Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lescol 40 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40 mg fluvastatin (as fluvastatin sodium).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

Product sourced from Spain.
Hard gelatin capsule with a reddish brown opaque cap and an orange yellow opaque body with 'XU 40 mg' imprinted in red.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Lescol 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 hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb).

Lescol is also indicated for the secondary prevention of major adverse cardiac events (coronary revascularization, 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

Before starting the treatment, the patient placed on a low-cholesterol diet, which should then be adhered to throughout the course of LESCOL treatment.

The recommended dose is 40 mg fluvastatin daily (1 capsule of LESCOL 40 or 2 capsules of LESCOL 20) to be taken in the evening or at bedtime, although 20 mg (1 capsule of LESCOL 20) may be tried in appropriate cases. At very high cholesterol levels dosage may be increased to 80 mg (1 LESCOL XL 80 or LESCOL 40 twice a daily. The lowest effective dose should be used with titration at 4 week intervals, depending on response and safety parameters. LESCOL should be taken either with or after meals and swallowed whole with a little water.

Doses adjustment as a function of the patients LDL-cholesterol level should not be undertaken for at least 4 weeks.

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

Use in patients with impaired kidney function: Since fluvastatin is cleared by the liver and less than 6% of the dose is excreted into the urine, dose adjustment is not normally necessary in patients with mild to moderate renal impairment (creatinine less than 260 µmol/l).

The use of LESCOL in children and adolescents up to 18 years of age is not recommended owing to the lack of sufficient data for these age groups.

Use in the elderly: The results of studies do not suggest that dosage requires adjusting for such patients.

4.3 Contraindications

- Known hypersensitivity to fluvastatin or any of the drug's other components.
- Active liver disease or persistent unexplained elevation of transaminase levels *(see 4.8);* cholestasis.
- Myopathic disorders.
- Pregnancy and lactation *(see 4.6).*
- The use of LESCOL in children and adolescents up to 18 years of age is not recommended owing to the lack of sufficient experience in these age groups *(see 4.2).*
- LESCOL should be used with caution in patients with a history of liver disease or high alcohol consumption *(see 4.8).*
- In the rare condition known as homozygous familial hypercholesterolaemia there is a deficiency of cellular LDL receptors, which means that an HMG-Co-enzyme-A reductase inhibitor is likely to be less effective. No clinical data is available for LESCOL in such patients.

4.4 Special warnings and precautions for use

Liver Function
Serum transaminase levels should be determined before and periodically during treatment with LESCOL. 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 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 creatinine 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 creatinine 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 the 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 5x 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.

With fluvastatin myopathy has rarely been reported, whereas myositis and rhabdomyolysis have been reported very rarely.

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. Lescol/Lescol XL can be used with caution in patients receiving such concomitant medication *(see 4.5 Interaction with other forms of interaction).*

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 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

Ion-exchange resins
If given 4 hours after a dose of cholestyramine LESCOL increases the lipid- lowering effect. LESCOL should be taken in the evening with an interval of at least 4 hours after ingestion of the bile-sequestering agent (e.g. cholestyramine) to avoid interaction due to fluvastatin binding to the resin.

Nicotinic acid/Propranolol
Concomitant administration of LESCOL with nicotinic acid and/or propranolol has no effect on the bioavailability of fluvastatin.

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

Digoxin
Concomitant administration of LESCOL with digoxin has no effect on digoxin plasma concentrations.

Warfarin/salicylic acid/glibenclamide
In vitro protein-binding studies revealed no interactions at therapeutic concentrations.

Antipyrine
Concomitant administration of LESCOL 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 metabolized in the same way are unlikely.

Rifampicin
Blood levels of fluvastatin were approx. 50% lower in patients who had previously taken a dose of rifampicin.

Immunosuppressants (including cyclosporin), gemfibrozil, nicotinic acid and erythromycin
There have been reports of myopathy following concomitant administration of immunosuppressants (including cyclosporin), gemfibrozil, nicotinic acid, and erythromycin with other HMG-CoA reductase inhibitors. The potential risk and benefits should be carefully weighed before proceeding *(See section 4.8)*

Other concomitant medications
No evidence was found in clinical studies in which LESCOL was given concomitantly with ACE inhibitors, ß-blockers, calcium antagonists, salicylic acid, H_2-receptor blockers and NSAIDs of any interactions affecting its safety.

Oral sulphonylureas
Although no clinical effects have been noted, fluvastatin is associated with increases in C_{max} and AUC of glibenclamide.

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.

4.6 Fertility, pregnancy and lactation

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. They are therefore contraindicated in pregnancy and lactation *(see 4.3).*

Women of childbearing age should only take LESCOL if they are practising an effective method of contraception. If a patient taking LESCOL becomes pregnant the drug should be discontinued.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

(Frequency estimate: very rare < 0.01 %; rare ≥ 0.01 % to < 0.1 %; uncommon ≥ 0.1 % to <1 %; common ≥ 1 % to < 10 %.)

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

Gastrointestinal tract
Common: dyspepsia, abdominal pain, nausea

Central and peripheral nervous system
Common: headache, insomnia
Very rare: paresthesia, dysesthesia and hypoesthesia, also known to be associated with the underlying hyperlipidemic disorders.

Hypersensitivity reactions
Rare: rash, urticaria
Very rare: other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face edema, angioedema, thrombocytopenia, vasculitis, lupus erythematosus-like reactions.

Musculoskeletal system *(see 4.4 Special warnings and special precautions for use)*
Rare: myalgia, muscle tenderness, muscle weakness, myopathy
Very rare: myositis, rhabdomyolysis

Liver *(see 4.4 Special warnings and special precautions for use)*
Very rare: hepatitis

Laboratory values
Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitoris 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%)

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

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 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.

In the Lescol Intervebation Prevention study (LIPS), the effect of fluvastatin on major adverse cardiac events (MACE) was assessed in male and female patients 918-80 years old) with coronary heart disease and a broad range of cholesterol levels (baseline TC: 3.5-7.0 mmol/L). In this randomized, double-blind, placebo-controlled trial fluvastatin (N=844), given as 80mg 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 verses 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.

5.2 Pharmacokinetic properties

Fluvastatin is absorbed rapidly and completely (98%) following oral administration to fasted volunteers. If taken after food, absorption is slower.

The AUC (area under the curve) is the same, however, whether the drug is taken with the evening meal or 4 hours later.

Blood levels of fluvastatin are independent of age and sex.

Fluvastatin acts mainly in the liver, which is also the main site of metabolism. Absolute bioavailability is 24% and apparent volume of distribution 330 L. More than 98% of the circulating drug is bound to plasma proteins, a proportion that is independent of the concentration in the blood.

Circulating drug comprises primarily unchanged fluvastatin and the pharmacologically inactive metabolise N-desisopropyl-propionic acid. The hydroxylated metabolises are active but do not circulate.

Following administration of ^{3}H-fluvastatin sodium about 6% of the radioactivity was recovered in the urine and 93% in the faeces, with fluvastatin accounting for less than 2% of the total. Plasma clearance has been calculated to be 1.8 ± 0.8L per minute in man and steady-state plasma concentrations at a dosage of 40mg daily showed no evidence of accumulation. The terminal half-life was 2.3 ± 0.9 hours after a dose of 40mg.

The possibility of accumulation cannot be excluded in patients with hepatic insufficiency in view of the fact that excretion is predominantly biliary and there is significant pre-systemic biotransformation *(see 4.3).*

5.3 Preclinical safety data

Acute toxicity
Fluvastatin has an oral LD_{50} 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, 9.2, 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

Magnesium stearate
Sodium hydrogen carbonate
Talc
Microcrystalline cellulose
Maize starch
Calcium carbonate
Gelatin
Red iron oxide (E 172)
Yellow iron oxide (E 172)
Titanium dioxide (E 171)
Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product is 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°C.
Store in the original container.

6.5 Nature and contents of container

Blister packs containing 28 capsules.

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
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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/090/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 December 2002

Date of last renewal: 06 December 2007

10 DATE OF REVISION OF THE TEXT

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