NOVARTIS

Drug Regulatory Affairs

# LESCOL®
(fluvastatin sodium)

Gelatine capsules 20 mg and 40 mg

# LESCOL® XL
(fluvastatin sodium)

Prolonged release tablets 80 mg

## Basic Prescribing Information

**NOTICE**

**The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.**

**National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.**

Authors: Céline Clauss, Gautier Sala, Sabina Hernandez Penna, Samuel Rigourd

GLC approval: 07 June 2005, amended 15 November 2005, 29 November 2005, 22 August 2006, and 06 May 2008

Release date: 07 May 2008

Tracking Number: 2008-PSB/GLC-0133-s

Document status: Final

Number of pages: 28

# 1 Name of the medicinal product

LESCOL®, 20 mg and 40 mg, gelatine capsules

LESCOL® XL, 80 mg, prolonged release tablets

# 2 Qualitative and quantitative composition

Active substance: [R*,S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoate (fluvastatin sodium)

One capsule of Lescol contains 21.06 mg or 42.12 mg fluvastatin sodium equivalent to 20 mg or 40 mg fluvastatin free acid.

One prolonged release tablet of Lescol XL contains 84.24 mg fluvastatin sodium equivalent to 80 mg fluvastatin free acid.

For a full list of excipients, see section 6.1 List of excipients.

# 3 Pharmaceutical forms

Capsules and prolonged release tablets for oral administration.

Information might differ in some countries.

# 4 Clinical particulars

## 4.1 Therapeutic indications

#### Dyslipidaemia

##### Adults

Lescol/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).

##### Paediatric population

Lescol/Lescol XL is indicated as an adjunct to diet for the reduction of elevated total-C, LDL-C, apo B and TG levels and for the increase of HDL-C in children and adolescents aged 9 years and older with heterozygous familial hypercholesterolaemia.

#### Other indications

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

Lescol/Lescol XL is also indicated for the secondary prevention of major adverse cardiac events (cardiac death, non-fatal myocardial infarction and coronary revascularisation) in adults with coronary heart disease after coronary transcatheter therapy.

## 4.2 Posology and method of administration

Lescol may be taken in the evening or at bedtime without regard to meals. Lescol XL can be administered as single dose at any time of the day with or without food. Lescol and 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/Lescol XL is maintained with prolonged administration.

### Adults

Prior to initiating treatment with Lescol/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 40 mg (1 capsule Lescol 40 mg once daily) or 80 mg (1 tablet Lescol XL 80 mg once daily or 1 capsule Lescol 40 mg twice daily). The dose of 20 mg fluvastatin (1 capsule Lescol 20 mg) may be adequate in mild cases. 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/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 4.5 Interaction with other medicinal products and other forms of interaction).

### Paediatric population

Prior to initiating treatment with Lescol/Lescol XL, the patient should be placed on a standard cholesterol-lowering diet for 6 months. Dietary therapy should be continued during treatment.

The recommended starting dose is 40 mg (1 capsule Lescol 40 mg once daily) or 80 mg (1 tablet Lescol XL 80 mg once daily or 1 capsule Lescol 40 mg twice daily). The dose of 20 mg fluvastatin (1 capsule Lescol 20 mg) may be adequate in mild cases. Starting doses should be individualized according to baseline LDL-C levels and the recommended goal of therapy to be accomplished.

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

### Patients with impaired kidney function

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. No dose adjustments are therefore necessary in these patients.

### Patients with impaired liver function

Lescol/Lescol XL is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

### Elderly population

In clinical studies with Lescol/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.

## 4.3 Contraindications

Lescol/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 lactation (see section 4.6 Pregnancy and lactation).

## 4.4 Special warnings and precautions for use

### Liver function

As with other lipid-lowering drugs, it is recommended that liver function tests be performed before the initiation of treatment and at 12 weeks following initiation of treatment or elevation in 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, possibly drug-related hepatitis was observed that resolved upon discontinuation of treatment.

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

### Skeletal muscle

With fluvastatin myopathy has rarely been reported, 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.

### Creatine kinase measurement

There is no current evidence to require routine monitoring of plasma total creatine kinase or other muscle enzyme levels in asymptomatic patients on statins. If creatine kinase has to be

measured it should not be done following strenuous exercise or in the presence of any plausible alternative cause of CK-increase as this makes the value interpretation difficult.

**Before the treatment**

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

- Renal impairment.
- Hypothyroidism.
- Personal or familial history of hereditary muscular disorders.
- Previous history of muscular toxicity with a statin or fibrate.
- Alcohol abuse.
- In elderly (age >70 years), the necessity of such measurement should be considered, according to 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 later to confirm the results. If CK-levels are still significantly elevated (>5 x ULN) at baseline, treatment should not be started.

**Whilst on treatment**

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

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, then 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 immunosuppressive 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/Lescol XL should be used with caution in patients receiving such concomitant medication (see 4.5 Interaction with other medicinal products and other forms of interaction).

**Paediatric population**

In patients aged <18 years, efficacy and safety have not been studied for treatment periods longer than two years.

Fluvastatin has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia (for details see section 5.1 Pharmacodynamic properties).

### Homozygous familial hypercholesterolemia

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

## 4.5 Interaction with other medicinal products and other forms of interaction

### 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 4.4 Special warnings and precautions for use).

### 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 patents 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 wherein Lescol XL (80 mg fluvastatin) was administered to renal transplant patients who were on 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 4.4 Special warnings and precautions for use).

### 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, 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, 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 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 IR (40 mg fluvastatin) and 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, have 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 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.

## 4.6 Pregnancy and lactation

(see section 4.3 Contraindications)

### Pregnancy

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

Women of childbearing potential have to use effective contraception. If a patient becomes pregnant while taking Lescol/Lescol XL, therapy should be discontinued.

### Lactation

Lescol/Lescol XL is contraindicated in nursing mothers.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: 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), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

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** | |
| Very rare: | Anaphylactic reaction |
| **Psychiatric disorders** | |
| Common: | Insomnia. |
| **Nervous system disorders** | |
| Common: | Headache. |
| Very rare: | Paraesthesia, dysaesthesia, hypoaesthesia also known to be associated with the underlying hyperlipidemic disorders. |
| **Vascular disorders** | |
| Very rare: | Vasculitis. |
| **Gastrointestinal disorders** | |
| Common: | Dyspepsia, abdominal pain, nausea. |
| Very rare: | Pancreatitis. |
| **Hepatobiliary disorders** | |
| Very rare: | Hepatitis. |

| | |
|---|---|
| **Skin and subcutaneous tissue disorders** | |
| Rare: | Hypersensitivity reactions such as rash, urticaria. |
| Very rare: | Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema. |
| **Musculoskeletal and connective tissue disorders** | |
| Rare: | Myalgia, muscle weakness, myopathy. |
| Very rare: | Rhabdomyolysis, myositis, lupus erythematosus-like reactions. |

**Paediatric population**

The safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolemia assessed in two clinical trials was similar to the one observed in adults. In both clinical trials, all children and adolescents continued with their normal growth and sexual maturation.

**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 5 x ULN developed in a very small number of patients (0.3 to 1.0%).

## 4.9 Overdose

In a placebo-controlled study including 40 hypercholesterolemic patients, doses 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 recommendations concerning the treatment of an overdosage can be made. Should an overdose occur, it should be treated symptomatically and supporting measures should be undertaken as required.

# 5 Pharmacological properties

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors (ATC Code: C10A A04).

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.

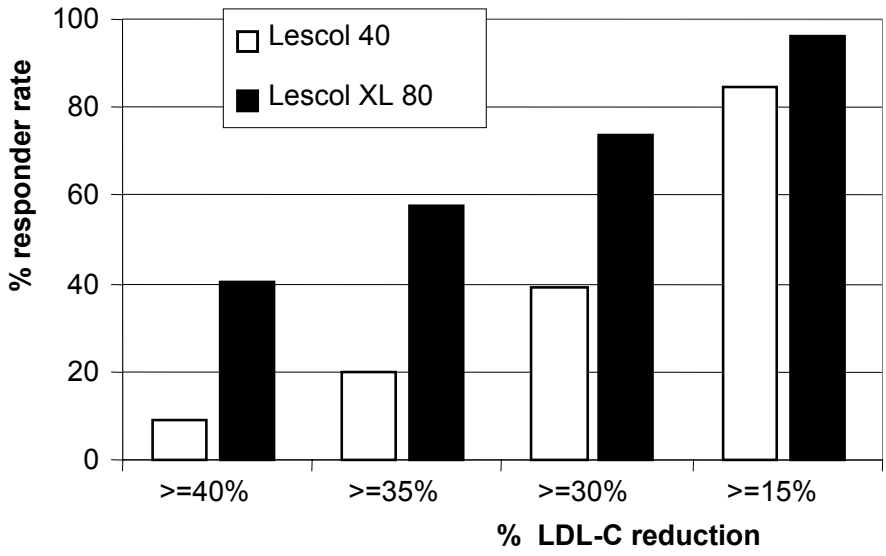
Lescol/Lescol XL reduces total-C, LDL-C, apo-B, and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is well established within 2 weeks, and maximum response is achieved within 4 weeks from treatment initiation and maintained during chronic therapy.

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 decrease 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 randomised, double-blind, placebo-controlled trial fluvastatin (N = 844), given as 80 mg daily over 4 years, significantly reduced the risk of the first MACE by 22% (p = 0.013) as compared to placebo (N = 833). These beneficial effects were particularly noteworthy, in diabetics and in patients with multivessel disease. Therapy with fluvastatin reduced the risk of cardiac death and/or myocardial infarction by 31% (p = 0.065).

**Paediatric population**

In two open label, dose titration studies (ZA01 and 2301), the efficacy and safety of fluvastatin 20 to 80mg were investigated during a period of 2 years for each study in a total of 113 children and adolescents with heterozygous familial hypercholesterolemia.

The studies included patients aged 9 years and above with an established diagnosis of heterozygous familial hypercholesterolemia defined as:

- LDL-C levels ≥190 mg/dL (4.9 mmol/L)
- or LDL-C levels ≥160 mg/dL (4.1 mmol/L) and one or more risk factors (family history of premature coronary heart disease (CHD), current cigarette 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/L) serum triglyceride levels at or below 600 mg/dL.

The main exclusion criteria were patients with homozygous familial hypercholesterolemia; secondary forms of dyslipoproteinemia; serum triglycerides levels >600 mg/dL; ALAT, ASAT or creatinine levels >1.5 x ULN; serum CK or serum TSH >2 x ULN; BMI >30 kg/$m^2$.

The starting dose of fluvastatin was 20 mg for the first week and up-titrated (at 6 weeks interval) to 40 mg and then 80 mg (two times 40 mg capsules or 80 mg extended release tablets) if LDL-C levels were >3.2 mmol/L or 3.4 mmol/L respectively.

Fluvastatin significantly decreased plasma levels of Total-C, LDL-C, 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) | Baseline (mmol/L) N=29 | Month 24 (mmol/L) 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/L) N=84** | **Month 24 (mmol/L) 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 younger than 9 years of age.

These studies did not permit to extrapolate cardiovascular outcomes of early initiation of statin therapy in children.

## 5.2 Pharmacokinetic properties

### 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, and 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 faeces, and fluvastatin accounts for less than 2% of the total radioactivity excreted. The plasma clearance (CL/f) for fluvastatin in man 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 disposition 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.

### Characteristics in patients

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.

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 4.3 Contraindications and 4.4 Special warnings and precautions for use).

## 5.3 Preclinical 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, with gallbladder changes in dog, monkey and hamster, thyroid weight increases in the rat, and testicular degeneration in the hamster. 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 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 plasma drug levels approximately 0.2, 10 and 21 times the mean human plasma drug concentration after a 40 mg oral dose.

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. The increased incidence of thyroid follicular cell neoplasms in male rats given fluvastatin appears to be consistent with species-specific findings with other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no treatment-related increases in the incidence of hepatic adenomas or carcinomas were observed.

### 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 mutagenicity *in vivo* in either a rat or mouse micronucleus test.

**Reproductive toxicity**

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 the fertility or reproductive performance. Teratology studies in rats (1, 12 and 36 mg/kg) and rabbits (0.05, 1 and 10 mg/kg) 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 foetal and neonatal lethality. No effects on the pregnant females or foetuses occurred at the low dose level of 2 mg/kg per day.

A second study 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 pharmacologic effect during pregnancy.

# 6 Pharmaceutical particulars

## 6.1 List of excipients

**Lescol 20 mg and 40 mg capsules**

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

Information might differ in some countries.

**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.

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

### Lescol 20 mg and 40 mg capsules

3 years.

Information might differ in some countries.

### Lescol XL 80 mg tablets

2 years.

Information might differ in some countries.

## 6.4 Special precautions for storage

### Lescol 20 mg and 40 mg capsules

Do not store above 25 C. Capsules should be left in the blister pack until required for use.

Information might differ in some countries.

### Lescol XL 80 mg tablets

Do not store above 25 C. Tablets should be left in the blister pack until required for use.

Information might differ in some countries.

Lescol/Lescol XL must be kept out of the reach and sight of children.

## 6.5 Nature and contents of the container

Country specific.

## 6.6 Instructions for use/handling

No special requirements.