NOVARTIS

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 IIa and IIb) 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 postmenarchal 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 revascularization 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 dose adjustments made 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)
Postmenarchal 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, cholestyramine 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 susceptible to rhabdomyolysis and its complications. 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 metabolic, 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 possible 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 x 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 ciclosporin 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 ciclosporin), fibrates, nicotinic acid, erythromycin, or antifungal azole derivatives in combination with ciclosporin (see "Interactions"). There have been isolated post-marketing reports of myopathy following concomitant administration of fluvastatin with ciclosporin and fluvastatin with colchicine. 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 ciclosporin and fluvastatin who also require treatment with a substance of the azole group, ciclosporin 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 postmenarchal 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* (mibefradil) 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").

Itraconazole and erythromycin: Concomitant administration of fluvastatin with the potent cytochrome P450 (CYP) 3A4 inhibitors itraconazole and erythromycin (only single doses investigated) has minimal effects on the bioavailability of fluvastatin. Given the minimal effects of this enzyme on fluvastatin metabolism, other CYP3A4 inhibitors (e.g. ketoconazole) are unlikely to have a major effect on the bioavailability of fluvastatin. As regards ciclosporin, see below.

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.

Ciclosporin: 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 ciclosporin 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 ciclosporin 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 H_2-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 H_2-receptor antagonists or proton pump inhibitors.

Phenytoin: The minimal effect of phenytoin on fluvastatin pharmacokinetics means 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 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: Both Lescol capsules (40 mg fluvastatin) and Lescol XL tablets (80 mg fluvastatin) had no effect on ciclosporin bioavailability when co-administered with ciclosporin (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).

Oral antidiabetics: In patients receiving oral sulphonylureas (glibenclamide, 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 glibenclamide-treated NIDDM patients (n = 32), concomitant administration of fluvastatin (40 mg twice daily for 14 days) increased the C_{max}, AUC, and $t_{½}$ 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 or C-peptide levels. However, patients on concomitant therapy with glibenclamide and fluvastatin should continue to be monitored 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
Pregnancy
Since HMG-CoA reductase inhibitors decrease the synthesis of cholesterol and, possibly, of biologically active cholesterol derivatives, they may harm the fetus or infant. HMG-CoA reductase inhibitors are therefore contraindicated during pregnancy and lactation, as well as in women of childbearing potential not using a reliable method of contraception. If pregnancy does occur during treatment, the drug must be discontinued.

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
Frequencies were 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).*
The most commonly reported adverse effects are minor gastrointestinal symptoms, insomnia and headache.

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 adverse effect.
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.

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%).

Overdose
In a placebo-controlled study including 40 hypercholesterolaemic patients, doses of up to 320 mg/day (n=7 per dose group) administered as Lescol XL (80 mg prolonged release tablets) over two weeks were well tolerated.
No specific recommendations can be made regarding the management of overdose. Should an overdose occur, it should be treated symptomatically and necessary supporting measures should be taken. Liver function tests and serum CK levels should be monitored.

Properties / Actions
ATC code: C10A A04

Mechanism of action
Fluvastatin is a fully synthetic cholesterol-lowering agent that is a competitive inhibitor of HMG-CoA reductase. It is a catalyst in the conversion of HMG-CoA to mevalonate, a precursor of sterols including cholesterol.
Fluvastatin exerts its main effect in the liver. It is a racemate, consisting primarily of two erythro enantiomers, only one of which is responsible for its 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.

Pharmacodynamics
In patients with hypercholesterolaemia and mixed dyslipidaemia, fluvastatin reduces total cholesterol (total-C), LDL cholesterol (LDL-C), apolipoprotein B (apo B) and triglycerides (TG), while increasing HDL cholesterol (HDL-C). The therapeutic response is established within two weeks, and maximum response is achieved within four weeks of treatment initiation and maintained during long-term therapy.

Clinical efficacy
In three multicentre, double-blind, active-controlled studies in nearly 1700 patients with primary hypercholesterolaemia or primary mixed dyslipidaemia, Lescol XL (80 mg/day) was compared to Lescol (40 mg at bedtime or 40 mg twice daily) over 24 weeks of therapy. The responder rates following achievement of the maximum therapeutic response are shown in Table 1 for Lescol once daily (mean LDL-C reduction = 26%) and Lescol XL (mean LDL-C reduction = 36%).

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

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

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

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

** median percent change*

Of the 857 patients randomized to Lescol XL, 271 with primary mixed dyslipidaemia (Frederickson type IIb), as defined by baseline levels ≥ 200 mg/dl, showed a median 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 low HDL-C levels at baseline (i.e. < 35 mg/dl), who had a mean increase in HDL-C of 16%. A significant decrease 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) Lescol XL (80 mg, once daily)	– 17% – 24%	– 23% – 33%	+ 7% + 13%	– 17% – 24%	– 18% – 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).

Children and adolescents
In two open-label dose-titration studies (ZA01 and 2301), 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 (ZA01) and boys and postmenarchal girls between 10 and 16 years of age (2301) with an established diagnosis of heterozygous familial hypercholesterolaemia. This was defined as follows:
- LDL-C levels ≥ 190 mg/dl (4.9 mmol/litre),
- or LDL-C levels ≥ 160 mg/dl (4.1 mmol/litre) and one or more risk factors (family history of premature coronary heart disease [CHD], smoking, hypertension, confirmed high density lipoprotein-cholesterol [HDL-C] < 35 mg/dl, diabetes mellitus);
- or proven LDL-C receptor deoxyribonucleic acid (DNA) defect and LDL-C levels > 160 mg/dl (4.1 mmol/litre) with serum triglyceride levels at or below 600 mg/dl.

The main exclusion criteria were patients with homozygous familial hypercholesterolaemia; secondary forms of dyslipoproteinaemia; serum triglycerides > 600 mg/dl; ALT, AST or creatinine levels > 1.5 × ULN (upper limit of normal); serum CK or serum TSH > 2 × ULN; body mass index (BMI) > 30 kg/m².
The starting dose of fluvastatin was 20 mg for the first week; this was up-titrated (at 6 week intervals) to 40 mg and then 80 mg (two 40 mg capsules or one 80 mg prolonged release tablet) if LDL-C levels were > 3.2 mmol/litre or 3.4 mmol/litre, respectively.
Fluvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides (TG) and Apo B, and increased HDL-C during 2 years of follow-up (see Table 4).

Table 4: Lipid lowering effect of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia

Study ZA 01 (prepubertal boys)	Baseline (mmol/litre) n=29	Month 24 (mmol/litre) n=27	Mean % change from baseline (95% CI) n=27
LDL-cholesterol [mean (SD)]	5.8 (1.4)	4.2 (1.5)	-27.0 % (-34.7 %, -19.4 %)
Total cholesterol [mean (SD)]	7.7 (1.4)	5.9 (1.5)	-21.1 % (-26.8 %, -15.4 %)
HDL-cholesterol [mean (SD)]	1.4 (0.3)	1.4 (0.4)	1.3 % (-8.0 %, 10.7 %)
Triglycerides [median (range)]	0.8 (0.4-2.5)	0.7 (0.4-2.8)	- 7.0 % (-22.1 %, 8.0 %)
Study 2301 (prepubertal, pubertal and postpubertal)	**Baseline (mmol/litre) n=84**	**Month 24 (mmol/litre) n=84**	**Mean % change from baseline (95% CI) n=84**
LDL-cholesterol [mean (SD)]	6.0 (1.27)	4.1 (1.14)	-30.5 % (-34.8 %, -26.2 %)
Total cholesterol [mean (SD)]	7.7 (1.33)	5.8 (1.16)	-23.6 % (-27.2 %, -19.9 %)
HDL-cholesterol [mean (SD)]	1.2 (0.23)	1.3 (0.23)	5.0 % (1.6 %, 8.5 %)
Triglycerides [median (range)]	0.93 (0.5-3.0)	0.84 (0.4-2.4)	-5.2 % (-13.2 %, 2.7 %)

In both studies, all patients continued with their normal growth and sexual maturation. Fluvastatin has not been investigated in children under 9 years of age.
These studies did not permit extrapolation of cardiovascular outcomes of early initiation of statin therapy in children.

Pharmacokinetics
Absorption
Fluvastatin is absorbed rapidly and completely (98%) after administration of a solution to fasted healthy volunteers. After oral administration of Lescol XL prolonged release tablets, the rate of absorption is slower than that of the capsules (t_{max} of Lescol XL around 3 hours, t_{max} of Lescol around 1 hour), while the mean residence time of fluvastatin is increased by approximately 4 hours. Ingestion after a meal results in slower absorption of the active substance. Peak plasma concentrations are attained about one hour after ingestion of one Lescol / Lescol mite capsule. Peak plasma concentrations are approximately 140 and 365 ng/ml, respectively.
The AUC is the same whether fluvastatin is taken with a low-fat evening meal or 4 hours later. The absolute bioavailability of Lescol/Lescol mite assessed from systemic blood concentrations is 24%. After a high-fat meal, bioavailability is increased by approximately 50%. The pharmacokinetics of fluvastatin are non-linear; doubling the dose from 40 mg to 80 mg (one 40 mg Lescol capsule twice daily) results in an increase of around 50% in AUC and C_{max} (saturable first-pass effect).
AUC and C_{max} are markedly lower following ingestion of Lescol XL compared with Lescol (higher first-pass effect due to delayed release of fluvastatin). The bioavailability of Lescol XL (80 mg) is approx. 25% that of Lescol (two 40 mg capsules).

Distribution
The apparent volume of distribution (V_z/f) is 330 litres. 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 exerts its main effect in the liver, which is also the main organ for its metabolism. The major components circulating in the blood are the active substance and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate in the blood.
There are multiple, alternative cytochrome P450 (CYP450) pathways for fluvastatin biotransformation, and fluvastatin metabolism is relatively insensitive to CYP450 inhibition, a major cause of many adverse drug-drug interactions.
Several detailed *in vitro* studies have investigated the inhibitory potential of fluvastatin on common CYP isoenzymes. They have shown that fluvastatin is a potent inhibitor of CYP2C9 and thus affects the metabolism of substances metabolized by CYP2C9. Despite the potential shown by these studies for competitive interaction between fluvastatin and CYP2C9 substrates such as diclofenac, phenytoin, tolbutamide and warfarin, clinical data indicate that this interaction is unlikely (see "Interactions").
Given the minimal involvement of the CYP3A4 enzyme in the metabolism of fluvastatin, CYP3A4 inhibitors should not affect overall fluvastatin metabolism.
Similarly, CYP3A4 substrates should not be affected by fluvastatin because it is not known to either induce or inhibit CYP3A4 (IC50 > 100 µM).

Elimination
Following administration of ^{3}H-fluvastatin to healthy volunteers, approximately 6% of the radioactivity is recovered in the urine and 93% in the faeces, and fluvastatin accounts for less than 2% of the total radioactivity excreted. Plasma clearance (CL/F) in humans has been calculated at 1.8 ± 0.8 litres/minute. Steady-state plasma concentrations show no evidence of accumulation following administration of 80 mg daily. Following oral administration of 40 mg fluvastatin, the terminal half-life was 2.3 ± 0.9 hours.

Pharmacokinetics in special patient populations
Since fluvastatin is eliminated primarily via the biliary route and is subject to pronounced pre-systemic metabolism, the possibility of accumulation cannot be ruled out in patients with hepatic impairment (see "Contraindications" and "Warnings and precautions").
Plasma concentrations of fluvastatin are normally independent of age and gender. However, a tendency for enhanced treatment response was observed in women and elderly people.

Preclinical data
Carcinogenicity
At fluvastatin plasma concentrations approximately 9, 13, 26 or 35 times higher than those in humans after a 40 mg oral dose, forestomach squamous cell papillomas developed in rats, as did one carcinoma of the forestomach at the 24 mg/kg/day dose level. However, this was interpreted to be the result of chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a systemic (genotoxic) effect. Furthermore, an increased incidence of thyroid follicular adenomas and carcinomas was seen in male rats initially given 18 mg/kg/day for one year, then 24 mg/kg/day for an additional year. The increase in these neoplasms in male rats given fluvastatin is consistent with species-specific findings for other HMG-CoA reductase inhibitors. Adenomas or carcinomas of the liver were not reported for fluvastatin.
A carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg/day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg/day and in females at 15 mg/kg/day. These dosages correspond to plasma drug levels approximately 0.2, 10 and 21 times those in humans 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. There was no evidence of increased neoplasia at these doses, but hyperkeratosis and hyperplasia of the squamous epithelium were shown.

Mutagenicity
Fluvastatin was extensively studied *in vitro* and *in vivo* – both with and without metabolic activation – to determine mutagenicity. None of the testing systems yielded any evidence of mutagenicity.
The following testing systems were used: Ames test using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, malignant transformation assay in BALB/3T3 cells, unscheduled DNA synthesis in rat primary hepatocytes, chromosomal aberration tests in V79 cells, HGPRT tests in V79 Chinese hamster cells and micronucleus tests in mice and rats.

Reproductive toxicity
In studies in rats at dose levels in females of 0.6, 2 and 6 mg/kg/day and in males of 2, 10 and 20 mg/kg/day, there was no impairment of fertility or reproductive performance at any of the specified dosages. Teratology studies in rats and rabbits showed maternal toxicity at high doses, but there was no evidence of embryotoxic or teratogenic potential.
A study in which female rats were given 12 and 24 mg/kg/day fluvastatin during the third trimester showed maternal peripartum mortality, as well as fetal and neonatal lethality. No maternal or fetal effects were seen at the low dose of 2 mg/kg/day.
These results were confirmed in a second study involving doses of 2, 6, 12 and 24 mg/kg/day. A modified perinatal and postnatal study was then carried out using 12 and 24 mg/kg/day. In this study, mevalonic acid, an intermediate in cholesterol biosynthesis, was either co-administered or withheld. Concurrent administration of mevalonic acid completely prevented both maternal and neonatal mortality. This is indirect proof of the pharmacodynamic effect of fluvastatin (inhibition of HMG-CoA reductase and thus of mevalonic acid synthesis), which is exaggerated during pregnancy.

Other information
Shelf life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
Lescol and Lescol mite capsules: Do not store above 25°C. Lescol XL prolonged release tablets: Do not store above 30°C.
Keep out of the reach of children.

Pack sizes
Country specific pack sizes.

Manufacturer
See folding box.

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® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament
– A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed for you.
– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists