Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lescol XL 80 mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 80 mg of Fluvastatin as Fluvastatin Sodium

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.
Product imported from Italy and Greece:
Yellow, round tablets, debossed with “NVR” on one side and “LE” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

LESCOL/LESCOL XL is indicated as an adjunct to diet for the reduction of elevated total cholesterol (total-C) and low-density lipoprotein cholesterol (LDL-C), in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson Types IIa and IIb).

LESCOL/Lescol XL is also indicated for the secondary prevention of major adverse cardiac events (coronary revascularisation, cardiac death and non-fatal myocardial infarction) in patients with coronary heart disease after coronary transcatheter therapy (see section 5.1).

4.2 Posology and method of administration

Dosage for 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 or 1 Lescol 40 mg capsules 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 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.

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).

Children and adolescents with heterozygous familial hypercholesterolemia.

Prior to initiating treatment with Lescol/Lescol XL in children and adolescents aged 9 years and older with heterozygous familial hypercholesterolaemia, the patients should be places on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

The recommended starting dose is 40 mg (1 capsules Lescol 40 mg). The dose can be increased to 80 mg (1 tablet Lescol XL 80 mg once daily or one capsules Lescol 40 mg twice daily) if necessary. The dose of 20 mg fluvastatin (1 capsules 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 accomplised. 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 section 4.3 Contraindications and section 4.4 Special warnings and special precautions for use).

Elderly

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 XL is contraindicated :

• in patients with known hypersensitivity to fluvastatin or any of the excipients.

• in patients with active liver disease or persistent unexplained elevation of transaminase levels (see 4.8); cholestasis.

• in patients with myopathic disorders.

• during pregnancy and lactation (see 4.6).

• in patients with a history of liver disease or high alcohol consumption (see 4.8).

4.4 Special warnings and precautions for use

Liver Function
Serum transaminase levels should be determined before and at 12 weeks following initiation of treatment or elevation in dose and periodically during treatment with LESCOL XL. Patients whose levels increase in response to the drug should be monitored particularly closely, with immediate repetition of the measurement followed by more frequent measurements. If levels continue to increase, and particularly if they persistently exceed the upper limit of the normal range by a factor of 3 or more, LESCOL XL should be withdrawn.
Hepatitis that might have been drug-related has been reported in a few, very isolated instances, with remission after withdrawal of the drug.

Skeletal muscle function
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 > 5xULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated > 5xULN) 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 > 5xULN). 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. LESCOL XL can be used with caution in patients receiving such concomitant medication (see 4.5 Interaction with other medicinal products and other forms of interaction).

Children and adolescents with heterozygous familial hypercholesterolemia.

In patients aged <18 years, efficacy and safety have not been studied for treatment periods longer then two years. No data are available about the physical, intellectual and sexual maturation for prolonged treatment period. The long-term efficacy of Lescol/ Lescol XL therapy in childhood to reduce morbidity and mortality in adulthood has not been established. (see section 5.1).

Fluvastatin has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia (for details see section 5.1 Pharmacodynamic properties). In the case of per-pubertal children, as experience is very limited in this group, the potential risks and benefits should be carefully evaluated before the initiation of treatment.

Patients with impaired renal function

Fluvastatin is excreted via the bile. No data is available for patients with renal function impairment and its use is not recommended in cases of severe renal impairment (creatinine >260 µmol/L) (See 4.2).

Homozygous familial hypercholesterolaemia.

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 special 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 (Cmax) 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 special 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 H2-receptor antagonists and proton pump inhibitors.

Concomitant administration of fluvastatin with cimetidine, ranitidine, or omeprazole results in an increase in the bioavailability of fluvastatin, which, however, is of no clinical relevance. While additional interaction studies have not been performed, it is expected that other H2-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 anecdoatally 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, 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 Cmax, AUC, and t1/2 of glibenclamide approximately 50%, 69% and 121%, respectively. Glibenclamide (5 to 20 mg daily) increased the mean Cmax 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.

Cimetidine/ranitidine/omeprazole
Concomitant administration of LESCOL XL with cimetidine, ranitidine or omeprazole results in an increase in the blood level of fluvastatin, but this is of no clinical significance.

Antipyrine
Concomitant administration of LESCOL XL does not affect the metabolism or excretion of antipyrine. As antipyrine is a model for drugs metabolised by the microsomal hepatic enzyme system, interactions with other drugs metabolised in the same way are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy
Since HMG-CoA reductase inhibitors reduce the synthesis of cholesterol and, possibly, some of the precursors in its biosynthesis, they could harm the foetus if given to a pregnant woman. Therefore LESCOL XL is contraindicated during pregnancy.

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

Lactation
LESCOL XL is contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines

There is no information about whether LESCOL XL affects the ability to drive and operate 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.

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 tenderness, muscle weakness, myopathy.
Very rare: Rhabdomyolysis, myositis, lupus erythematosus-like reactions.

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 (1-2%).
Marked elevations of CPK levels to more than 5 x ULN developed in a very small number of patients (0.3-1.0%).

Children and adolescents with heterozygous familial hypercholesterolemia

The safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolemia assessed in 114 patients aged 9-17 years treated in two open noncomparative clinical trials was similar to the one observed in adults. In both clinical trials no effect was observed on growth and sexual maturation. The ability of the trials to detect any effect of treatment in this area was however limited.

4.9 Overdose

Should an accidental overdosage occur, administration of activated charcoal is recommended. In the case of very recent oral intake, gastric lavage may be considered. Treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Fluvastatin, a wholly synthetic hydrophilic cholesterol-lowering agent, is a competitive inhibitor of HMG-CoA reductase, the enzyme responsible for the conversion of HMG-CoA to mevalonic acid, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces its level in liver cells, which stimulates the production of LDL receptors, thereby increasing the uptake of LDL particles. By this mechanism the plasma concentration of cholesterol is lowered.

Fluvastatin is a racemate, with only one of its two enantiomers responsible for its pharmacological activity.

LESCOL XL lowers total cholesterol, LDL cholesterol and apolipoprotein B levels in patients with hypercholesterolaemia. It also causes a slight fall in triglycerides but an increase in HDL cholesterol.

Clinical studies have demonstrated that LESCOL XL 80 mg once daily is as efficacious as LESCOL 40 mg twice daily. LESCOL XL 80 mg offers a simple once daily dose regimen, with lower systemic drug concentrations.

In the Lescol Intervention Prevention Study (LIPS), the effect of fluvastatin on major adverse cardiac events (MACE) was assessed in male and female patients (18-80 years old) with coronary heart disease and a broad range of cholesterol levels (baseline TC: 3.57.0 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). This was largely due to a reduction in the rate of coronary re-intervention from 143 events (16.9%) on fluvastatin versus 171 (20.5%) on placebo. Overall, 181 (21.4%) patients on fluvastatin and 222 (26.7%) patients on placebo experienced the primary endpoint. 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). However, there was no significant reduction in overall mortality with fluvastatin.

Children and adolescents with hetetozygous familial hypercholesterolaemia

The safety and efficacy of Lescol and Lescol XL in children and adolescent patients aged 9-16 years of age with heterozygous familial hypercholesterolemia has been evaluated in 2 open label, uncontrolled clinical trials of 2 years duration. 114 patients (66 boys and 48 girls) were treated with fluvastatin administered as either Lescol capsules 20 mg-40 mg bid Lescol XL 80 mg extended release tablets using a dose-titration regimen based upon LDL-C response.

The first study enrolled 29 pre-pubertal boys, 9-12 years of age, who had an LDL-C level > 90th percentile for age and one parent with primary hypercholesterolemia and either a family history of permature ischemic heart disease or tendon xanthomas. The mean baseline LDL-C was 226 mg/dL equivalent to 5,8 mmol/L (range:137-354 mg/dL equivalent to 3,6-9,2 mmol/L). All patients were started on Lescol capsules 20 mg dialy with dose adjustment every 6 weeks to 40mg daily then 80mg daily (40 mg bid) to achieve and LDL-C goal of 96,7 to 123,7 mg/dL (2,5 mmol/L to 3,2 mmol).

The second study enrolled 85 male and female patients, 10 to 16 years of age, who had an LDL-C > 190 mg/dL (equivalent to 4.9mmol/L) or LDL-C >160mg /dL (equivalent to 4,1 mmol/L) and one or more risk factors for coronary heard disease, or LDL-C > 160 mg/dL (equilvalent to 4,1 mmol/L) and a proven LDL-receptor defect. The mean baseline LDL-C was 225 mg/dL equilvalent to 5,8 mmol/L (range: 137-354 mg/dL equivalent to 3,6-9,2 mmol/L). All patients were started on Lescol capsules 20 mg daily with dose adjustment every 6 weeks to 40 mg daily then 80 mg daily (Lescol 80 mg XL tablet) to achieve an LDL-C goal of <130 mg/dL (3,4 mmol/L).

In the first study, Lescol 20 to 80 mg daily doses decreased plasma levels of total- C and LDLC by 21% and 27% respectively. The mean achieved LDL-C was 161 mg/dL equivalent to 4,2 mmol/L (range: 74-336 mg/dL equivalent to 1,9-8,7 mmol/L). In the second study, Lescol 20 to 80 mg daily doses decreased plasma levels to total-C and LDL- by 22% and 28%, respectively. The mean achieved LCL-C was 159 mg/dL equivalent to 4,1 mmol/L (range: 90-295 mg/dL equivalent to 2,3-7,6 mmol/L).

The majority of patients in both studies (83% in the first study and 89% in the second study) were titrated to the maximum daily dose of 80mg. At study endpoint, 26 to 30% of patients inboth studies achieved a targeted LDL-C goan of <130 mg/dL (3,4 mmol/L).

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 (Vz/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 3H-fluvastatin to healthy volunteers, excretion of radioactivity is about 6% in the urine and 93% in the feces, and fluvastatin accounts for less than 2% of the total radioactivity excreted. The plasma clearance (CL/f) 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 section 4.3 Contraindications and section 4.4 Special warnings and special precautions for use).

Children and adolescents with heterozygous familial hypercholesterolaemia

No pharmacokinetic data in children are available.

5.3 Preclinical safety data

Acute toxicity
Fluvastatin has an oral LD50 of> 2g/kg in mice and of> 0.7g/kg in rats. It had a low toxicity level in all species studied and signs of possible CNS toxicity observed in acute studies were not confirmed by repeated dosing.

Chronic toxicity
The safety of fluvastatin was comprehensively investigated in mice, rats, hamsters, dogs and monkeys and a number of changes observed that are characteristic of HMG-CoA reductase inhibitors. These were as follows: hyperplasia and hyperkeratosis in the non-glandular region of the forestomach of rodents, myopathies in rodents, cataracts in dogs, slight liver changes in most species accompanied in hamsters, dogs and monkeys by gallbladder changes, in rats by an increase in the weight of the thyroid, and in hamsters by testicular degeneration. Degenerative and vascular changes in the CNS did not occur with fluvastatin in investigations in dogs.

The highest tolerated dose was determined in a 2-years study in rats with dose levels of 6, 9 and 18mg/kg/day, the high dose being increased to 24mg/kg/day after one year. The plasma fluvastatin levels attained were 9, 13 and 26 (or 35) times higher than those attained in humans given an oral dose of 40mg. The mucosal changes that occurred were confined to structures not present in the human stomach.

Changes were observed in the liver, fluvastatin's target organ; there were transient increases in hepatic function values in both dogs and non-human primates, with pathological changes (congestion, focal necrosis and hydropic changes) at doses up to 108mg/kg/day in the primates but only at the lethal dose of 48mg/kg/day in the dogs.

In the carcinogenicity studies histopathological evidence of liver damage was found only in mice and rats given high doses. The changes were reversed by withdrawal of fluvastatin.

Carcinogenicity
Squamous-cell papillomas occurred in the forestomach of rats with fluvastatin plasma levels approximately 9, 13 and 26 (or 35) times higher than in humans after an oral dose of 40mg and a tumour in 1 rat given 24mg/kg/day. These findings were interpreted as being due to persistent hyperplasia caused by direct contact with fluvastatin rather than as a systemic (genotoxic) effect.

The incidence of follicular-cell adenomas and carcinomas of the thyroid was found to be increased in male rats treated for one year at 18mg/kg/day and for a further year at 24mg/kg/day. This is consistent with species-specific findings for other HMG-CoA reductase inhibitors. Hepatic adenomas or carcinomas have not been observed with fluvastatin.

In a carcinogenicity study in which mice were given 0.3, 15 and 30mg/kg/day fluvastatin there was also - as in the rat studies - a statistically significant increase in the incidence of squamous-cell papillomas of the forestomach. This occurred in both male and female animals at 30mg/kg/day but in females also at 15mg/kg/day. These doses produce blood levels that are, respectively, 0.2, 10 and 30 times higher than the level in a human given an oral dose of 40mg.

In the second carcinogenicity study in mice using doses of 50, 150 and 350mg/kg, reduced body weight gain was recorded at all dose levels, and forestomach changes confirmed in the rodent - specific irritant properties of fluvastatin which, over a prolonged period, resulted in an increased incidence and severity of squamous epithelial hyperplasia and hyperkeratosis at all dose levels. There was additionally no evidence for an increased incidence of neoplasia and the no toxic effect dose level was < 50mg/kg/day.

Mutagenicity
Fluvastatin was extensively investigated for mutagenicity both in vivo and in vitro and in the presence/absence of metabolic activation. No evidence of mutagenic potential was found in any of the systems used, which were as follows: the Ames test employing mutated strains of Salmonella typhimurium or Escherichia coli, the test for malignant transformation in BALB/3T3 cells, unscheduled DNA synthesis in rat primary hepatocytes, the chromosome aberration test in V79 cells and HGPRT tests in V79 cells from Chinese hamsters, and the micronucleus test in mice and rats.

Reproduction toxicity
Studies were performed in female rats with doses of 0.6, 2 and 6mg/kg/day. No adverse effect on fertility or reproductive performance was found at any of these dose levels. Teratogenicity studies in rats and rabbits revealed maternal toxicity at high dose levels but no evidence of embryotoxic or teratogenic potential. A study in female rats given fluvastatin in the third trimester of pregnancy showed an increased incidence of peripartal mortality as well as of fatal and neonatal deaths at 12 and 24mg/kg/day. There were no effects on either dams or foetuses in the low-dose group (2mg/kg/day).

A second study at levels of 2, 6, 12 and 24mg/kg/day confirmed the findings in the first study. A modified peri- and postnatal study was performed at dose levels of 12 or 24mg/kg/day 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 maternal and neonatal mortality. Therefore, the maternal and neonatal lethality observed with fluvastatin reflects its exaggerated pharmacological effect during pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Hypromellose
Hyprolose

Potassium hydrogen carbonate
Povidone
Magnesium stearate
Iron oxide yellow (E172)
Titanium dioxide (E171)
Macrogol 8000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original package.

6.5 Nature and contents of container

Overlabelled pack of 28 tablets in blister foil.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 465/90/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 10th November 2006

10 DATE OF REVISION OF THE TEXT

April 2011