Pharmacokinetic and pharmacodynamic studies conducted with drugs in healthy subjects may not detect the possibility of potential drug interactions in some patients due to differences in underlying disease(s), age or renal function (see also Geriatric Use; Renal Impairment; Patients with Severe Hypercholesterolemia).

Concomitant Therapy with other Lipid Metabolism Regulators

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

A drug interactive effect (pharmacokinetic and/or clinical) has been shown for the following drugs in combination with fluvastatin sodium:

Cholestyramine:

The cholesterol-lowering effects of LESCOL/LESCOL XL and the bile acid sequestrant, cholestyramine, are additive.

Administration of immediate release fluvastatin sodium concomitantly 2 to 4 hours after cholestyramine, results in fluvastatin decreases of more than 50% for the fluvastatin AUC and 50-80% for the fluvastatin C_{max}. However,

administration of immediate release fluvastatin sodium 4 hours after cholestyramine resulted in a clinically significant additive effect in reducing Total-C and LDL-C compared with that achieved with either component drug.

Gemfibrozil/Fenofibrate/Niacin:

Myopathy, including rhabdomyolysis, has occurred in patients who were receiving co-administration of HMG-CoA reductase inhibitors with fibric acid derivatives and niacin (in lipid lowering doses), particularly in subjects with pre-existing renal insufficiency (see **WARNINGS:** Skeletal Muscle Effects). LESCOL capsules has been safely administered concomitantly with nicotinic acid, gemfibrozil and bezafibrate in clinical studies. In short-term studies involving a small number of patients, myopathy was not reported during administration of bezafibrate and LESCOL capsules at doses of 40 mg/day and 60 mg/day. To date, the 80 mg/day dose has not been evaluated with bezafibrate.

Other Concomitant Therapy

Cimetidine/Ranitidine/Omeprazole:

Concomitant administration of LESCOL capsules with cimetidine, ranitidine and omeprazole results in a significant increase in the fluvastatin C_{max} (43%, 70% and 50%, respectively) and AUC (24 to 33%), with an 18 to 23% decrease in apparent oral plasma clearance (Cl/F).

Digoxin:

In a crossover study involving 18 patients chronically receiving digoxin, concomitant administration of a single 40 mg dose of LESCOL capsule had no effect on digoxin AUC and small but clinically insignificant increases in the digoxin C_{max} and urinary clearance were noted.

Rifampicin:

Administration of LESCOL capsules to subjects pretreated with rifampicin results in significant reduction in C_{max} (59%) and AUC (51%) of fluvastatin, with a large increase (95%) in plasma clearance.

Antipyrine:

Administration of fluvastatin sodium does not influence the metabolism and excretion of antipyrine, either by induction or inhibition.

Beta-Adrenergic Blocking Drugs:

Concomitant administration of propranolol has no effect on the bioavailability of fluvastatin sodium.

Warfarin and other coumarin derivatives:

In vitro protein binding studies demonstrated no interaction at therapeutic concentrations. In a drug interaction study, the concomitant use of LESCOL capsules and warfarin did not alter the plasma levels and prothrombin times compared to warfarin alone. However, isolated incidences of bleeding episodes and/or increased prothrombin times have been reported very rarely in patients on fluvastatin receiving concomitant warfarin or other coumarin derivatives. It is recommended that prothrombin times are monitored when fluvastatin treatment is initiated, discontinued, or the dosage changed in patients receiving warfarin or other coumarin derivatives.

Cytochrome P450

Fluvastatin is predominantly metabolized by the hepatic microsomal CYP2C9 subclass of the P450 cytochromes. It is not metabolized to a significant extent by other cytochrome subclasses, including CYP3A4. The clearance of drugs which are also CYP2C9 substrates may decrease when co-administered with fluvastatin. However, for those CYP2C9-metabolized drugs which have been studied directly, including diclofenac, tolbutamide, and warfarin, the effect on clearance is small and no clinically significant drug interactions of fluvastatin with other CYP2C9 substrates have been demonstrated. Caution should nevertheless be exercised with concomitant use of drugs metabolized by the CYP2C9 subclass of the P450 cytochromes such as phenytoin, oral anticoagulants (e.g. warfarin), oral hypoglycemic agents (e.g. tolbutamide, chlorpropamide) and nonsteroidal anti-inflammatory drugs (e.g. diclofenac) (see **WARNINGS** - Skeletal Muscle Effects).

Since LESCOL/LESCOL XL are predominantly metabolized by the CYP2C9 subclass of the P450 cytochromes and not metabolized to a significant extent by other cytochrome subclasses, including CYP3A4, it is not expected to increase the risks of drug interactions when combined with drugs or common agents such as grapefruit juice that inhibit this enzyme (immunosuppressants, azole-type antifungal agents, macrolide

antibiotics or antidepressants). (see **WARNINGS** - Pharmacokinetics Interactions - Skeletal Muscle Effects and SELECTED BIBLIOGRAPHY).

Itraconazole and erythromycin

Concomitant administration of fluvastatin with the potent cytochrome P450 (CYP) 3A4 inhibitors itraconazole and erythromycin has minimal effects on the bioavailability of fluvastatin. Given the minimal involvement of this enzyme in the metabolism of fluvastatin, it is expected that other CYP3A4 inhibitors (e.g. ketoconazole, cyclosporin) are unlikely to affect the bioavailability of fluvastatin (see WARNINGS - Skeletal Muscle Effects).

Oral Antidiabetic Agents

For patients receiving oral sulfonylureas (glibenclamide [glyburide], tolbutamide) for the treatment of non-insulin-dependent (type 2) diabetes, addition of fluvastatin does not lead to clinically significant changes in glycemic control.

Phenytoin

The overall magnitude of the changes in phenytoin pharmacokinetics during co-administration with fluvastatin are relatively small and not clinically significant. Thus, routine monitoring of phenytoin plasma levels is sufficient during co-administration with fluvastatin. The minimal effect of phenytoin on fluvastatin pharmacokinetics indicates that dosage adjustment of fluvastatin is not warranted when co-administered with phenytoin.

Patients with severe hypercholesterolemia

Higher dosages (80 mg/day) required for some patients with severe hypercholesterolemia are associated with increased plasma levels of fluvastatin. Caution should be exercised in such patients who are also significantly renally impaired, elderly, or are also concomitantly being administered digoxin, or CYP 450 inhibitors (See WARNINGS - Pharmacokinetic Interactions and Skeletal Muscle Effects and PRECAUTIONS - Drug Interactions).

Although specific interaction studies were not performed with all drugs listed below, in clinical studies, LESCOL capsules was used concomitantly with angiotensin-converting enzyme (ACE) inhibitors, beta blockers,

calcium-channel blockers, oral sulphonylureas, antacids, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence to date of clinically significant interactions.

Immunosuppressive Drugs, Erythromycin:

See **WARNINGS**: Skeletal Muscle Effects.

LABORATORY INTERACTIONS

The HMG-CoA reductase inhibitors may cause elevation of transaminase levels (see WARNINGS). Marked elevations of CK levels to more than 5 x ULN developed in a very small number (0.3-1.0%) of patients on fluvastatin sodium. In the differential diagnosis of chest pain in a patient on LESCOL/LESCOL XL, cardiac and noncardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

In all clinical studies (controlled and uncontrolled) with LESCOL capsules, 1% (32/2969) of LESCOL patients were discontinued due to adverse experiences attributed to study drug (mean exposure of approximately 16 months ranging in duration from one to more than 36 months). This results, in controlled studies, in an exposure adjusted incidence of 0.8 % per patient year in fluvastatin patients compared to an incidence of 1.1% in placebo patients. Adverse events were usually mild and transient.

In controlled phase IIb and phase III clinical studies, 3.9% (51/1318) of patients treated with Lescol XL 80 mg discontinued due to adverse events (causality not determined)

Clinical adverse reactions of positive or uncertain relationship to study medication occurring at a frequency $ 1% in controlled clinical trials with LESCOL capsules and LESCOL XL tablets are shown in the table below.

ADVERSE EVENT	LESCOL[1]			PLACEBO[1]	LESCOL XL[2]
	20 mg OD (N = 1425) %	40 mg OD (N= 1136) %	40 mg BID (N= 369) %	(N = 960) %	80 mg OD (N = 1318) %
GASTROINTESTINAL					
Dyspepsia	4.7	4.8	7.3	2.3	1.4
Constipation	2.8	1.8	2.4	2.5	0.8
Abdominal Pain	2.7	2.1	3.8	2.0	0.9
Flatulence	2.5	1.9	1.6	2.2	0.8
Diarrhea	2.5	1.5	1.6	2.1	1.5
Nausea	2.0	1.6	0.8	1.4	1.4
Eructation	1.4	0.6	0.5	1.1	0.0
MUSCULOSKELETAL					
Myalgia	1.7	1.8	2.7	2.3	1.5
Arthralgia	1.4	1.4	1.4	1.5	0.2
Back pain	1.0	0.8	1.1	1.6	0.4
CENTRAL NERVOUS SYSTEM					
Dizziness	0.9	1.1	0.5	1.8	0.5
Abnormal vision	1.0	0.9	1.1	1.4	0.0
PSYCHIATRIC					
Insomnia	1.9	1.3	0.3	0.9	0.2
RESPIRATORY					
Upper respiratory infection	1.1	0.9	2.4	1.9	0.2
INTEGUMENTARY					
Rash	1.5	0.8	1.9	1.6	0.2
MISCELLANEOUS					
Headache	3.8	2.7	1.9	3.0	0.9
Fatigue	1.8	1.5	0.5	1.8	0.6
Chest pain	0.3	0.9	1.4	0.5	0.2

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

Clinical studies have shown that adverse events observed with LESCOL XL 80 mg used once daily are similar in frequency, nature, and severity to those reported with a 40 mg capsule administered once or twice daily

Other clinical adverse reactions of positive or uncertain relationship to study medication occurring in 0.5% to 1.0% of patients receiving 20-80 mg LESCOL capsules monotherapy in controlled clinical trials (N=2326) are listed below:

Gastro-intestinal: Vomiting, gastritis.

Musculoskeletal: Arthritis.

Central Nervous System: conjunctivitis, paresthesia.

Respiratory: Rhinitis

Integumentary: Pruritus.

Miscellaneous: Leg pain, influenza-like symptoms, allergy.

Post-Marketing Adverse Reactions:

Hypersensitivity Reaction

Rare cases of hypersensitivity reactions, such as rash, urticaria, eczema, and other skin reactions (e.g.dermatitis, bullous exanthema), thrombocytopenia, angioedema, face edema, vasculitis, and lupus erythematosus syndrome have been reported during post-marketing experience.

An apparent hypersensitivity syndrome has also been reported rarely with other HMG-CoA reductase inhibitors and has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocytes sedimentation rate (ESR) increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiform, including Stevens-Johnson syndrome.

Skeletal: Rarely: muscle tenderness, muscle weakness and myopathy. Very Rarely: myositis, rhabdomyolysis. (See **WARNINGS**).

Central and Peripheral nervous System: Very rarely: dysesthesia and hypoesthesia, also know to be associated with the underlying hyperlipidemic disorder.

Liver: Very rarely: hepatitis.

The following effects have been reported with drugs of this class:

Skeletal:

myopathy, rhabdomyolysis (see **WARNINGS**), muscle cramping/pain.

Neurological:

paresthesia, peripheral neuropathy, psychiatric disturbances/anxiety.

Gastrointestinal:

hepatitis, cholestatic jaundice, anorexia, vomiting.

Skin:

alopecia.

Miscellaneous:

Asthenia, sweating, hot flushes.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The maximum single oral dose of LESCOL capsules (fluvastatin sodium) 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., ALT and AST).

There has been a single report of two children, one 2 year old and the other 3 years of age, either of whom may have possibly ingested fluvastatin sodium. The maximum amount of fluvastatin sodium ingested was 80 mg (4 x 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 overdose occur, treatment should be symptomatic and supporting measures should be undertaken as required. The dialysability of LESCOL/LESCOL XL and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

Prior to initiating LESCOL/LESCOL XL (fluvastatin sodium), the patient should be placed on a standard cholesterol-lowering diet (at least equivalent to the Adult Treatment Panel III (ATP III TLC diet)), which should be continued during treatment. If appropriate, a program of weight control and physical exercise should be implemented.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of LESCOL capsule or LESCOL XL tablet if cholesterol levels fall below the targeted range, such as that recommended by current guidelines.

Hypercholesterolemia and Mixed Hyperlipidemia

For patients requiring LDL-C reduction of at least 25%, the recommended starting dose is 40 mg daily of LESCOL capsule taken once daily. If necessary, the dosage of fluvastatin may then be increased to 80 mg of LESCOL XL tablet, taken once daily in the evening, or alternatively, 80 mg of LESCOL capsule, taken in divided doses of 40 mg twice daily.

For patients requiring LDL-C reduction of less than 25%, a starting dose of 20 mg LESCOL capsule taken once daily is recommended.

LESCOL capsule or LESCOL XL tablets may be taken with or without food, but should be so taken consistently.

Since maximal reduction in LDL-C is seen within 4 weeks of administration of a given dose of LESCOL capsule or LESCOL XL tablet, periodic lipid level determination should be performed with dosage adjusted to a maximum of 80 mg of fluvastatin daily, according to patient response.

Severe Hypercholesterolemia

In patients with severe hypercholesterolemia, higher dosages (80 mg/day) may be required (see WARNINGS - Pharmacokinetic Interactions and Skeletal Muscle Effects and PRECAUTIONS - Drug Interactions).

Secondary Prevention of Cardiovascular Events (See Hypercholesterolemia and Mixed Hypercholesterolemia)

During the LESCOL Intervention Prevention Study (LIPS), patients were initiated on fluvastatin treatment at 40 mg twice a day with no titration from a lower dose level. This daily dose was proven to be as well tolerated as placebo.

Therefore, in patients with coronary heart disease who have undergone a percutaneous intervention procedure, the appropriate dose of LESCOL is 40 mg twice a day.

Concomitant Therapy

See PRECAUTIONS - Drug Interactions

Dosage in Patients with Renal Impairment

See PRECAUTIONS - Renal Impairment

Dosage in Patients with Hepatic Impairment

See CONTRAINDICATIONS and WARNINGS - Hepatic Effects

Use in the Elderly

See PRECAUTIONS - Geriatric Use

Use in Children

See PRECAUTIONS - Pediatric Use

PHARMACEUTICAL INFORMATION

Drug Substance

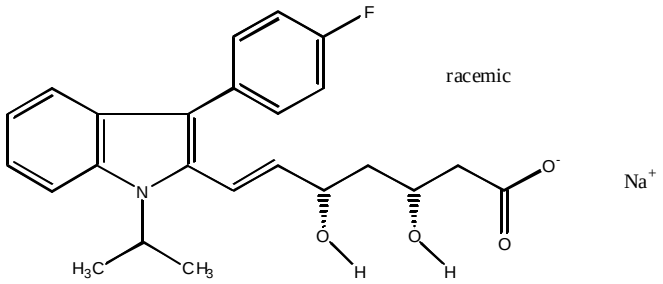
Proper Name: fluvastatin sodium

Chemical Name: [R*,S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy -6-heptenoic acid, monosodium salt

Empirical Formula: C24H25FNO4 Na

Molecular Weight: 433.46

Structural Formula:



Description: Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. The pKa value is approximately 5.5. The pH of a 1% solution (w/v) varies between 8.2–10.0 due to trace amounts of residual sodium hydroxide or carbonates. The octanol/water partition coefficient is 6.8.

COMPOSITION

Active Ingredient: fluvastatin sodium

Capsules:

Inactive Ingredients: sodium bicarbonate, calcium carbonate, microcrystalline cellulose, pregelatinized starch, talc, magnesium stearate. Capsule shell and printing ink: gelatin, iron oxide red, iron oxide yellow, iron oxide black, titanium dioxide, silicon dioxide, sodium laurel sulphate, benzyl alcohol, sodium propionate, edetate calcium disodium, carboxymethyl cellulose sodium, butyl paraben, propyl paraben, methyl paraben, shellac, polyvinylpyrrolidone, ethyl alcohol, isopropyl alcohol, propylene glycol, n-butyl alcohol, sodium hydroxide, ammonium hydroxide.

Extended Release Tablets:

Inactive Ingredients: microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, potassium bicarbonate, povidone, magnesium stearate, iron oxide yellow, titanium dioxide and polyethylene glycol 8000.

STABILITY AND STORAGE RECOMMENDATIONS

LESCOL capsules: Store between 15 and 30°C in a tight container. Protect from light and humidity.

LESCOL XL tablets: Store between 15 and 25°C .

AVAILABILITY OF DOSAGE FORMS

LESCOL Capsules 20 mg - Each brown opaque cap and light brown opaque body gelatin capsule contains 20 mg fluvastatin (from 21.06 mg fluvastatin sodium). Sandoz Triangle printed twice and "20" in white ink on the cap; "Lescol" and product logo in red ink on the body. Available in bottles of 100.

LESCOL Capsules 40 mg - Each brown opaque cap and gold opaque body gelatin capsule contains 40 mg fluvastatin (from 42.12 mg fluvastatin sodium). Sandoz Triangle printed twice and "40" in white ink on the cap; "Lescol" and product logo in red ink on the body. Available in bottles of 100.

LESCOL XL (fluvastatin sodium) Extended Release Tablets 80 mg - Each yellow, round, slightly biconvex film-coated tablet with beveled edges debossed with "Lescol XL" on one side and "80" on the other contains 80 mg fluvastatin (from 84.24 mg fluvastatin sodium). Available in blister packs of 28 tablets.

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