NOVARTIS

Lescol® XL

HMG-CoA reductase inhibitor

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Capsules and prolonged release tablets for oral administration.

Active substance

Fluvastatin sodium

One prolonged release tablet of Lescol XL contains 84.24 mg fluvastatin sodium equivalent to

80 mg fluvastatin free acid.

Certain dosage strengths and dosage forms may not be available in all countries.

Active moiety

Fluvastatin

EXCIPIENTS

Lescol XL 80 mg tablets

Cellulose microcrystalline; hypromellose; hydroxypropyl cellulose; potassium hydrogen carbonate; povidone; magnesium stearate; iron oxide yellow; titanium dioxide; macrogol 8000.

Pharmaceutical formulations may vary between countries.

INDICATIONS

Dyslipidemia

Adults

Lescol XL is indicated as an adjunct to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B) and triglycerides (TG) levels and for the increase of high-density lipoprotein cholesterol (HDL-C) in adults with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson Types IIa and IIb).

Other indications

Lescol XL is indicated to slow the progression of coronary atherosclerosis in adults with primary hypercholesterolaemia, including mild forms, and coronary heart disease.

Lescol XL is also indicated for the secondary prevention of major adverse cardiac events in adults with coronary heart disease after coronary transcatheter therapy.

DOSAGE REGIMEN AND ADMINISTRATION

Lescol XL can be administered as a single dose at any time of the day with or without food. Lescol XL must be swallowed whole with a glass of water. The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of Lescol XL is maintained with prolonged administration.

General target population

Adults

Prior to initiating treatment with Lescol XL, the patient should be placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

The recommended starting dose is 80 mg

(1 tablet Lescol XL 80 mg once daily). Starting doses should be individualized according to baseline LDL-C levels and the recommended goal of therapy to be accomplished.

In patients with coronary heart disease after coronary transcatheter therapy, the appropriate dose is 80 mg daily.

Lescol XL is efficacious in monotherapy. Data exist to support the efficacy and safety of fluvastatin in combination with nicotinic acid, cholestyramine, or fibrates (see section INTERACTIONS).

Special populations

Renal impairment

No dose adjustments are necessary in patients with renal impairment (see section CLINICAL PHARMACOLOGY).

Hepatic impairment

Lescol XL is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see sections CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Geriatric patients

In clinical studies with Lescol XL, efficacy and tolerability were demonstrated in age groups both above and under 65 years. In the elderly group (>65 years), response to treatment was enhanced and there was no evidence of reduced tolerability. Therefore there is no need to adjust the dose based on age.

Pediatrics

The efficacy and safety of Lescol have not been established in paediatric patients, its use cannot be recommended in such patients.

CONTRAINDICATIONS

Lescol XL is contraindicated:

- in patients with known hypersensitivity to fluvastatin or any of the excipients.
- in patients with active liver disease, or unexplained, persistent elevations in serum transaminases.
- during pregnancy and breast-feeding (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

WARNINGS AND PRECAUTIONS

Liver function

Post-marketing cases of fatal and non-fatal hepatic failure have been reported with some statins, including Lescol XL. Although a causal relationship with Lescol XL treatment has not been determined, patients should be advised to report any potential symptoms or signs of hepatic failure (e.g. nausea, vomiting, loss of appetite, jaundice, impaired brain function, easy bruising or bleeding), and treatment discontinuation should be considered.

As with other lipid-lowering drugs, it is recommended that liver function tests be performed before initiating of treatment, and at 12 weeks following initiation of treatment or an elevation in the dose, and periodically thereafter in all patients. Should an increase in aspartate aminotransferase or alanine aminotransferase exceed 3 times the upper limit of normal and persist, therapy should be discontinued. In very rare cases, hepatitis (possibly drug-related) was observed that resolved upon discontinuation of treatment.

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

Skeletal muscle

With fluvastatin, myopathy has been reported rarely, whereas myositis and rhabdomyolysis have been reported very rarely. In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked elevation of creatine kinase (CK) values, myopathy, myositis or rhabdomyolysis have to be considered. Patients should therefore be advised to promptly report unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.

Immune mediated necrotizing myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Creatine kinase measurement

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

Before commencing treatment

As with all other statins physicians should prescribe fluvastatin with caution in patients with predisposing factors for rhabdomyolysis and its complications. The 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.
- Sepsis
- Hypotension
- Trauma
- Major surgery
- Severe metabolic, endocrine or electrolyte disorders
- Uncontrolled epilepsy
- In elderly patients (aged >70 years), the necessity of such measurement should be considered, depending on the presence of other predisposing factors for rhabdomyolysis.

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 ULN), levels should be re-measured within 5 to 7 days to confirm the results. If CK-levels are still significantly elevated (>5 x ULN) upon re-measurement, treatment should not be started.

During treatment

If muscular symptoms such as 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).

If muscular symptoms are severe and cause daily discomfort, even if CK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

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

The risk of myopathy has been reported to be increased in patients receiving immunosuppressant drugs (including ciclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. However, in clinical trials in patients receiving fluvastatin in combination with nicotinic acid, fibrates, or ciclosporin, myopathy has not been observed. Isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with ciclosporin and fluvastatin with colchicine. Lescol XL should be used with caution in patients receiving such concomitant medication (see section INTERACTIONS).

Use of statins and effects on glucose metabolism

Increased glycosylated hemoglobin (HbA1C) and/or fasting plasma glucose levels were observed in patients treated with HMG-CoA reductase inhibitors (statins). New- onset diabetes mellitus was also reported in patients with risk factors for diabetes mellitus.

Homozygous familial hypercholesterolemia

No data are available for the use of fluvastatin in patients with a rare condition known as homozygous familial hypercholesterolemia.

INTERACTIONS

Food interactions

There are no apparent differences in the lipid-lowering effects of fluvastatin when administered with the evening meal or 4 hours after the evening meal. Based on the lack of interaction of fluvastatin with other CYP3A4 substrates, fluvastatin is not expected to interact with grapefruit juice.

Drug interactions

Effect of other drugs on fluvastatin

Fibric acid derivatives (fibrates) and niacin (nicotinic acid)

Concomitant administration of fluvastatin with bezafibrate, gemfibrozil, ciprofibrate or niacin (nicotinic acid) has no clinically relevant effect on the bioavailability of fluvastatin or the other lipid-lowering agent. However, since an increased risk of myopathy has been observed in patients receiving other HMG-CoA reductase inhibitors together with any of these molecules, these combinations should be used with caution (see section WARNINGS AND PRECAUTIONS).

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, ciclosporin) are unlikely to affect the bioavailability of fluvastatin.

Fluconazole

Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor) resulted in an increase in the exposure and peak concentration of fluvastatin by about 84% and 44%. Although there was no clinical evidence that the safety profile of fluvastatin was altered in patients pre-treated with fluconazole for 4 days, caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Ciclosporin

Studies in renal transplant patients indicate that the bioavailability of fluvastatin (up to 40 mg/day) is not elevated to a clinically significant extent in patients on stable regimens of ciclosporin. The results from another study in which Lescol XL (80 mg fluvastatin) was administered to renal transplant patients who were on a stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration (C_{max}) were increased by 2 fold compared to historical data in healthy subjects. Although these increases in fluvastatin levels were not clinically significant, this combination should be used with caution (see section WARNINGS AND PRECAUTIONS).

Bile acid sequestrants

Fluvastatin should be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding of the resin.

Rifampicin (rifampin)

Administration of fluvastatin to healthy volunteers pre-treated with rifampicin (rifampin) resulted in a reduction of the bioavailability of fluvastatin by about 50%. Although at present there is no clinical evidence that fluvastatin efficacy in lowering lipid levels is altered, appropriate adjustment of the fluvastatin dosage may be warranted in patients undergoing long-term rifampicin therapy (e.g. treatment of tuberculosis) in order to ensure a satisfactory reduction in lipid levels.

Histamine H2-receptor antagonists and proton pump inhibitors

Concomitant administration of fluvastatin with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of fluvastatin, which, however, is of no clinical relevance. While additional interaction studies have not been performed, it is expected that other H_2- receptor antagonists/proton pump inhibitors are unlikely to affect the bioavailability of fluvastatin.

Phenytoin

The minimal effect of phenytoin on fluvastatin pharmacokinetics indicates that dosage adjustment of fluvastatin is not warranted when co-administered with phenytoin.

Cardiovascular agents

No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with propranolol, digoxin, losartan, clopidogrel or amlodipine. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with these agents.

Effects of fluvastatin on other drugs

Ciclosporin

Lescol XL (80 mg fluvastatin) had no effect on ciclosporin bioavailability when co-administered (see also Effects of other drugs on fluvastatin).

Colchicines

No information is available on the pharmacokinetic interaction between fluvastatin and colchicines. However, myotoxicity, including muscle pain and weakness and rhabdomyolysis, has been reported anecdotally with concomitant administration of colchicine.

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.

Warfarin and other coumarin derivatives

In healthy volunteers, the use of fluvastatin and warfarin (single dose) did not adversely influence warfarin 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.

Oral antidiabetic agents

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

In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean C_{max}, AUC, and $t_{1/2}$ of glibenclamide by approximately 50%, 69% and 121%, respectively. Glibenclamide (5 to 20 mg daily) increased the mean C_{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin and C-peptide levels. However, patients on concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 80 mg per day.

Clopidogrel

Fluvastatin did not affect the anti-platelet aggregation activity of clopidogrel. Therefore, fluvastatin and clopidogrel can be co-administered without any dosage adjustments.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

Since HMG-CoA reductase inhibitors decrease the synthesis of cholesterol and possibly of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, Lescol XL is contraindicated during pregnancy (see section CONTRAINDICATIONS).

Animal Data

Teratology studies in rats (1, 12 and 36 mg/kg per day) and rabbits (0.05, 1 and 10 mg/kg per day) showed maternal toxicity at high dose levels, but there was no evidence of embryotoxic or teratogenic potential. A study in which female rats were dosed at 12 and 24 mg/kg per day during late gestation until weaning of the pups resulted in maternal mortality at or near term and post- partum, accompanied by fetal and neonatal lethality. No effects on the pregnant females or fetuses occurred at the low dose level of 2 mg/kg per day.

A second study in rats at levels of 2, 6, 12 and 24 mg/kg per day during late gestation and early lactation showed similar effects at 6 mg/kg per day and above caused by cardiotoxicity. In a third study, pregnant rats were administered 12 or 24 mg/kg per day during late gestation until weaning of the pups, with or without the presence of concurrent supplementation with mevalonic acid, a derivative of HMG-CoA that is essential for cholesterol biosynthesis. The concurrent administration of

mevalonic acid completely prevented the cardiotoxicity and the maternal and neonatal mortality. Therefore, the maternal and neonatal lethality observed with fluvastatin reflects its exaggerated pharmacological effect during pregnancy.

Lactation

Lescol XL is contraindicated in nursing mothers (see section CONTRAINDICATIONS).

Females and males of reproductive potential

Contraception

Women of child-bearing potential must use effective contraception. If a patient becomes pregnant while taking Lescol XL, therapy should be discontinued.

Infertility

There is no relevant information available in humans. In a study in rats at dose levels in females of 0.6, 2 and 6 mg/kg per day and in males of 2, 10 and 20 mg/kg per day, fluvastatin had no adverse effects on fertility or reproductive performance.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No data exist on the effects of fluvastatin on the ability to drive and use machines.

ADVERSE DRUG REACTIONS

Adverse drug reactions (Table 1) are listed by medDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first., Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction : very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000).

The most commonly reported adverse drug reactions are minor gastrointestinal symptoms, insomnia and headache.

Table 1

Blood and lymphatic system disorders	
Very rare:	Thrombocytopenia.
Immune system disorders	
Rare:	Hypersensitivity reactions (rash, urticaria).
Very rare:	Anaphylactic reaction.
Psychiatric disorders	
Common:	Insomnia.
Nervous system disorders	
Common:	Headache.
Very rare:	Paresthesia, dysesthesia, hypoesthesia also known to be associated with the underlying hyperlipidemic disorders.

Vascular disorders	
Very rare:	Vasculitis.
Gastrointestinal disorders	
Common:	Nausea, abdominal pain, dyspepsia.
Very rare:	Pancreatitis.
Hepatobiliary disorders	
Very rare:	Hepatitis.
Skin and subcutaneous tissue disorders	
Very rare:	Angioedema, face edema and other skin reactions (e.g. eczema, dermatitis, bullous exanthema).
Musculoskeletal and connective tissue disorders	
Rare:	Myalgia, muscular weakness, myopathy.
Very rare:	Rhabdomyolysis, lupus-like syndrome, myositis.
Investigations	
Common:	Blood creatine phosphokinase increased, blood transaminases increased.

Other adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Lescol via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks)

Reproductive system and breast disorders: Erectile dysfunction.

Musculoskeletal and connective tissue disorders: Immune-mediated necrotizing myopathy (see section WARNING AND PRECAUTIONS)

Laboratory findings

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in a small number of patients (1 to 2%).

Marked elevations of CK levels to more than 5x ULN developed in a very small number of patients

(0.3 to 1.0%).

OVERDOSAGE

In a placebo-controlled study including 40 hypercholesterolemic patients, doses of up to 320 mg/day (n=7 per dose group) administered as Lescol XL 80-mg tablets over two weeks were well tolerated. No specific treatment is available for Lescol XL overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures should be undertaken as required. Liver function tests should be performed, and serum CK levels monitored.

CLINICAL PHARMACOLOGY

Pharmacodynamics (PD)

Fluvastatin, a fully synthetic cholesterol-lowering agent, is a competitive inhibitor of HMG- CoA reductase, which is responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Fluvastatin exerts its main effect in the liver and is mainly a racemate of the two erythro enantiomers, of which one exerts the pharmacological activity. 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 in the plasma cholesterol concentration.

Lescol XL reduces total-C, LDL-C, apo -B and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is well established within 2 weeks, and maximum response is achieved within 4 weeks from treatment initiation and maintained during chronic therapy.

Pharmacokinetics (PK)

Absorption

Fluvastatin is absorbed rapidly and completely (98%) after oral administration of a solution to fasted volunteers. After oral administration of Lescol XL 80, and in comparison with the capsules, the absorption rate of fluvastatin is almost 60% slower while the mean residence time of fluvastatin is increased by approximately 4 hours. In a fed state, the drug is absorbed at a reduced rate.

Distribution

Fluvastatin exerts its main effect in the liver, which is also the main organ for its metabolism. The absolute bioavailability assessed from systemic blood concentrations is 24%. The apparent volume of distribution (V_z/f) for the drug is 330 L. More than 98% of the circulating drug is bound to plasma proteins, and this binding is not affected either by the concentration of fluvastatin, or by warfarin, salicylic acid or glyburide.

Metabolism

Fluvastatin is mainly metabolized in the liver. The major components circulating in the blood are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate systemically. The hepatic pathways of fluvastatin metabolism in humans have been completely elucidated. There are multiple, alternative cytochrome P450 (CYP450) pathways for fluvastatin biotransformation and thus

fluvastatin metabolism is relatively insensitive to CYP450 inhibition, a major cause of adverse drug-drug interactions.

Several detailed *in vitro* studies have addressed the inhibitory potential of fluvastatin on common CYP isoenzymes. Fluvastatin inhibited only the metabolism of compounds that are metabolized by CYP2C9. Despite the potential that therefore exists for competitive interaction between fluvastatin and compounds that are CYP2C9 substrates, such as diclofenac, phenytoin, tolbutamide, and warfarin, clinical data indicate that this interaction is unlikely.

Elimination

Following administration of ^{3}H-fluvastatin to healthy volunteers, excretion of radioactivity is about 6% in the urine and 93% in the feces, and fluvastatin accounts for less than 2% of the total radioactivity excreted. The plasma clearance (CL/f) of fluvastatin in humans is calculated to be 1.8 ± 0.8 L/min. Steady-state plasma concentrations show no evidence of fluvastatin accumulation following administration of 80 mg daily. Following oral administration of 40 mg Lescol, the terminal elimination half-life for fluvastatin is 2.3 ± 0.9 hours.

No significant difference in AUC was observed when fluvastatin was administered with the evening meal or 4 hours after the evening meal.

Special populations

Age and gender

Plasma concentrations of fluvastatin do not vary as a function of either age or gender in the general population. However, enhanced treatment response was observed in women and in elderly people.

Hepatic impairment

Since fluvastatin is eliminated primarily via the biliary route and is subject to significant pre- systemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency (see sections CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Renal impairment

Fluvastatin is cleared by the liver, with less than 6% of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency.

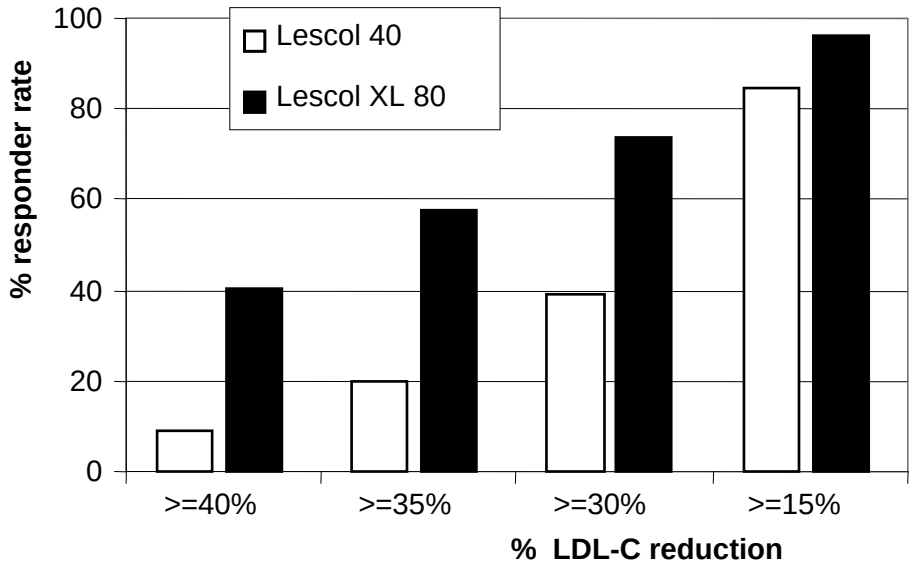
CLINICAL STUDIES

In three multicenter, double-blind, active-controlled studies in nearly 1,700 patients with primary hypercholesterolemia or mixed dyslipidemia, Lescol XL 80 mg was compared to Lescol 40 mg given at bedtime or b.i.d. over 24 weeks of therapy.

Responder rates at the time when maximum therapeutic response is achieved are illustrated in Figure 1 for the Lescol 40 mg (mean LDL-C reduction of 26%) and Lescol XL 80 mg doses (mean LDL-C reduction of 36%).

Figure 1 Responder rates by category of percent reduction in LDL-C at Week 4

(Results are pooled from 3 upper dose comparative studies)



In these studies, Lescol/Lescol XL significantly reduced total-C, LDL-C, apo B, and TG, and increased HDL-C after 24 weeks of therapy in a dose-ordered fashion (Table 2).

Table 2 Mean percent change from baseline after 24 weeks (all patients)

Dose	Total-C	LDL-C	HDL-C	HDL-C (baseline ≤35 mg/dL)	Apo B	TG*
Lescol 40	- 17%	- 25%	+ 6%	+ 10%	- 18%	- 12%
Lescol XL 80	- 23%	- 34%	+ 9%	+ 14%	- 26%	- 19%

** median percent change*

Of the 857 patients randomized to Lescol XL 80 mg, 271 with primary mixed dyslipidemia (Fredrickson Type IIb) as defined by baseline plasma triglycerides levels ≥200 mg/dL, had a median reduction in triglycerides of 25%. In these patients, Lescol XL 80 mg produced meaningful increases in HDL-C of 13%. This effect was even more pronounced in those patients with very low HDL-C levels at baseline (i.e. <35 mg/dL), who had mean increases in HDL-C of 16%. Significant decreases in total-C, LDL-C, and apo-B were also achieved (Table 3). In these studies, patients with triglycerides >400 mg/dL were excluded.

Table 3 Mean percent change from baseline after 24 weeks (Primary Mixed Dyslipidemia)

Dose	Total-C	LDL-C	HDL-C	Apo B	TG*
Lescol 40	– 17%	– 23%	+ 7%	– 17%	– 18%
Lescol XL 80	– 24%	– 33%	+ 13%	– 24%	– 25 %

** median percent change*

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of fluvastatin on coronary atherosclerosis was assessed by quantitative coronary angiography in male and female patients (35 to 75 years old) with coronary artery disease and mild to moderate hypercholesterolemia (baseline LDL-C 115 to 190 mg/dL). In this randomized, double-blind, controlled clinical study, 429 patients were treated with either fluvastatin 40 mg/day or placebo. Quantitative coronary angiograms were evaluated at baseline and after 2.5 years of treatment.

Fluvastatin treatment slowed the progression of coronary atherosclerosis lesions by 0.07 mm (95% confidence intervals for treatment difference from -0.1222 to -0.022 mm) over 2.5 years as measured by change in minimum lumen diameter (fluvastatin -0.028 mm vs. placebo - 0.100 mm).

In the Lescol Intervention Prevention Study (LIPS), the effect of fluvastatin on major adverse cardiac events (MACE) was assessed in male and female patients (18 to 80 years old) with coronary heart disease and a broad range of cholesterol levels (baseline TC: 3.5 to 7.0 mmol/L). In this randomized, double-blind, placebo-controlled trial, a total of 1677 patients were recruited (844 in fluvastatin group and 833 in placebo group). The MACE was defined as cardiac death, non-fatal MI and re-intervention (including CABG, repeat TCT, or TCT of a new lesion). The dose of fluvastatin used in this study was 80 mg daily over 4 years. Although the overall composite endpoint showed significant reduction in MACE (22%) compared to placebo (p=0.013), the individual components (cardiac death, non-fatal MI and re-intervention) failed to reach statistical significance. There was however a trend in favor of fluvastatin. Therapy with fluvastatin reduced the risk of cardiac death and/or myocardial infarction by 31% (p = 0.065).

NON-CLINICAL SAFETY DATA

Acute toxicity

The approximate oral LD_{50} of fluvastatin is greater than 2 g/kg in mice and greater than 0.7 g/kg in rats.

Repeated dose toxicity

The safety of fluvastatin was extensively investigated in toxicity studies in rats, rabbits, dogs, monkeys, mice and hamsters. A variety of changes were identified that are common to HMG-CoA reductase inhibitors, for example hyperplasia and hyperkeratosis of the rodent non-glandular stomach, cataracts in dogs, myopathy in rodents, mild liver changes in most laboratory animals, gallbladder changes in dogs, monkeys and hamsters, thyroid weight increases in rats, and testicular degeneration in hamsters. Fluvastatin is devoid of the CNS vascular and degenerative changes recorded in dogs with other members of this class of compounds.

Carcinogenicity

A carcinogenicity study was performed in rats at dose levels of 6, 9 and 18 mg/kg per day (escalated to 24 mg/kg per day after 1 year) to establish a clear maximum tolerated dose. These treatment levels

yielded plasma drug levels approximately 9, 13 and 26 to 35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and one carcinoma of the forestomach was observed at the 24 mg/kg per day dose level. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded in male rats treated with 18 to 24 mg/kg per day. The increased incidence of thyroid follicular cell neoplasm in male rats with fluvastatin sodium appears to be consistent with findings from other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg per day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg per day and in females at 15 mg/kg per day. These treatment levels yielded blood drug levels approximately 0.03 – 0.04, 1.3 – 4.8 and 5 – 15 times the mean human plasma drug concentration (C_{max} of 365 ng/ml) after a 40 mg oral dose.

The carcinogenicity study in mice was repeated at oral dose levels of 50, 150 and 350 mg/kg/day. Reduced body weight gain was recorded at all dose level & excessive mortality at the high dose confirmed that the maximum tolerated dose (MTD) is less than 50mg/kg/day in the mouse. There was no evidence of increased neoplasia at these doses.

The forestomach neoplasms observed in rats and mice reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug.

Mutagenicity

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.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Lescol XL should not be used after the date marked “EXP” on the pack. Lescol XL must be kept out of the reach and sight of children.

Manufacturer:

See folding box.

Package Leaflet

Information issued: Dec 2017.SIN

® = registered trademark

Novartis Pharma AG, Basel, Switzerland