

Lescol® / Lescol® mite/ Lescol® XL

Composition

Active substance: Fluvastatin as fluvastatin sodium.

Excipients: Lescol 20 mg and 40 mg capsules

Magnesium stearate; sodium hydrogen carbonate; talc; cellulose microcrystalline, pregelatinised starch, calcium carbonate; titanium dioxide; iron oxide red, iron oxide yellow, gelatine; shellac.

Lescol XL 80 mg tablets

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

Information might differ in some countries.

Pharmaceutical form and quantity of active substance per unit

Lescol: 40 mg capsules.
Lescol mite: 20 mg capsules.
Lescol XL: 80 mg prolonged release tablets.

Indications / Potential uses

Dyslipidaemia

Adults: Reduction of elevated levels of total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides, and increase in HDL cholesterol, in adults with primary hypercholesterolaemia and primary mixed dyslipidaemia (Fredrickson types Ia and Ib) in whom dietary measures have proved insufficiently effective.

Children and adolescents: Reduction of elevated levels of total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides, and increase in HDL cholesterol, in boys (9-16 years of age) and postmenarcheal girls (10-16 years of age) with heterozygous familial hypercholesterolaemia, in whom dietary measures have proved insufficiently effective.

Other indications: To reduce the need for additional coronary revascularisation procedures in adults with coronary heart disease.

Dosage / Administration

Lescol/Lescol mite capsules are taken in the evening or at bedtime. Lescol XL may be taken as a single dose at any time of the day. Lescol/Lescol mite capsules and Lescol XL tablets must be swallowed whole with a glass of water, but may be taken with or without food.

Usual dosage recommendations

Adults: Prior to initiating treatment, the patient should be placed on a cholesterol-lowering diet, which should be continued during treatment. The recommended dose is 20 mg/day, 40 mg/day or 80 mg/day (1 Lescol mite or Lescol capsule, or 1 Lescol XL prolonged release tablet). The starting dose should be individualized according to baseline LDL cholesterol (LDL-C) and the therapeutic goal.

The appropriate dose following percutaneous coronary intervention in patients with coronary heart disease is 80 mg/day.

The maximum lipid-lowering effect with a given dose is achieved within 4 weeks. Doses should be adjusted according to the patient's response, with blood lipid levels measured at intervals of 4 weeks or more. The therapeutic effect of Lescol is maintained with long-term administration.

Lescol is efficacious in monotherapy.

Studies have demonstrated the efficacy and tolerability of fluvastatin in combination with nicotinic acid, colestyramine or fibrates (see "Interactions"). Patients should, however, be monitored closely due to the risk of myopathy.

Special dosage recommendations

Dosage in children and adolescents with heterozygous familial hypercholesterolaemia

Boys (9–16 years of age)

Postmenarcheal girls (10–16 years of age)

Prior to initiating treatment, the patient should be placed on a cholesterol-lowering diet for 6 months, which should be continued during treatment. The starting dose should be individualized according to baseline LDL cholesterol (LDL-C) and the therapeutic goal. In clinical studies, a starting dose of 20 mg/day was administered. The recommended dose is 20 mg/day, 40 mg/day or 80 mg/day (1 Lescol mite or Lescol capsule, or 1 Lescol XL prolonged release tablet).

The use of fluvastatin in combination with nicotinic acid, colestyramine or fibrates in children and adolescents has not been investigated.

Renal impairment

Fluvastatin is cleared almost exclusively by the liver, with only about 6% of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency. No dose adjustments are therefore necessary in these patients.

Hepatic impairment

Lescol is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see "Contraindications" and "Warnings and precautions").

Elderly patients

In clinical studies, the efficacy and tolerability of Lescol were demonstrated in patients both above and below 65 years of age. Response to treatment tended to be enhanced in elderly patients (> 65 years), but with no reduction in tolerability. Dose adjustment is therefore not necessary.

Contraindications

Known hypersensitivity to fluvastatin or any of the excipients. Active liver disease or persistent, unexplained elevation of serum transaminase levels (see "Warnings and precautions"). Pregnancy and lactation (see "Pregnancy / Lactation").

Warnings and precautions

Hepatic function

Post-marketing cases of fatal and non-fatal hepatic failures have been reported during treatment with statins, including Lescol/Lescol mite/ Lescol XL. Patients should be advised to immediately report any potential signs or symptoms of hepatic failure (e.g. nausea, vomiting, loss of appetite, jaundice, impaired cognitive 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 in all patients before the initiation of treatment, at 12 weeks following initiation of treatment or elevation in dose, and periodically thereafter. The drug should be discontinued if AST or ALT persistently exceed three times the upper limit of normal (ULN). In very rare cases, hepatitis – possibly drug-related – has been observed.

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

Skeletal muscle

With fluvastatin, there have been only rare reports of myopathy and very rare reports of myositis and rhabdomyolysis. In patients with diffuse myalgias of unknown origin, muscle tenderness or muscle weakness, and/or marked elevation of creatine kinase (CK) values, the presence of myopathy, myositis or rhabdomyolysis has to be considered. Patients should therefore be instructed to promptly report unexplained muscle pain, tenderness or weakness, particularly if these symptoms are accompanied by malaise or fever.

Creatine kinase measurement:

Creatine kinase should not be measured following strenuous exercise, or in the presence of any other possible cause of elevated levels of CK, as this would make interpretation of results difficult.

Before treatment:

As with all other statins, physicians should prescribe fluvastatin with caution in patients with the following conditions and their concomitant therapy. The creatine kinase level should be measured before starting treatment with a statin in the following situations:

- Renal impairment
- Hypothyroidism
- Personal or family history of hereditary muscular disorders

- History of muscular toxicity with statins or fibrates
- Alcohol abuse
- Sepsis
- Hypotension
- Trauma
- Major surgery

- Severe hepatic, endocrine or electrolyte disorders
- Uncontrolled epilepsy
- In elderly patients (> 70 years of age), the necessity of such measurement should be considered, given the possible presence of predisposing factors for rhabdomyolysis

In such situations, the risk of treatment should be considered in relation to the expected therapeutic benefit. Clinical monitoring is recommended. If CK levels are significantly elevated at baseline (> 5 × ULN), they should be measured again 5 to 7 days later to confirm the results. If CK levels remain significantly elevated (> 5 × ULN), the patient should not be treated with a statin.

During treatment

If muscle pain, weakness or cramps occur in patients treated with fluvastatin, their plasma CK levels should be measured. Treatment should be stopped if these levels are found to be significantly elevated (> 5 × ULN). If muscular symptoms are severe and cause daily discomfort, even if the elevation in CK levels is ≤5 × ULN, treatment discontinuation should be considered.

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

Concomitant treatment with inhibitors of CYP3A4 isoenzymes, fibrates or cyclosporin may increase the risk of rhabdomyolysis.

An increased risk of myopathy has been reported in patients given other HMG-CoA reductase inhibitors concomitantly with immunosuppressants (including cyclosporin), fibrates, nicotinic acid, erythromycin, or antifungal azole derivatives in combination with cyclosporin (see "Interactions"). There have been isolated post-marketing reports of myopathy following concomitant administration of fluvastatin with cyclosporin and fluclozine. Fluvastatin should therefore be used with caution in patients receiving such concomitant medication (see "Interactions").

HMG-CoA reductase inhibitors and antifungal azole derivatives inhibit cholesterol biosynthesis at different stages. In patients concomitantly receiving cyclosporin and fluvastatin who also require treatment with a substance of the azole group, cyclosporin levels should be closely monitored. Patients with concomitant fungal infections should preferably not be given preparations which interact with fluvastatin.

Use of statins and effects on glucose metabolism

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

Homozygous familial hypercholesterolaemia

No data are available on the use of fluvastatin in patients with the rare condition of homozygous familial hypercholesterolaemia.

Paediatric use

In clinical studies, 11 patients treated with Lescol were observed for up to 5 years. Fluvastatin has only been investigated in boys aged 9-16 years and in postmenarcheal girls aged 10-16 years with heterozygous familial hypercholesterolaemia (see "Properties / Actions").

Interactions

Based on the results of studies with CYP3A4 inhibitors carried out in vitro (mefenbradil) and in vivo (itraconazole and erythromycin), no relevant drug interactions are expected with CYP3A4 inhibitors because CYP3A4 plays a minor role in the metabolism of fluvastatin. Moreover, fluvastatin neither induces nor inhibits CYP3A4. For this reason, no drug interactions are likely to occur between fluvastatin and CYP3A4 substrates.

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. Due to the minimal effect of CYP3A4 on fluvastatin metabolism, fluvastatin is not expected to interact with grapefruit juice.

Drug interactions

Effects of other drugs on fluvastatin

Fibric acid derivatives (fibrates) and niacin (nicotinic acid): Concomitant administration of fluvastatin with gemfibrozil or niacin (nicotinic acid) has no clinically relevant effect on the bioavailability of fluvastatin or the other lipid-lowering agent.

Concomitant administration of Lescol and bezafibrate increases the bioavailability of fluvastatin by approx. 50%. Since an increased risk of myopathy has been observed in patients receiving other HMG-CoA reductase inhibitors concomitantly with one of these substances, these combinations should be used with caution (see "Warnings and precautions").

Oral antidiabetics: In patients receiving oral sulphonylureas (glipizamide, tolbutamide) for the treatment of non-insulin-dependent (type 2) diabetes mellitus (NIDDM), concomitant administration of fluvastatin does not result in a significant change in glycaemic control.

In glipizamide-treated NIDDM patients (n = 32), concomitant administration of fluvastatin (40 mg twice daily for 14 days) increased the C_{max}, AUC, and t_{1/2} of glipizamide by approximately 50%, 69% and 121%, respectively. Glipizamide (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 or C-peptide levels. However, patients on concomitant therapy with glipizamide and fluvastatin should continue to be monitored when their fluvastatin dose is increased to 80 mg per day.

Fluconazole: Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor) resulted in increases in AUC and C_{max} of about 84% and 44%, respectively. Caution should thus be exercised when fluvastatin is administered concomitantly with fluconazole.

Cyclosporin: Studies in renal transplant patients show that the bioavailability of fluvastatin (up to 40 mg/day) is increased in patients on a stable, well-tolerated cyclosporin regimen (increase of 94% in fluvastatin AUC).

The results of another study, in which Lescol XL (80 mg fluvastatin) was administered to renal transplant patients who were on a concomitant, stable cyclosporin regimen, showed that fluvastatin AUC and C_{max} were doubled compared to historical data in healthy volunteers. This combination should therefore be used with caution (see "Warnings and precautions").

Ion exchange resins: Fluvastatin should not be given for at least 4 hours after an ion exchange resin (e.g. colestyramine) in order to avoid interactions caused by fluvastatin binding to the resin.

Rifampicin: Administration of fluvastatin to healthy volunteers pre-treated with rifampicin 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, for patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis), appropriate adjustment of fluvastatin dosage may be warranted 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 (increase of 24–33% in AUC). This is of no clinical relevance, however. No interaction studies have been carried out with other H₂ receptor antagonists or proton pump inhibitors.

Phenytin: The minimal effect of phenytin on fluvastatin pharmacokinetics is measured when patients are given fluvastatin with phenytin. It is concluded that dosage adjustment of fluvastatin is not necessary with co-administration.

Cardiovascular agents: No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with propranolol, losartan, clopidogrel, digoxin or amlopidine. 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

Cyclosporin: Both Lescol capsules (40 mg fluvastatin) and Lescol XL tablets (80 mg fluvastatin) had no effect on cyclosporin bioavailability when co-administered with cyclosporin (see also Effects of other drugs on fluvastatin).

Colchicine: No data are available on the pharmacokinetic interaction between fluvastatin and colchicine. However, myotoxicity, including muscle pain, muscle weakness and rhabdomyolysis, has been reported in association with concomitant administration of colchicine.

Phenytoin: The overall magnitude of the changes in phenytoin pharmacokinetics during co-administration with fluvastatin is relatively small (estimated increase in AUC at steady state = approx. 33%). This increase could, however, be clinically relevant in patients requiring high phenytoin levels to control attacks. Except in these cases, routine monitoring of phenytoin plasma levels is sufficient during co-administration with fluvastatin.

Warfarin and other coumarin derivatives: In healthy volunteers, concomitant administration of a single dose of fluvastatin and warfarin did not lead to any

differences in plasma levels and prothrombin times compared to the administration of warfarin alone. However, isolated incidences of bleeding and/or increased prothrombin times have been reported very rarely in patients on fluvastatin receiving concomitant warfarin or other coumarin derivatives. It is therefore recommended that prothrombin times be monitored when fluvastatin treatment is initiated, discontinued, or the dosage changed in patients receiving warfarin or other coumarin derivatives. No interaction studies are available with anticoagulants used in Switzerland (acenocoumarol, phenprocoumon).

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

The following adverse effects 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 effects are listed according to system organ classes in MedDRA. Within each system organ class, the effects are presented according to their severity.

Hepatobiliary disorders
Hepatic failure.

Reproductive system and breast disorders
Erectile dysfunction.

Children and adolescents
In two clinical trials, the safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that in adults. In both clinical trials, all children and adolescents continued with their normal growth and sexual maturation.

Laboratory findings: Biochemical changes in liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of serum transaminase levels to more than three times the upper limit of normal (ULN) developed in a small number of patients (1-2%). Marked elevations of CK levels to more than 5 × ULN were reported in a very small number of patients (0.3-1.0%).

Lactation
There are no data on the excretion of fluvastatin in breast milk, and the product should therefore not be used by breastfeeding women.

Effects on ability to drive and use machines

The patient's reactions and ability to drive and use tools and machines may be impaired due to the potential adverse effects.

Adverse effects

Frequency was defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1000); very rare (< 1/10 000).

Phenytin: The minimal effect of phenytin on fluvastatin pharmacokinetics is measured when patients are given fluvastatin with phenytin. It is concluded that dosage adjustment of fluvastatin is not necessary with co-administration.

Blood and lymphatic system disorders
Very rare: Thrombocytopenia.

Immune system disorders
Very rare: Anaphylactic reaction.

Nervous system disorders
Common: Headache, fatigue, insomnia, dizziness.
Very rare: Paraesthesia, dysaesthesia and hypoaesthesia, also known to be associated with existing disorders of lipid metabolism; polyneuropathy.

Vascular disorders
Very rare: Vasculitis.

Gastrointestinal disorders
Common: Dyspepsia, abdominal pain, nausea, heartburn, constipation, flatulence, diarrhoea.
Very rare: Pancreatitis.

Hepatobiliary disorders (see "Warnings and precautions").
Very rare: Hepatitis.

Skin and subcutaneous tissue disorders
Rare: Hypersensitivity reactions such as rash or urticaria.
Very rare: Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), facial oedema, angioedema, lupus erythematosus-like reactions.

Musculoskeletal disorders (see "Warnings and precautions").
Rare: Myalgia, muscle weakness, myopathy.

Very rare: Myositis, rhabdomyolysis, lupus-like syndrome. Rhabdomyolysis is a potentially life-threatening condition. Isolated cases of symptoms affecting the Achilles tendon, associated in rare instances with rupture of the Achilles tendon.

Investigations
Common: Blood creatine phosphokinase increased, blood transaminases increased.

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Very rare: Thrombocytopenia.

Immune system disorders
Very rare: Anaphylactic reaction.

Nervous system disorders
Common: Headache, fatigue, insomnia, dizziness.
Very rare: Paraesthesia, dysaesthesia and hypoaesthesia, also known to be associated with existing disorders of lipid metabolism; polyneuropathy.

Vascular disorders
Very rare: Vasculitis.

Gastrointestinal disorders
Common: Dyspepsia, abdominal pain, nausea, heartburn, constipation, flatulence, diarrhoea.
Very rare: Pancreatitis.

Hepatobiliary disorders (see "Warnings and precautions").
Very rare: Hepatitis.

Skin and subcutaneous tissue disorders
Rare: Hypersensitivity reactions such as rash or urticaria.
Very rare: Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), facial oedema, angioedema, lupus erythematosus-like reactions.

Musculoskeletal disorders (see "Warnings and precautions").
Rare: Myalgia, muscle weakness, myopathy.

Table 1: Responder rates in % LDL-C reduction after 4 weeks (pooled data from the three comparative studies)

% responder rate	≥15%	≥30%	≥35%	≥40%
Lescol (40 mg, once daily)	84.8	39.0	19.7	9.1
Lescol XL (80 mg, once daily)	95.9	73.5	58.0	40.2

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

Medicinal product	Total-C	LDL-C	HDL-C	HDL-C (baseline ≤39 mg/dl)	Apo B	TG*
Lescol (40 mg, once daily)	-1.7%	-25%	+6%	+10%	-18%	-12%
Lescol XL (80 mg, once daily)	-2.3%	-34%	+9%	+14%	-26%	-19%

* median percent change

Of the 857 patients randomized to Lescol XL 271 with primary mixed dyslipidaemia (Fredrickson type IIb), as defined by baseline levels ≥ 200 mg/dl, showed a mean reduction in triglycerides of 25%. In these patients, Lescol XL produced a meaningful increase in HDL-C of 13%. This effect was even more pronounced in patients with very high HDL-C levels at baseline (i.e. < 45 mg/dl, who had a mean increase in HDL-C of 25%). Significant decreases in total-C, LDL-C, and apo B was also achieved (see Table 3). (Patients with triglycerides >400 mg/dl were excluded from these studies.)

Table 3: Mean change from baseline after 24 weeks (primary mixed dyslipidaemia)

Medicinal product	Total-C	LDL-C	HDL-C	Apo B	TG*
Lescol (40 mg, once daily)	-1.7%	-23%	+7%	-17%	-18%
Lescol XL (80 mg, once daily)	-2.4%	-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 hypercholesterolaemia (baseline LDL-C: 115-190 mg/dl, or 3.0-4.9 mmol/litre). In this randomized, controlled, double-blind clinical study, 429 patients were given either 20 mg fluvastatin twice daily or placebo in addition to standard therapy. Angiograms were evaluated at baseline and after 2.5 years.

Fluvastatin significantly slowed the progression of coronary atherosclerotic lesions as measured by intrapatient change in minimum lumen diameter (MLD, primary endpoint), percent diameter stenosis or formation of new lesions. In the Lescol Intervention Prevention Study (LIPS), the effect of fluvastatin on major adverse cardiac events (MACE) was investigated in male and female patients (18-80 years of age) with coronary heart disease and a wide range of cholesterol levels (baseline total cholesterol: 3.5-7.0 mmol/litre). In this randomized, double-blind, placebo-controlled study, fluvastatin (n = 542), at a dose of 80 mg/day for 4 years, significantly (p = 0.045) reduced the need for additional coronary revascularization procedures in coronary patients, as compared with placebo (n = 425). The beneficial effect was particularly marked in patients with diabetes and patients with multivessel disease. Treatment with fluvastatin did not reduce the risk of cardiac death and/or myocardial infarction (p = 0.958).

Clinical efficacy
In three multicentre, double-blind, active-controlled studies in nearly 1700 patients with moderate-to-severe hypercholesterolaemia, the efficacy and safety of 20 to 80 mg fluvastatin were investigated for 2 years for each study in a total of 113 children and adolescents with heterozygous familial hypercholesterolaemia.

The studies included boys between 9 and 12 years of age