

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lescol<sup>®</sup> XL safely and effectively. See full prescribing information for Lescol<sup>®</sup> XL.

Lescol<sup>®</sup> XL (fluvastatin) extended-release tablets, for oral use  
Initial U.S. Approval: 1993

### RECENT MAJOR CHANGES

Contraindications, Pregnancy and Lactation (4) Removed 11/2023

### INDICATIONS AND USAGE

LESCOL XL is indicated (1):

- To reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in adults with clinically evident coronary heart disease.
- As an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia.
- As an adjunct to diet to reduce LDL-C in adults and pediatric patients 10 years of age and older with heterozygous familial hypercholesterolemia (HeFH) who require 80 mg

### DOSAGE AND ADMINISTRATION

- LESCOL XL can be taken with or without food and may be taken at any time of the day. (2.1)
- Do not break, crush or chew LESCOL XL tablets prior to administration. (2.1)
- Adults:** The recommended starting dose is 80 mg (administered as one 80 mg LESCOL XL once daily). (2.2)  
**Children:** The recommended dose is 80 mg once daily in pediatric patients 10 years of age and older who require 80 mg of fluvastatin. LESCOL XL is not recommended for dosage initiation in pediatric patients because the recommended starting dosage cannot be achieved with the available strength of 80 mg. (2.3)

### DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 80 mg of fluvastatin (3)

### CONTRAINDICATIONS

- Acute liver failure or decompensated cirrhosis (4)
- Hypersensitivity to fluvastatin or any excipient in LESCOL XL (4)

### WARNINGS AND PRECAUTIONS

- Myopathy and Rhabdomyolysis:** Risk factors include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, and concomitant use with certain other drugs. Discontinue LESCOL XL if markedly elevated creatine kinase (CK) levels occur, or myopathy is diagnosed or suspected. Temporarily discontinue LESCOL XL in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis. Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing LESCOL XL dosage. Instruct patients to promptly report

unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. (5.1)

- Immune-Mediated Necrotizing Myopathy (IMNM):** Rare reports of IMNM, an autoimmune myopathy, have been reported with statin use. Discontinue LESCOL XL if IMNM is suspected. (5.2)
- Hepatic Dysfunction:** Increases in serum transaminases have occurred, some persistent. Rare reports of fatal and non-fatal hepatic failure have occurred. Consider testing liver enzyme before initiating therapy and as clinically indicated thereafter. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LESCOL XL (5.3)

### ADVERSE REACTIONS

Most frequent adverse reactions occurring in  $\geq 2.5\%$  of subjects treated with LESCOL XL and more than placebo are: influenza-like symptoms, sinusitis, dyspepsia, urinary tract infection, bronchitis, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Gemfibrozil:** Avoid use with LESCOL XL. (7.1)
- Cyclosporine and Fluconazole:** Avoid use with LESCOL XL. (7.1)
- Fibrates, Lipid-modifying doses ( $\geq 1$  g/day) of Niacin, and Colchicine:** Consider if the benefit of concomitant use with LESCOL XL outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration. (7.1)
- Warfarin:** Obtain an International Normalized Ratio (INR) before starting and frequently enough after initiation or discontinuation to ensure that no significant alteration in INR occurs. Once the INR is stable, monitor INR at regular intervals. (7.2)
- Glyburide:** Monitor blood glucose levels when LESCOL XL is initiated. (7.2)
- Phenytoin:** Monitor plasma phenytoin levels when LESCOL XL treatment is initiated. (7.2)

### USE IN SPECIFIC POPULATIONS

- Pregnancy:** May cause fetal harm (8.1)
- Lactation:** Breastfeeding not recommended during treatment with LESCOL XL (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2023

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

LESCOL XL is indicated:

- To reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in adults with clinically evident coronary heart disease.
- As an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia.
- As an adjunct to diet to reduce LDL-C in adults and pediatric patients 10 years of age and older with heterozygous familial hypercholesterolemia (HeFH) who require 80 mg of fluvastatin daily.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Important Dosage Information

- Take LESCOL XL tablets orally once daily as a single dose, with or without food.
- Do not break, crush, or chew LESCOL XL tablets.
- LESCOL XL is only available as an 80 mg tablet. LESCOL XL cannot be titrated [*see Dosage and Administration (2.2, 2.3)*].
- For patients that require a high-intensity statin or are unable to achieve their LDL-C goal receiving LESCOL XL 80 mg daily, prescribe alternative LDL-C-lowering treatment.
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating LESCOL XL.

#### 2.2 Recommended Dosage in Adult Patients

The recommended dosage for LESCOL XL is 80 mg once daily.

#### 2.3 Recommended Dosage in Pediatric Patients Aged 10 Years of Age and Older with HeFH

LESCOL XL is not recommended for dosage initiation in pediatric patients because the recommended starting dosage cannot be achieved with the available strength of 80 mg. Recommend use of another fluvastatin product to initiate dosing in pediatric patients.

The recommended dosage of LESCOL XL is 80 mg once daily in pediatric patients 10 years of age and older who require 80 mg of fluvastatin.

### 3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 80 mg of fluvastatin: yellow, round, slightly biconvex film-coated tablets with beveled edges debossed with “LESCOL XL” on one side and “80” on the other.

### 4 CONTRAINDICATIONS

LESCOL XL is contraindicated in patients with:

- Acute liver failure or decompensated cirrhosis [*see Warnings and Precautions (5.3)*].
- Hypersensitivity to fluvastatin or any of the excipients in LESCOL XL. Hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens-Johnson syndrome have been reported [*see Adverse Reactions (6.2)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Myopathy and Rhabdomyolysis

LESCOL XL may cause myopathy (muscle pain, tenderness, or weakness associated with elevated creatine kinase [CK]) and rhabdomyolysis. Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis with statins, including LESCOL XL.

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in CK, values to greater than 10 times the upper limit of normal (ULN) was < 0.1% in fluvastatin clinical trials [*see Adverse Reactions (6.1)*].

#### Risk Factors for Myopathy

Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, and concomitant use with certain other drugs (including other lipid-lowering therapies) [*see Drug Interactions (7.1)*].

#### Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

Avoid concomitant use of LESCOL XL with gemfibrozil, cyclosporin, and fluconazole. When used concomitantly with LESCOL XL, lipid modifying doses ( $\geq 1$  g/day) of niacin, fibrates, and colchicine may also increase the risk of myopathy and rhabdomyolysis [see *Drug Interactions (7.1)*].

Discontinue LESCOL XL if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Muscle symptoms and CK increases may resolve if LESCOL XL is discontinued. Temporarily discontinue LESCOL XL in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis, e.g., sepsis, shock, severe hypovolemia, major surgery, trauma, severe metabolic, endocrine, or electrolyte disorders, or uncontrolled epilepsy.

Inform patients of the risk of myopathy and rhabdomyolysis when starting LESCOL XL. Instruct patients to promptly report any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

## 5.2 Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use, including reports of recurrence when the same or a different statin was administered. IMNM is characterized by proximal muscle weakness and elevated serum CK, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody, muscle biopsy showing necrotizing myopathy, and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Discontinue LESCOL XL if IMNM is suspected.

## 5.3 Hepatic Dysfunction

Increases in serum transaminases have been reported with use of LESCOL XL [see *Adverse Reactions (6.1)*]. In most cases, these changes appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or improved on continued therapy or after a brief interruption in therapy. Persistent increases to more than three times the ULN in serum transaminases have occurred in approximately 1.1% of patients receiving fluvastatin in clinical trials. Marked persistent increases of hepatic transaminases have also occurred with fluvastatin. There have been rare post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including LESCOL XL.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury.

Consider liver enzyme testing before LESCOL XL initiation and thereafter, when clinically indicated. LESCOL XL is contraindicated in patients with acute liver failure or decompensated cirrhosis [see *Contraindications (4)*]. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LESCOL XL.

## 5.4 Increases in HbA1c and Fasting Serum Glucose Levels

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including LESCOL XL. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

# 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Myopathy and Rhabdomyolysis [see *Warnings and Precautions (5.1)*]
- Immune-Mediated Necrotizing Myopathy [see *Warnings and Precautions (5.2)*]
- Hepatic Dysfunction [see *Warnings and Precautions (5.3)*]
- Increases in HbA1c and Fasting Serum Glucose Levels [see *Warnings and Precautions (5.4)*]

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the fluvastatin capsule, clinical trials there were 2326 patients treated with fluvastatin (age range, 18 to 75 years, 44% women, 94% White, 4% Black or African American, 2% other ethnicities) with a median treatment duration of 24 weeks. The most common adverse reactions that led to treatment discontinuation and occurred at an incidence greater than placebo were: transaminase increased (0.8%), upper abdominal pain (0.3%), dyspepsia (0.3%), fatigue (0.2%), and diarrhea (0.2%).

In the LESCOL XL clinical trials there were 912 patients treated with LESCOL XL (age range, 21 to 87 years, 52% women, 91% White, 4% Black of African American, 5% other ethnicities) with a median treatment duration of 24 weeks. The most common adverse reactions that led to treatment discontinuation were abdominal pain (0.7%), diarrhea (0.5%), nausea (0.4%), dyspepsia (0.4%) and chest pain (0.3%).

Adverse reactions occurring in the fluvastatin capsules and LESCOL XL controlled trials with a frequency  $\geq 2\%$  included the following:

**Table 1. Adverse Reactions Reported in  $\geq 2\%$  in Patients Treated with Fluvastatin Capsules/LESCOL XL and at an Incidence Greater Than Placebo in Placebo-Controlled Trials Pooled Dosages**

<b>Adverse reaction</b>	<b>Placebo<sup>a</sup> N = 960 (%)</b>	<b>Fluvastatin capsules<sup>a</sup> N = 2326 (%)</b>	<b>LESCOL XL<sup>b</sup> N = 912 (%)</b>
Influenza-like symptoms	5.7	5.1	7.1
Headache	7.8	8.9	4.7
Myalgia	4.5	5.0	3.8
Abdominal pain	3.8	4.9	3.7
Dyspepsia	3.2	7.9	3.5
Sinusitis	1.9	2.6	3.5
Diarrhea	4.2	4.9	3.3
Arthropathy	NA	NA	3.2
Urinary tract infection	1.1	1.6	2.7
Nausea	2.0	3.2	2.5
Bronchitis	1.0	1.8	2.6
Fatigue	2.3	2.7	1.6
Flatulence	2.5	2.6	1.4
Arthritis	2.0	2.1	1.3
Allergy	2.2	2.3	1.0
Insomnia	1.4	2.7	0.8
<sup>a</sup> Controlled trials with fluvastatin capsules (20 mg and 40 mg daily and 40 mg twice daily) compared to placebo.			
<sup>b</sup> Controlled trials with LESCOL XL 80 mg Tablets as compared to fluvastatin capsules.			

In the LESCOL Intervention Prevention Study (LIPS), the effect of LESCOL (fluvastatin capsules) 40 mg, administered twice daily on the risk of recurrent cardiac events was assessed in 1677 patients with coronary heart disease who had undergone a percutaneous coronary intervention. This was a multicenter, randomized, double-blind, placebo-controlled trial, patients were treated with dietary/lifestyle counseling and either fluvastatin capsules 40 mg (n = 844) or placebo (n = 833) given twice daily for a median of 3.9 years [see *Clinical Studies (14.3)*]. Table 2. Adverse Reactions Reported in  $\geq 2\%$  in Patients Treated with Fluvastatin Capsules/LESCOL XL and at an Incidence Greater Than Placebo in the LIPS Trial

**Table 2. Adverse Reactions Reported in  $\geq 2\%$  in Patients Treated with Fluvastatin Capsules/LESCOL XL and at an Incidence Greater Than Placebo in the LIPS Trial**

Adverse reaction	Placebo N = 818 (%)	Fluvastatin Capsules 40 mg twice daily N = 822 (%)
Abdominal pain upper	4.5	6.3
Hypertension	4.2	5.8
Fatigue	3.8	4.7
Dyspepsia	4.0	4.5
Edema peripheral	2.9	4.4
Pain in extremity	2.7	4.1
Dizziness	3.5	3.9
Constipation	2.1	3.3
Nasopharyngitis	2.1	2.8
Dyspnea exertional	2.4	2.8
Gastric disorder	2.1	2.7
Nausea	2.3	2.7
Atrial fibrillation	2.0	2.4
Syncope	2.2	2.4
Bronchitis	2.0	2.3
Intermittent claudication	2.1	2.3
Myalgia	1.6	2.2
Arthralgia	1.8	2.1

#### Elevations in Liver Enzyme Tests

Approximately 1.1% of patients treated with fluvastatin capsules in clinical trials developed dose-related, persistent elevations of serum transaminase levels to more than 3 times the ULN. 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 ULN on two consecutive weekly measurements) occurred in 0.2%, 1.5%, and 2.7% of patients treated with daily doses of 20, 40, and 80 mg (titrated to 40 mg twice daily) fluvastatin capsules, respectively. Ninety-one percent of the cases of persistent ALT/AST increased 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 24-week controlled trials, persistent transaminase elevation occurred in 1.9%, 1.8%, and 4.9% of patients treated with LESCOL XL 80 mg, fluvastatin capsules 40 mg and fluvastatin capsules 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.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of fluvastatin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Musculoskeletal:* Muscle cramps, myopathy, rhabdomyolysis, arthralgias, muscle spasms, muscle weakness, myositis. There have been rare reports of IMNM associated with statin use [see *Warnings and Precautions (5.2)*].

*Neurological:* Dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, paresthesia, hypoesthesia, dysesthesia, peripheral neuropathy, peripheral nerve palsy. There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with the use of all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks). There have been rare reports of new-onset or exacerbation of myasthenia gravis, including ocular myasthenia, and reports of recurrence when the same or a different statin was administered.

*Psychiatric:* Anxiety, depression, psychic disturbances

*Respiratory:* Interstitial lung disease

*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 (erythrocyte sedimentation rate) increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity reaction, 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, cirrhosis, fulminant hepatic necrosis, hepatoma, anorexia, vomiting, fatal and non-fatal hepatic failure.

*Skin:* Rash, dermatitis, including bullous dermatitis, eczema, alopecia, pruritus, lichen planus, a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails).

*Reproductive:* Gynecomastia, loss of libido, erectile dysfunction.

*Eye:* Progression of cataracts (lens opacities), ophthalmoplegia.

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

## 7 DRUG INTERACTIONS

### 7.1 Drug Interactions That Increase the Risk of Myopathy and Rhabdomyolysis with LESCOL XL

Table 3 includes a list of drugs that increase the risk of myopathy and rhabdomyolysis when used concomitantly with fluvastatin and instructions for preventing or managing them [see *Warnings and Precautions (5.1)*, *Clinical Pharmacology (12.3)*].

**Table 3. Drug Interactions That Increase the Risk of Myopathy and Rhabdomyolysis with LESCOL XL**

<b>Gemfibrozil</b>	
Clinical impact	There is an increased risk of myopathy/rhabdomyolysis when LESCOL XL is administered with gemfibrozil
Intervention	Avoid concomitant use of gemfibrozil with LESCOL XL.
<b>Cyclosporine</b>	
Clinical impact	Cyclosporine coadministration increases fluvastatin exposure. The risk of myopathy and rhabdomyolysis may be increased with concomitant use of cyclosporine with LESCOL XL.
Intervention	Avoid concomitant use of cyclosporine with LESCOL XL.
<b>Fluconazole</b>	

Clinical impact	Fluconazole coadministration increases fluvastatin exposure. The risk of myopathy and rhabdomyolysis may be increased with concomitant use of fluconazole with LESCOL XL.
Intervention	Avoid concomitant use of fluconazole with LESCOL XL.
<b>Niacin</b>	
Clinical impact	Risk of myopathy and rhabdomyolysis may be enhanced with concomitant use with lipid-modifying doses ( $\geq 1$ g/day) of niacin with LESCOL XL.
Intervention	Consider if the benefit of using lipid-modifying doses ( $\geq 1$ g/day) of niacin concomitantly with LESCOL XL outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration.
<b>Fibrates</b>	
Clinical impact	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis may be increased with concomitant use of fibrates with LESCOL XL.
Intervention	Consider if the benefit of using fibrates concomitantly with LESCOL XL outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration.
<b>Colchicine</b>	
Clinical impact	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with fluvastatin.
Intervention	Consider if the benefit of using colchicine concomitantly with LESCOL XL outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration.

## 7.2 LESCOL XL Effects on Other Drugs

Table 4 presents LESCOL XL's effect on other drugs and instructions for preventing or managing them.

**Table 4. LESCOL XL Effects on Other Drugs**

<b>Warfarin</b>	
Clinical impact	There are postmarketing reports of clinically evident bleeding and/or increased INR in patients taking concomitant statins and warfarin.
Intervention	In patients taking warfarin, obtain an INR before starting LESCOL XL and frequently enough after initiation or discontinuation to ensure that no significant alteration in INR occurs. Once the INR is stable, monitor INR at regularly recommended intervals.
<b>Glyburide</b>	
Clinical impact	Concomitant administration of fluvastatin and glyburide increased glyburide exposures [see <i>Clinical Pharmacology</i> (12.3)].
Intervention	Monitor blood glucose levels when LESCOL XL is initiated.
<b>Phenytoin</b>	
Clinical impact	Concomitant administration of fluvastatin and phenytoin increased phenytoin exposures [see <i>Clinical Pharmacology</i> (12.3)].
Intervention	Monitor plasma phenytoin levels when LESCOL XL is initiated.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Discontinue LESCOL XL when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient. LESCOL XL decreases synthesis of cholesterol and possibly other biologically active substances derived from cholesterol; therefore, LESCOL XL may cause fetal harm when administered to pregnant patients based on the mechanism of action [see *Clinical Pharmacology (12.1)*]. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. 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 hyperlipidemia for most patients.

Available data from case series and prospective and retrospective observational cohort studies over decades of use with statins in pregnant women have not identified a drug-associated risk of major congenital malformations. Published data from prospective and retrospective observational cohort studies with LESCOL XL use in pregnant women are insufficient to determine if there is a drug-associated risk of miscarriage (see *Data*).

In animal reproduction studies, no adverse developmental effects were observed in pregnant rats or rabbits orally administered fluvastatin during the period of organogenesis at doses that resulted in 2 and 5 times, respectively, the human exposure at the maximum recommended human dosage of 40 mg/day, based on body surface area (mg/m<sup>2</sup>) (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### Data

##### *Human Data*

A Medicaid cohort linkage study of 1152 statin-exposed pregnant women compared to 886,996 controls did not find a significant teratogenic effect from maternal use of statins in the first trimester of pregnancy, after adjusting for potential confounders, including maternal age, diabetes mellitus, hypertension, obesity, and alcohol and tobacco use using propensity score-based methods. The relative risk of congenital malformations between the group with statin use and the group with no statin use in the first trimester was 1.07 (95% CI: 0.85 to 1.37) after controlling for confounders, particularly preexisting diabetes mellitus. There were also no statistically significant increases in any of the organ-specific malformations assessed after accounting for confounders. In the majority of pregnancies, statin treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. Study limitations include reliance on physician coding to define the presence of a malformation, lack of control for certain confounders such as body mass index, use of prescription dispensing as verification for the use of a statin, and lack of information on non-live births.

##### *Animal Data*

Fluvastatin sodium given to rats during organogenesis at doses of 12 mg/kg/day and in rabbits at doses of 10 mg/kg/day produced delays in skeletal development. 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<sup>2</sup> surface area. Malaligned thoracic vertebrae were seen in rats at 36 mg/kg, a dose that produced significant maternal toxicity. A study in which female rats were given fluvastatin 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. Rats were given fluvastatin from Gestation Day 15 to Lactation Day 21 at doses 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.

## 8.2 Lactation

### Risk Summary

There is no information about the presence of fluvastatin in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production. However, it has been shown that another drug in this class passes into human milk. Studies in rats have shown that fluvastatin and/or its metabolites are present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk (*see Data*). Statins, including LESCOL XL, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol and may cause harm to the breastfed infant.

Because of the potential for serious adverse reactions in a breastfed infant, based on the mechanism of action, advise patients that breastfeeding is not recommended during treatment with LESCOL XL [*see Use in Specific Populations (8.1), Clinical Pharmacology (12.1)*].

### Data

Following a single oral administration of 1 mg/kg of radioactive fluvastatin to lactating rats, the concentration of total radioactivity was determined. Fluvastatin and/or its metabolites were measured in the breast milk at a 2:1 ratio (milk:plasma).

## 8.4 Pediatric Use

The safety and effectiveness of LESCOL XL as an adjunct to diet to reduce LDL-C have been established in pediatric patients 10 years of age and older with HeFH. Use of LESCOL XL for this indication is based on open-label, uncontrolled clinical trials in 114 pediatric patients 9 years of age and older with HeFH. In these limited uncontrolled studies, there was no significant effect on growth or sexual maturation in the males or females, or on menstrual cycle length in females.

The safety and effectiveness of LESCOL XL have not been established in pediatric patients younger than 10 years of age with HeFH or in pediatric patients with other types of hyperlipidemia (other than HeFH).

## 8.5 Geriatric Use

Fluvastatin exposures were not significantly different between the nonelderly and elderly populations (age  $\geq$  65 years) [*see Clinical Pharmacology (12.3)*].

Advanced age ( $\geq$  65 years) is a risk factor for LESCOL XL-associated myopathy and rhabdomyolysis. Dose selection for an elderly patient should be cautious, recognizing the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of myopathy. Monitor geriatric patients receiving LESCOL XL for the increased risk of myopathy [*see Warnings and Precautions (5.1)*].

## 8.6 Renal Impairment

Renal impairment is a risk factor for myopathy and rhabdomyolysis. 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, use LESCOL XL with caution in patients with severe renal impairment. Monitor all patients with renal impairment for development of myopathy [*see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)*].

## 8.7 Hepatic Impairment

LESCOL XL is contraindicated in patients with acute liver failure or decompensated cirrhosis [*see Contraindications (4), Warnings and Precautions (5.3)*].

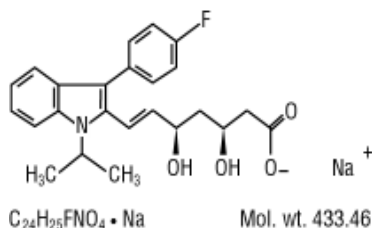
## 10 OVERDOSAGE

No specific antidotes for LESCOL XL are known. In the event of an overdose of LESCOL XL, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

## 11 DESCRIPTION

Fluvastatin sodium inhibits 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<sub>24</sub>H<sub>25</sub>FNO<sub>4</sub>•Na, its molecular weight is 433.46 g/mol and its structural formula is:



Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. LESCOL XL is supplied as extended-release tablets containing 84.24 mg of fluvastatin sodium, equivalent to 80 mg of fluvastatin, for oral use. LESCOL XL tablets contain the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, potassium bicarbonate, povidone, titanium dioxide, and yellow iron oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Fluvastatin is a competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of cholesterol.

### 12.2 Pharmacodynamics

Inhibition of HMG-CoA reductase by fluvastatin accelerates the expression of LDL-receptors, followed by the uptake of LDL-C from blood to the liver, leading to a decrease in plasma LDL-C and total cholesterol. Sustained inhibition of cholesterol synthesis in the liver also decreases levels of very-low-density lipoproteins. The maximum LDL-C reduction of LESCOL XL is usually achieved by 4 weeks and is maintained after that.

### 12.3 Pharmacokinetics

#### Absorption

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% to 66%) compared to that of the fluvastatin 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%. However, the maximum concentration of LESCOL XL seen after a high-fat meal is less than the peak concentration following a single dose or twice daily dose of the 40 mg fluvastatin capsule.

#### Distribution

Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution ( $VD_{ss}$ ) is estimated at 0.35 L/kg. At therapeutic concentrations, the protein binding of fluvastatin is not affected by warfarin, salicylic acid and glyburide.

#### Elimination

##### *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. Fluvastatin has two enantiomers. Both enantiomers of fluvastatin are metabolized in a similar manner.

In vitro data indicate that fluvastatin metabolism involves multiple Cytochrome P450 (CYP) isozymes. CYP2C9 isoenzyme is primarily involved in the metabolism of fluvastatin (approximately 75%), while CYP2C8 and CYP3A4 isoenzymes are involved to a much less extent, i.e., approximately 5% and approximately 20%, respectively.

##### *Excretion*

Following oral administration, fluvastatin is primarily (about 90%) excreted in the feces as metabolites, with less than 2% present as unchanged drug. Approximately 5% of a radiolabeled oral dose were recovered in urine. The elimination half-life ( $t_{1/2}$ ) of fluvastatin is approximately 3 hours.

### Specific Populations

#### *Geriatric Patients*

Plasma levels of fluvastatin are not significantly different in patients age > 65 years compared to patients age 21 to 49 years.

#### *Gender*

In a study evaluating the effect of age and gender on fluvastatin pharmacokinetics, there were no significant differences in fluvastatin exposures between males and females, except between younger females and younger males (both ages 21-49 years), where there was an approximate 30% increase in area under the curve (AUC) in females. Adjusting for body weight decreases the magnitude of the differences seen. For LESCOL XL, the AUC increases 67% and 77% for women compared to men under fasted and high- fat meal fed conditions, respectively.

#### *Pediatric Patients*

Pharmacokinetic data in the pediatric population are not available.

#### *Patients with Renal Impairment*

In patients with moderate to severe renal impairment (CLCr 10-40 mL/min), AUC and  $C_{max}$  increased approximately 1.2-fold after administration of a single dose of 40 mg fluvastatin compared to healthy volunteers. In patients with end-stage renal disease on hemodialysis, the AUC increased by approximately 1.5-fold. LESCOL XL was not evaluated in patients with renal impairment [see *Use in Specific Populations (8.6)*]. However, systemic exposures after administration of LESCOL XL are lower than after the 40 mg immediate release capsule.

#### *Patients with Hepatic Impairment*

In patients with hepatic impairment due to liver cirrhosis, fluvastatin AUC and  $C_{max}$  increased approximately 2.5-fold compared to healthy subjects after administration of a single 40 mg dose [see *Use in Specific Populations (8.7)*]. The enantiomer ratios of the two isomers of fluvastatin in hepatic impairment patients were comparable to those observed in healthy subjects.

### Drug Interaction Studies

Data from drug-drug interactions studies involving coadministration of gemfibrozil, niacin, itraconazole, erythromycin, tolbutamide or clopidogrel indicate that the PK disposition of fluvastatin is not significantly altered when fluvastatin is coadministered with any of these drugs.

The below listed drug interaction information is derived from studies using fluvastatin capsules. Similar studies have not been conducted using the LESCOL XL tablet.

**Table 5. Effect of Coadministered Drugs on Fluvastatin Systemic Exposure**

Coadministered drug and dosing regimen	Fluvastatin		
	Dose (mg) <sup>a</sup>	Change in AUC <sup>b</sup>	Change in $C_{max}$ <sup>b</sup>
Cyclosporine – stable dose (twice daily) <sup>c</sup>	20 mg once daily for 14 weeks	↑90%	↑30%
Fluconazole 400 mg once daily 1,200 mg twice daily 2 to 4 <sup>c</sup>	40 mg once daily	↑84%	↑44%
Cholestyramine 8 g once daily	20 mg once daily administered 4 hrs after a meal plus cholestyramine	↓51%	↓83%
Rifampicin 600 mg once daily for 6 days	20 mg once daily	↓53%	↓42%

Cimetidine 400 mg twice daily for 5 days, once daily on Day 6	20 mg once daily	↑30%	↑40%
Ranitidine 150 mg twice daily for 5 days, once daily on Day 6	20 mg once daily	↑10%	↑50%
Omeprazole 40 mg once daily for 6 days	20 mg once daily	↑20%	↑37%
Phenytoin 300 mg once daily	40 mg twice daily for 5 days	↑40%	↑27%
Propranolol 40 mg twice daily for 3.5 days	40 mg once daily	↓5%	No change
Digoxin 0.1 to 0.5 mg once daily for 3 weeks	40 mg once daily	No change	↑11%
Diclofenac 25 mg once daily	40 mg once daily for 8 days	↑50%	↑80%
Glyburide 5 mg to 20 mg once daily for 22 days	40 mg twice daily for 14 days	↑51%	↑44%
Warfarin 30 mg once daily	40 mg once daily for 8 days	↑30%	↑67%
Clopidogrel 300 mg loading dose on Day 10, 75 mg once daily on Days 11 to 19	80 mg XL once daily for 19 days	↓2%	↑27%

Abbreviation: AUC, area under the curve.

<sup>a</sup>Single dose unless otherwise noted.

<sup>b</sup>Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.

<sup>c</sup>Considered clinically significant [see *Dosage and Administration (2.4)*, *Drug Interactions (7.1)*].

Data from drug-drug interaction studies involving fluvastatin and coadministration of either gemfibrozil, tolbutamide or losartan indicate that the PK disposition of either gemfibrozil, tolbutamide or losartan is not significantly altered when coadministered with fluvastatin.

**Table 6. Effect of Fluvastatin Coadministration on Systemic Exposure of Other Drugs**

Fluvastatin dosage regimen	Coadministered drug		
	Name and dose (mg) <sup>a</sup>	Change in AUC <sup>b</sup>	Change in C <sub>max</sub> <sup>b</sup>
40 mg once daily for 5 days	Phenytoin 300 mg once daily <sup>c</sup>	↑20%	↑5%
40 mg twice daily for 21 days	Glyburide 5 to 20 mg once daily for 22 days <sup>c</sup>	↑70%	↑50%
40 mg once daily for 8 days	Diclofenac 25 mg once daily	↑25%	↑60%
40 mg once daily for 8 days	Warfarin 30 mg once daily	S-warfarin: ↑7% R-warfarin: no change	S-warfarin: ↑10% R-warfarin: ↑6%

Abbreviation: AUC, area under the curve.

<sup>a</sup>Single dose unless otherwise noted.

<sup>b</sup>Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.

<sup>c</sup>Considered clinically significant [see *Drug Interactions (7.2)*].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at doses of 6, 9, and 18 to 24 (escalated after 1 year) mg/kg/day, there was an increased incidence of thyroid follicular cell adenomas and carcinomas in males treated with 18 to 4 mg/kg/day. Additionally, a low incidence of forestomach squamous papillomas and one forestomach carcinoma were observed at the 18 to 24 mg/kg/day dose, likely due to prolonged direct contact exposure rather than a systemic effect. This dose represents a plasma AUC exposure approximately 26 to 35 times the mean human plasma drug concentration after a 40 mg oral dose.

A carcinogenicity study conducted in mice at doses of 0.3, 15 and 30 mg/kg/day revealed a statistically significant increase in forestomach squamous cell papillomas in females at 15 mg/kg/day and in males and females at 30 mg/kg/day. These doses represent plasma AUC exposures approximately 2 and 7 times the mean human plasma drug concentration after a 40 mg oral dose.

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 genotoxicity in vivo in either a rat chromosome aberration study or mouse micronucleus test.

In a fertility study in rats with daily doses up to 6 mg/kg/day for females and 20 mg/kg/day for males, fluvastatin sodium had no adverse effects on the fertility or reproductive performance.

Hamsters treated for 3 months at 20 mg/kg/day (approximately three times the 40 mg human daily dose based on body surface area, mg/m<sup>2</sup>) showed small seminal vesicles and testes, along with tubular degeneration and aspermatogenesis in the testes and vesiculitis in the seminal vesicles. Rats treated for 2 years at 18 mg/kg/day (approximately four times human exposure based on body surface area) exhibited vesiculitis in the seminal vesicles and edema in the testes.

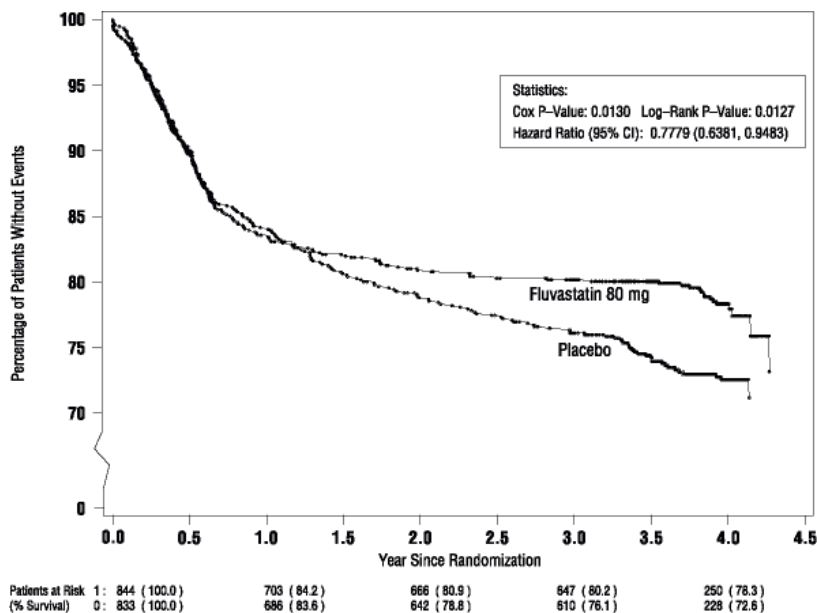
## 14 CLINICAL STUDIES

### Secondary Prevention of Cardiovascular Disease

In the LESCOL Intervention Prevention Study (LIPS), the effect of fluvastatin capsules 40 mg administered twice daily on the risk of recurrent cardiac events (time to first occurrence of cardiac death, nonfatal myocardial infarction, or revascularization) was assessed in 1677 adult patients with CHD who had undergone a percutaneous coronary intervention (PCI) procedure (mean time from PCI to randomization = 3 days). In this multicenter, randomized, double-blind, placebo-controlled trial, patients were treated with dietary/lifestyle counseling and either fluvastatin 40 mg (n = 844) or placebo (n = 833) given twice daily for a median of 3.9 years. The study population was 84% male, 98% White, with 37% > 65 years of age. Mean baseline lipid concentrations were: total cholesterol 201 mg/dL, LDL-C 132 mg/dL, triglycerides 70 mg/dL, and HDL-C 39 mg/dL.

Fluvastatin capsules significantly reduced the risk of recurrent cardiac events (Figure 1) by 22% (p = 0.013, 181 patients in the fluvastatin capsules group versus 222 patients in the placebo group). Revascularization procedures comprised the majority of the initial recurrent cardiac events (143 revascularization procedures in the fluvastatin capsules group and 171 in the placebo group). Consistent trends in risk reduction were observed in patients > 65 years of age.

**Figure 1. Primary Endpoint – Recurrent Cardiac Events (Cardiac Death, Nonfatal MI or Revascularization Procedure) (ITT Population)**



Outcome data for the LESCOL Intervention Prevention Study are shown in Figure 2. After exclusion of revascularization procedures (CABG and repeat PCI) occurring within the first 6 months of the initial procedure involving the originally instrumental site, treatment with fluvastatin capsules was associated with a 32% ( $p = 0.002$ ) reduction in risk of late revascularization procedures (CABG or PCI occurring at the original site > 6 months after the initial procedure, or at another site).

**Figure 2. LESCOL Intervention Prevention Study— Primary and Secondary Endpoints**

Event	Incidence*		Risk Reduction % (95% CI)	Cox Risk Ratio (95% CI)
	Lescol n (%) N=844	Placebo n (%) N=833		
<b>Primary Endpoint, Recurrent Cardiac</b>				
Events (as a first event)	181 (21.4)	222 (26.7)	22 (5, 36)	
Cardiac Death	8 (0.9)	18 (2.2)	—	
Nonfatal MI	30 (3.4)	33 (4.0)	—	
Revascularization	143 (16.2)	171 (20.5)	—	
<b>Secondary Endpoints (any time during the study)</b>				
Cardiac Death	13 (1.5)	24 (2.9)	47 (-5, 79)	
Nonfatal MI	30 (3.6)	38 (4.6)	22 (-27, 52)	
Revascularization	167 (19.8)	193 (23.2)	17 (-2, 33)	
Late Revascularization**	111 (13.2)	151 (18.1)	32 (13, 47)	
Noncardiac Death	23 (2.7)	25 (3.0)	16 (-49, 52)	

\*Number of patients with events

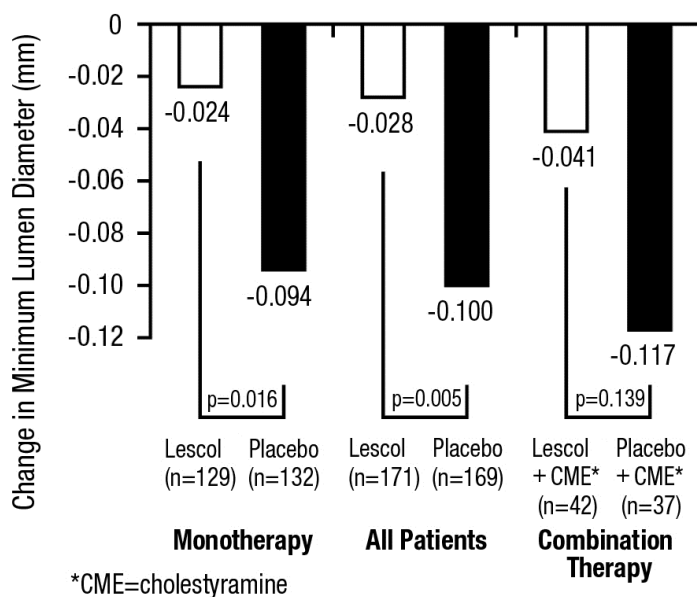
\*\*Excludes revascularization procedures of the target lesion within the first 6 months of the initial procedure

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of fluvastatin capsule therapy on coronary atherosclerosis was assessed by quantitative coronary angiography (QCA) in patients with CAD and mild to moderate

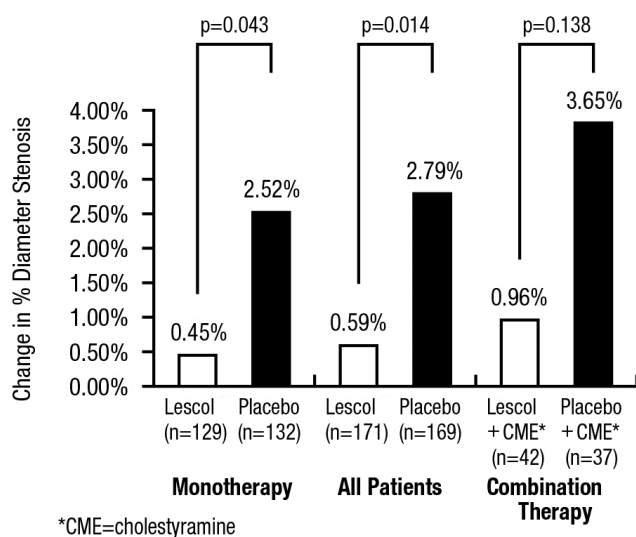
hypercholesterolemia (baseline LDL-C range 115 to 190 mg/dL). In this randomized double-blind, placebo-controlled trial, 429 patients were treated with conventional measures (Step 1, AHA Diet) and either fluvastatin 40 mg/day or placebo. In order to provide treatment to patients receiving placebo with LDL-C levels  $\geq 160$  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  $\geq 160$  mg/dL, which 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.

Compared to placebo, fluvastatin capsules significantly slowed the progression of coronary atherosclerosis as measured by within-patient per-lesion change in minimum lumen diameter (MLD), the primary endpoint (Figure 3 below), percent diameter stenosis (Figure 4), and the formation of new lesions (13% of all fluvastatin patients versus 22% of all placebo patients). A significant difference in favor of fluvastatin capsules 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 3. Change in Minimum Lumen Diameter (mm)**



**Figure 4. Change in % Diameter Stenosis**



Primary Hyperlipidemia in Adults

LESCOL XL has been studied in five controlled trials of adult patients with primary hyperlipidemia and mixed dyslipidemia. LESCOL XL was administered to over 900 patients in trials from 4 to 26 weeks in duration. In the three

largest of these trials, LESCOL XL given as a single daily dose of 80 mg significantly reduced Total-C, LDL-C, TG, and Apo B (Table 5).

In patients with primary mixed dyslipidemia as defined by baseline plasma TG levels  $\geq 200$  mg/dL and  $< 400$  mg/dL, treatment with LESCOL XL produced significant decreases in Total-C, LDL-C, TG, and Apo B (see Table 7).

**Table 7. Median Percent Change in Lipid Levels in Adult Patients with Primary Hyperlipidemia and Mixed Dyslipidemia From Baseline to Week 24 Endpoint All Active Controlled Trials (LESCOL XL)**

Dose	Total Chol		TG		LDL		Apo B		HDL	
	N	% $\Delta$	N	% $\Delta$	N	% $\Delta$	N	% $\Delta$	N	% $\Delta$
<b>All Patients</b>										
LESCOL XL 80 mg <sup>a</sup>	750	-25	750	-19	748	-35	745	-27	750	+7
<b>Baseline TG <math>\geq 200</math> mg/dL</b>										
LESCOL XL 80 mg <sup>a</sup>	239	-25	239	-25	237	-33	235	-27	239	+11

<sup>a</sup>Data for LESCOL XL 80 mg tablet from three 24-week controlled trials.

#### HeFH in Pediatric Patients Aged 10 Years and Older

Fluvastatin capsules were studied in two open-label, uncontrolled, dose-titration trials. The first trial enrolled 29 pre-pubertal males, 9 to 12 years of age, who had an LDL-C level  $> 90^{\text{th}}$  percentile for age and one parent with primary hypercholesterolemia and either a family history of premature ischemic heart disease or tendon xanthomas. The mean baseline LDL-C was 226 mg/dL (range, 137 to 354 mg/dL). All patients were started on fluvastatin capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (40 mg twice daily) to achieve an LDL-C goal between 97 to 124 mg/dL. Endpoint analyses were performed at Year 2. Fluvastatin decreased plasma levels of Total-C and LDL-C by 21% and 27%, respectively. The mean achieved LDL-C was 161 mg/dL (range, 74 to 336 mg/dL).

The second trial enrolled 85 male and female patients, 10 to 16 years of age, who had an LDL-C  $> 190$  mg/dL or LDL-C  $> 160$  mg/dL and one or more risk factors for coronary heart disease, or LDL-C  $> 160$  mg/dL and a proven LDL-receptor defect. The mean baseline LDL-C was 225 mg/dL (range, 148 to 343 mg/dL). All patients were started on fluvastatin capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (LESCOL XL tablet) to achieve an LDL-C goal of  $< 130$  mg/dL. Endpoint analyses were performed at Week 114. Fluvastatin decreased plasma levels of Total-C and LDL-C by 22% and 28%, respectively. The mean achieved LDL-C was 159 mg/dL (range, 90 to 295 mg/dL).

The majority of patients in both trials (83% in the first trial and 89% in the second trial) were titrated to the maximum daily dose of 80 mg.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### How Supplied

LESCOL XL extended-release tablets supplied as:

Strength	How supplied	NDC	Tablet description
80 mg of fluvastatin	bottles of 30	0078-0354-15	Yellow, round, slightly biconvex film-coated tablet with beveled edges debossed with “LESCOL XL” on one side and “80” on the other
	bottles of 100	0078-0354-05	

### Store and Dispense

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container. Protect from light.

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### Myopathy and Rhabdomyolysis

Advise patients that LESCOL XL may cause myopathy and rhabdomyolysis. Instruct patients to promptly report any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever [see *Warnings and Precautions (5.1), Drug Interactions (7.1)*].

### Hepatic Dysfunction

Inform patients that LESCOL XL may cause liver enzyme elevations and possibly liver failure. Advise patients to promptly report fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice [see *Warnings and Precautions (5.3)*].

### Increases in HbA1c and Fasting Serum Glucose Levels

Inform patients that increases in HbA1c and fasting serum glucose levels may occur with LESCOL XL. Encourage patients to optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices [see *Warnings and Precautions (5.4)*].

### Pregnancy

Advise pregnant patients and patients who can become pregnant of the potential risk to a fetus. Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if LESCOL XL should be discontinued [see *Use in Specific Populations (8.1)*].

### Lactation

Advise patients that breastfeeding is not recommended during treatment with LESCOL XL [see *Use in Specific Populations (8.2)*].

Mfd. by: Pfizer Ireland Pharmaceuticals  
Newbridge, Ireland for  
Sandoz Inc., Princeton, NJ 08540

## PATIENT INFORMATION

LESCOL<sup>®</sup> XL (lěs-cōl)  
(fluvastatin)  
extended-release tablets, for oral use

### **You must read and follow all instructions before using LESCOL XL.**

Read this Patient Information before you start taking LESCOL XL and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have any questions about LESCOL XL, ask your doctor or pharmacist.

### **What is LESCOL XL?**

LESCOL XL is a prescription medicine “that contains the cholesterol lowering medicine, fluvastatin.”

LESCOL XL is used in adults with heart disease (coronary artery disease) to:

- lower the need for heart and blood vessel procedures to improve flow to the heart, called coronary revascularization.
- slow the buildup of too much cholesterol in the arteries of the heart.

LESCOL XL is used along with diet to lower the level of:

- low-density lipoprotein cholesterol (LDL-C) or “bad” cholesterol in adults with hyperlipidemia (high levels of fat in the blood)
- LDL-C in adults and children 10 years of age and older with heterozygous familial hypercholesterolemia (HeFH), an inherited condition that causes high levels of LDL, who require 80 mg of fluvastatin daily.

The safety and effectiveness of LESCOL XL has not been established in children younger than 10 years of age with heterozygous familial hypercholesterolemia (HeFH) or in children with other types of hyperlipidemia (high levels in fat in the blood) other than HeFH.

### **Do not take LESCOL XL if you:**

- have liver problems (acute liver failure or decompensated cirrhosis)
- are allergic to fluvastatin or any of the ingredients in LESCOL XL. See the end of this Patient Information leaflet for a complete list of ingredients in LESCOL XL.

### **Before you take LESCOL XL, tell your healthcare provider about all of your medical conditions, including if you:**

- have muscle aches or weakness
- drink more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems
- are pregnant or plan to become pregnant. If you become pregnant while taking LESCOL XL, stop taking LESCOL XL and call your healthcare provider.
- are breastfeeding or plan to breastfeed. It is not known if LESCOL XL passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take LESCOL XL. You should not breastfeed while taking LESCOL XL

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Talk to your healthcare provider before you start taking any new medicines. Tell your healthcare provider who prescribes LESCOL XL if another healthcare provider increases the dose of another medicine you are taking.

LESCOL XL may affect the way other medicines work, and other medicines may affect how LESCOL XL works. Especially tell your healthcare provider if you take:

- warfarin (a medicine used to reduce blood clotting)

- glyburide (a medicine used to treat diabetes)
- phenytoin (a medicine used to treat epilepsy)

Taking LESCOL XL with certain medicines can also increase the risk of muscle problems. Especially tell your healthcare provider if you take:

- gemfibrozil (a medicine used to lower triglycerides)
- cyclosporine (a medicine used to suppress the immune system)
- fluconazole (a medicine used to treat fungal infections)
- fibrates or niacin
- colchicine

Ask your healthcare provider or pharmacist for a list of medicines if you are not sure. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

### How should I take LESCOL XL?

- Take LESCOL XL exactly as your healthcare provider tells you to take it.
- **Do not** change your dose or stop taking LESCOL XL without talking to your healthcare provider.
- Take LESCOL XL tablets 1 time each day, at any time of the day. LESCOL XL can be taken with or without food.
- LESCOL XL tablets must be swallowed whole with a liquid. Do not break, crush or chew LESCOL XL tablets. Tell your healthcare provider if you cannot swallow tablets whole. You may need fluvastatin capsules or a different medicine instead of LESCOL XL tablets.
- While taking LESCOL XL, continue to follow your cholesterol-lowering diet and exercise as your healthcare provider told you to.
- In case of overdose, get medical help or contact a Poison Center expert right away at 1-800-222-1222. Advice is also available online at [poisonhelp.org](http://poisonhelp.org).

### What are the possible side effects of LESCOL XL?

#### LESCOL XL may cause serious side effects, including:

- **Muscle pain, tenderness, and weakness (myopathy).** Muscle problems, including muscle breakdown, can be serious in some people and rarely cause kidney damage that can lead to death.

#### Tell your healthcare provider right away if you have:

- unexplained muscle pain, tenderness, or weakness, especially if you have a fever or feel more tired than usual, while you take LESCOL XL.
- muscle problems that do not go away even after your healthcare provider has advised you to stop taking LESCOL XL. Your healthcare provider may do further tests to diagnose the cause of your muscle problems. Your chances of getting muscle problems are higher if you:
  - are taking certain other medicines while you take LESCOL XL
  - are 65 years of age or older
  - have thyroid problems (hypothyroidism) that are not controlled
  - have kidney problems
- **Liver problems.** Your healthcare provider should do blood tests to check your liver before you start taking LESCOL XL, and if you have symptoms of liver problems while you take LESCOL XL. Call your healthcare provider right away if you have the following symptoms of liver problems:
  - feel tired or weak

- loss of appetite
- right sided upper belly pain
- dark amber colored urine
- yellowing of your skin or the whites of your eye
- **Increase in blood sugar (glucose) levels.** LESCOL XL may cause an increase in your blood sugar levels.

**The most common side effects of LESCOL XL include:**

- flu-like symptoms
- sinus infection
- upset stomach and stomach pain
- urinary tract infections
- bronchitis
- nausea

These side effects are usually mild and may go away. The following additional side effects have been reported with LESCOL XL:

- memory loss and confusion

Talk to your healthcare provider or pharmacist if you have side effects that bother you or does not go away.

These are not all the possible side effects of LESCOL XL. Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

**How should I store LESCOL XL?**

- Store LESCOL XL at room temperature 68°F to 77°F (20°C to 25°C). **Protect from light.**
- **Keep LESCOL XL out of the reach of children.** Be sure that if you throw medicines away, it is out of the reach of children.

**General information about safe and effective use of LESCOL XL.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use LESCOL XL for a condition for which it was not prescribed. Do not give LESCOL XL to other people, even if they have the same medical condition you have; it may harm them.

You can ask your pharmacist or healthcare provider for information about LESCOL XL that is written for health professionals.

**What are the ingredients in LESCOL XL?**

Active Ingredient: fluvastatin

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

For more information go to [www.sandoz.com](http://www.sandoz.com) or call 1-800-525-8747.

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Newbridge, Ireland for

Sandoz Inc., Princeton, NJ 08540