AUSTRALIAN PRODUCT INFORMATION – LESCOL® XL (FLUVASTATIN SODIUM) TABLETS

1 NAME OF THE MEDICINE

fluvastatin sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluvastatin sodium is a white to pale yellow powder, odourless or weak odour only. Fluvastatin sodium is a racemic mixture of the two enantiomers of which the 3R,5S form possesses more than 30 times the activity of the 3S,5R form.

Each prolonged release tablet contains 84.24 mg fluvastatin sodium equivalent to 80 mg fluvastatin free acid.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Prolonged release tablets.

Yellow, round, slightly biconvex, film-coated tablet, marked "LE" on one side and "NVR" on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypercholesterolaemia

Prior to initiating therapy with fluvastatin for treating hypercholesterolemia, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

Adults:

- As an adjunct to diet in the treatment of hypercholesterolaemia.

Heterozygous familial hypercholesterolemia in paediatric patients:

- As an adjunct to diet in adolescent boys and in adolescent girls who are at least one year post-menstruation, 10 -16 years of age, with heterozygous familial hypercholesterolaemia whose response to dietary restriction has not been adequate and in whom the following findings are present:

  1. LDL-C remains ≥ 4.9 mmol/L (190 mg/dL) or
  2. LDL-C remains ≥ 4.1 mmol/L (160 mg/dL) and:

- there is a positive family history of premature cardiovascular disease or
- two or more other cardiovascular disease risk factors are present.

Secondary Prevention of Cardiac Events:

- For the prevention of major adverse cardiac events in adult patients with coronary heart disease who have undergone successful coronary transcatheter therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Prior to initiating fluvastatin, the patient should be placed on a standard cholesterol-lowering diet for a minimum of 3 months. Dietary therapy should be continued during treatment.

Dosage Regimen for Adults

LESCOL 20mg and 40mg capsules are no longer marketed in Australia.

LESCOL XL 80mg must be swallowed whole with a glass of water and must not be chewed, crushed nor split or cut in half.

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

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

Lescol XL tablet can be administered as single dose at any time of the day with or without food. Lescol XL tablets must be swallowed whole with a glass of water. Lescol XL tablets must not be chewed, crushed, nor split or cut in half. Since the maximal reductions in LDL-C at a given dose are seen within four weeks, periodic lipid determinations should be performed and dosage adjusted according to the patient's response to therapy and established treatment guidelines at intervals of 4 weeks or more. The therapeutic effect of Lescol XL tablets are maintained with prolonged administration.

Lescol XL tablets are efficacious in monotherapy or in combination with bile acid sequestrants. When Lescol XL tablets are used in combination with colestyramine or other resins, it should be administered at bedtime at least four hours after the resin to avoid a significant interaction due to binding of the drug to the resin. Limited clinical data are available to support the use of Lescol XL tablets in combination with nicotinic acid or gemfibrozil. However, these combinations should be used with caution (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Skeletal Muscle).

No dosage adjustments are required for elderly patients or patients with impaired renal function (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Precautions in Special Patient Groups). For use in patients with impaired hepatic function, see Section 4.3 CONTRAINDICATIONS

and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Precautions in Special Patient Groups).

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients, aged 10-16 years

LESCOL 20mg and 40mg capsules are no longer marketed in Australia. LESCOL XL 80mg should not be used as a starting dose in children and should only be used for maintenance dosing in existing patients.

LESCOL XL tablets must not be chewed, crushed, cut in half or split (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

Paediatric patients should not be initiated on fluvastatin therapy with Lescol XL. The recommended starting dose is 20 mg fluvastatin once daily. Dosage adjustments, up to a maximum daily dose administered either as fluvastatin 40 mg twice daily or one Lescol XL 80 mg tablet once daily, should be made at intervals of at least 6 weeks after careful clinical and laboratory review. In line with the uncontrolled data available on such parameters as growth and sexual maturation, these latter parameters should be regularly reviewed while the child is on treatment and if treatment is ceased. Doses should be individualised according to the goal of therapy. Lescol XL tablets must not be chewed, crushed, cut in half or split.

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

4.3 CONTRAINDICATIONS

- In patients with known hypersensitivity to fluvastatin or any of the excipients of Lescol XL tablets.
- In patients with active liver disease or unexplained, persistent elevations in serum transaminases (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Liver enzymes).
- During pregnancy, in breast feeding mothers, and in women of child-bearing potential unless they are taking adequate contraceptive precautions (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in Pregnancy, and Use in Lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Before instituting therapy with fluvastatin, an attempt should be made to control hypercholesterolaemia with appropriate diet, exercise and weight reduction in obese patients, and to treat other underlying medical problems (see Section 4.1 THERAPEUTIC INDICATIONS, and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in patients with homozygous familial hypercholesterolaemia

HMG-CoA reductase inhibitors are reported to be less effective in patients with rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

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

Liver enzymes

Post marketing cases of fatal and non-fatal hepatic failures have been reported with some statins including fluvastatin. Although a causal relationship with fluvastatin treatment has not been determined, patients should be advised to report any potential symptoms or signs of hepatic failure (e.g. nausea, vomiting, loss of appetite, jaundice, impaired brain function, easy bruising or bleeding), and treatment discontinuation should be considered.

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 three times the upper limit of normal developed in a small number of patients (1-2%). The majority of these abnormal biochemical findings were asymptomatic and resolved or improved towards pre-treatment values after discontinuation of treatment.

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or an elevation in dose, and periodically thereafter in all patients (e.g. six monthly). Liver enzyme changes generally occur in the first three months of treatment with fluvastatin. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceed three 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.

The incidence of abnormal liver enzymes was higher in those patients receiving 80 mg per day than in those receiving 40 mg per day.

Use in hepatic impairment

As fluvastatin is subject to saturable first-pass metabolism/sequestration by the liver and is primarily eliminated via the biliary route, the potential exists for drug accumulation in patients with hepatic insufficiency. Caution should therefore be exercised when fluvastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Liver enzymes). Fluvastatin is contraindicated in patients with active liver disease or unexplained, persistent elevations in serum transaminases (see Section 4.3 CONTRAINDICATIONS).

Skeletal muscle

Myopathy has rarely been reported; myositis and rhabdomyolysis have very rarely been reported in patients receiving fluvastatin. Patients should be advised to promptly report unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever. In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked

elevation of creatine phosphokinase (CPK) values (greater than 5 times the upper limit of normal [>5xULN]), myopathy, myositis or rhabdomyolysis must be considered and fluvastatin therapy should be discontinued immediately.

Statins must not be co-administered with fusidic acid. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed e.g for the treatment of severe infections, the need for co-administration of statin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Immune mediated necrotizing myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation. Treatment involves discontunuation of fluvastatin and using immunosuppressive agents.

Creatine kinase measurement:

Measurement of CPK before commencing treatment: Physicians should prescribe fluvastatin with caution in patients with pre-disposing factors for rhabdomyolysis and its complications. A CPK 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
- sepsis
- hypotension
- trauma
- major surgery
- severe metabolic, endocrine or electrolyte disorders
- uncontrolled epilepsy
- in elderly patients (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 the CPK level is significantly elevated (>5xULN) before starting treatment with fluvastatin, the CPK level should be re-measured within 5 to 7 days to confirm the results. If the CPK level is still significantly elevated (> 5xULN), treatment should not be started.

Note: Measurement of CPK should not be done following strenuous exercise or in the presence of any plausible alternative cause of an increase in CPK level as this makes interpretation of the CPK value difficult.

Measurement of CPK during treatment: If muscular symptoms such as muscle pain, tenderness, weakness or cramps occur in patients receiving fluvastatin, their CPK level should be measured. Treatment should be stopped if the CPK level is found to be significantly elevated (>5xULN). If muscular symptoms are severe and cause daily discomfort, even if CPK levels are elevated to ≤5xULN, treatment discontinuation should be considered.

Should the symptoms resolve and the CPK level return to normal, re-introduction of fluvastatin or another statin should only be considered at the lowest dose and under close monitoring.

Fluvastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing them to the development of renal failure secondary to rhabdomyolysis e.g. sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy and/or rhabdomyolysis during treatment with HMG-CoA reductase inhibitors has been reported to be increased if therapy with ciclosporin, fibrates (e.g. gemfibrozil), erythromycin or nicotinic acid is administered concurrently. However, in clinical trials involving small numbers of 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. Fluvastatin should nevertheless be used with caution in patients receiving such concomitant medication (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Uncomplicated myalgia has been observed infrequently in patients treated with fluvastatin, at rates indistinguishable from placebo.

The incidence of elevations in CPK levels is increased with the higher doses of fluvastatin.

Use of statins and effects on glucose metabolism

Increased glycosylated haemoglobin (HbA1c) and/or fasting plasma glucose levels were observed in patients treated with HMG-CoA reductase inhibitors (statins). New onset of diabetes mellitus was also reported in patients with risk factors for diabetes mellitus.

Endocrine function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production.

Fluvastatin exhibited no effect upon non-stimulated cortisol levels and demonstrated no effect upon thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treatment groups, but no commensurate elevation in LH occurred, suggesting that the observation was not due to a direct effect upon testosterone production. No effect upon FSH in males was noted. Due to the limited number of premenopausal females studied to date, no conclusions regarding the effect of fluvastatin upon female sex hormones may be made.

Patients treated with fluvastatin sodium who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Myasthenia Gravis/ Ocular Myasthenia

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). Fluvastatin should be discontinued in case these conditions occur. Recurrences when the same or a different statin was (re-) administered have been reported.

Precautions in Special Patient Groups

Paediatric use

LESCOL 20mg and 40mg capsules are no longer marketed in Australia. LESCOL XL 80mg should not be used as a starting dose in children and should only be used for maintenance dosing in existing patients.

LESCOL XL tablets must not be chewed, crushed, cut in half or split (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 aged 9-16 years of age with heterozygous familial hypercholesterolaemia in two open-label, uncontrolled clinical trials.

The most common adverse events observed were influenza and infections. In these limited uncontrolled studies, there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls. The specific effects of fluvastatin on the safety and growth and sexual maturation parameters could not be directly compared between patients receiving fluvastatin and untreated controls, as these were uncontrolled studies. See Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials, Heterozygous Familial Hypercholesterolaemia in Paediatric Patients; Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS): Paediatric patients (9-16 years of age); and Section 4.2 DOSE AND METHOD OF ADMINISTRATION: Heterozygous Familial Hypercholesterolaemia in Paediatric Patients. Adolescent, pubertal and post-pubertal females who are sexually active should be counselled on appropriate contraceptive methods while on fluvastatin therapy (see Section 4.3 CONTRAINDICATIONS: Pregnancy and Lactation).

Use in the elderly:

There is no evidence of reduced tolerability or altered dosage requirements in elderly patients. Elderly patients (>65 years of age) demonstrated a greater treatment response in respect of LDL-C, Total-C and LDL/HDL ratio than patients <65 years of age.

Use in patients with impaired renal function:

The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency. Therefore, no dose adjustments are necessary in these patients.

Effects on laboratory tests

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Liver Enzymes, and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Laboratory findings.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Food: There were no apparent differences in the lipid-lowering effects of fluvastatin when administered with the evening meal or four hours after the evening meal. Based on the lack of interaction of fluvastatin with other CYP3A4 substrates, fluvastatin should not interact with grapefruit juice.

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 (80mg 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. No effect of fluvastatin (40 and 80 mg/day) on blood ciclosporin levels has been observed during co-administration. In an interaction study with small numbers of patients, concomitant administration of fluvastatin and ciclosporin resulted in an increase in the bioavailability of fluvastatin. Although this was not associated with an increase in the incidence of adverse events, the combination should be used with caution due to a theoretical potential for an increased risk of myopathy and/or rhabdomyolysis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Skeletal Muscle).

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 with concomitant administration of colchicine.

Fibric acid derivatives (fibrates) and niacin (nicotinic acid): Concomitant administration of fluvastatin with bezafibrate, gemfibrozil, ciprofibrate or nicotinic acid has no clinically relevant effect on the bioavailability of fluvastatin or 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, Skeletal muscle).

Itraconazole and erythromycin: Concomitant administration of fluvastatin with the potent cytochrome P450 (CYP) 3A4 inhibitors, itraconazole or 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) are unlikely to affect the bioavailability of fluvastatin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Skeletal muscle).

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.

Propranolol: Concomitant administration of fluvastatin with propranolol has no effect on the bioavailability of fluvastatin. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required.

Colestyramine: Administration of fluvastatin sodium concomitantly with or up to 4 hours after colestyramine results in fluvastatin decreases of more than 50% for AUC and 50-80% for C_{max}. However, administration of fluvastatin sodium 4 hours after colestyramine resulted in a clinically significant additive effect in reducing total-C and LDL-C compared with that achieved with either component drug alone (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Phenytoin: Co-administration of fluvastatin with phenytoin increased the AUC of phenytoin by approximately 20%. Routine monitoring of phenytoin plasma levels is sufficient during co-administration with fluvastatin. Phenytoin increased fluvastatin AUC by approximately 40% and fluvastatin Cmax by 27% but dosage adjustment of fluvastatin is not warranted when co-administered with phenytoin.

Losartan: No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with losartan. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required.

Digoxin: In a crossover study involving 18 patients chronically receiving digoxin, concomitant administration of a single 40 mg dose of fluvastatin had no effect on digoxin AUC and small but clinically insignificant increases in the digoxin Cmax and urinary clearance were noted. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required.

Amlodipine: No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with amlodipine. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required.

Histamine H_2 - receptor antagonists / proton pump inhibitors: Concomitant administration of fluvastatin with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of fluvastatin. The clinical relevance of this interaction has not been established. 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.

Rifampicin: Administration of fluvastatin to healthy volunteers pre-treated with rifampicin resulted in a reduction of the bioavailability of fluvastatin by about 50%. The clinical significance of this interaction has not been established. 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.

Warfarin / salicylic acid: *In-vitro* protein binding studies demonstrated no interaction at therapeutic concentrations. In healthy volunteers, the concomitant use of fluvastatin and warfarin did not influence warfarin plasma levels after one single dose compared with warfarin alone. AUC and Cmax of fluvastatin were increased by 31% and 67% respectively after a single 30 mg dose of racemic warfarin given to patients taking 40 mg fluvastatin daily. The possibility of an interaction after chronic concomitant use of both drugs has not been investigated. In very rare cases, a possible increase of the anticoagulant effect (bleeding episodes and/or increased prothrombin times) have been reported in patients concomitantly treated with fluvastatin and warfarin or other coumarin derivatives. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when fluvastatin therapy is initiated, discontinued, or the dosage of fluvastatin adjusted.

Glibenclamide and tolbutamide: For patients receiving oral sulfonylureas (glibenclamide, tolbutamide) for the treatment of non-insulin-dependent (type 2) diabetes mellutis (NIDDM), addition of fluvastatin does not lead to clinically significant changes in glycaemic control.

In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40mg twice daily for 14 days) increased the mean C_{max}, AUC, and $t_{½}$ of glibenclamide approximately 50%, 69% and 121%, respectively. Glibenclamide (5 to 20mg 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 80mg per day.

Fusidic acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic statins with fusidic acid. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, statin treatment should be discontinued throughout the duration of the fusidic acid treatment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Skeletal Muscle).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A study in rats given oral fluvastatin at dose levels up to 6 mg/kg/day (up to 0.6 times the human daily dose based on body surface BSA for females) and up to 20 mg/kg/day (up to 2 times the human daily dose based on BSA) for males showed no adverse effects on fertility or reproductive performance in either sex.

Seminal vesicles and testes were reduced in size in hamsters treated for 3 months at 20 mg/kg/day (about 1.4 times the human daily dose based on BSA). There was tubular degeneration and aspermatogenesis in the testes as well as vesiculitis of seminal vesicles. Vesiculitis of seminal vesicles and oedema of the testes were also seen in rats treated for 2 years at 18 mg/kg/day (1.8 times the human daily dose based on BSA).

In a study of 26 male volunteers treated for 16 weeks with fluvastatin 40 mg per day or placebo, no differences were observed between groups in sperm count, sperm motility or sex hormone levels. The effects of higher doses or longer treatment have not been studied.

Use in pregnancy – Pregnancy Category D

Definition of Category D: Drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

HMG-CoA reductase inhibitors are contraindicated during pregnancy. The risk of fetal injury outweighs the benefits of HMG-CoA reductase inhibitor therapy during pregnancy.

In two series of 178 and 143 cases where pregnant women took a HMG-CoA reductase inhibitor (statin) during the first trimester of pregnancy, serious fetal abnormalities occurred in several cases. These included limb and neurological defects, spontaneous abortions and fetal deaths. The exact risk of injury to the fetus occurring after a pregnant woman has been exposed to a HMG-CoA reductase inhibitor has not been determined. The current data do not indicate that the risk of fetal injury in women exposed to HMG-CoA reductase inhibitors is high. If a pregnant woman is exposed to a HMG-CoA reductase inhibitor she should be informed of the possibility of fetal injury and discuss the implications with her pregnancy specialist.

Since HMG-CoA reductase inhibitors decrease the synthesis of cholesterol and possibly of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women.

HMG-CoA reductase inhibitors are also contraindicated in women of childbearing potential not taking adequate contraceptive precautions. If a patient becomes pregnant while taking this class of drug, therapy should be discontinued. All women of childbearing potential should be warned of the potential hazard to the fetus should they become pregnant.

Animal studies with fluvastatin showed no evidence of teratogenic effects at oral doses up to 36 mg/kg per day in rats (up to 3.7 times the human dose based on BSA) and 10 mg/kg per day in rabbits (up to 1.9 times the human dose based on BSA), although an increased incidence of skeletal malformations has been reported in rats exposed to other HMG-CoA reductase inhibitors. Oral administration of fluvastatin (12-24 mg/kg per day; or 1.2-2.4 times the human dose based on BSA) to rats towards the end of the gestation period caused mortality associated with an increase in sensitivity to the cardiotoxic effects of the drug.

Use in lactation

It is not known whether fluvastatin is excreted into human milk, but a study in rats showed that unchanged drug is excreted in milk to a limited extent, although higher amounts of fluvastatin

metabolites are present. Peri/postnatal studies in rats showed that oral administration of fluvastatin (12-24 mg/kg per day or 1.2-2.4 times the human dose based on BSA) caused mortality associated with an increase in sensitivity to the cardiotoxic effects of the drug. Therefore, fluvastatin is contraindicated in breast feeding 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In all controlled clinical studies of fluvastatin and their open extensions, fluvastatin was discontinued in 5.9% of 2960 patients receiving fluvastatin monotherapy due to adverse experiences (mean exposure approximately 58 weeks). This results in an exposure adjusted discontinuation rate of 5.2% per year in fluvastatin patients compared with an adjusted rate of 6.4% per year in placebo patients. Adverse reactions have usually been mild and their incidences have been similar to those observed in the placebo group. A dose of 80 mg per day was associated with an increased incidence of abdominal pain and dyspepsia compared to a dose of 40 mg per day.

Adverse experiences occurring at an incidence of greater than 2% in controlled studies of fluvastatin at doses >20 mg/day, regardless of causality, include the following:

Adverse Event	**fluvastatin sodium (%) (N=2326)**	**Placebo (%) (N=960)**
Musculoskeletal		
Back pain	5.7	6.6
Arthralgia	4.0	4.1
Arthritis	2.1	2.0
Myalgia	5.0	4.5
Respiratory		
Upper respiratory tract infection	16.2	16.5
Pharyngitis	3.8	3.8
Rhinitis	4.7	4.9
Sinusitis	2.6	1.9
Coughing	2.4	2.9

Gastrointestinal		
Dyspepsia	7.9	3.2
Diarrhoea	4.9	4.2
Abdominal pain	4.9	3.8
Nausea	3.2	2.0
Constipation	3.1	3.3
Flatulence	2.6	2.5
Misc. Tooth disorder	2.1	1.7
Central Nervous System		
Dizziness	2.2	2.5
Psychiatric Disorders		
Insomnia	2.7	1.4
Miscellaneous		
Headache	8.9	7.8
Influenza-like symptoms	5.1	5.7
Accidental trauma	5.1	4.8
Fatigue	2.7	2.3
Allergy	2.3	2.2
Rash	2.3	2.4

Adverse Reactions from Clinical Trials and Post-marketing Experience

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <1/1000); 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.

Blood and lymphatic system disorders:

Very rare: thrombocytopenia

Immune system disorders:

Rare: hypersensitivity reactions such as rash, urticaria

Very rare: Anaphylactic reaction

Gastrointestinal disorders:

Common: dyspepsia, abdominal pain, nausea
Very rare: pancreatitis

Psychiatric disorders:

Common: insomnia

Nervous system disorders:

Common: headache

Very rare: paraesthesia, dysesthesia and hypoesthesia, also known to be associated with the underlying hyperlipidaemic disorders

Vascular disorders:

Very rare: vasculitis

Skin and subcutaneous tissue disorders:

Very rare: other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema

Musculoskeletal system and connective tissue disorders (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Skeletal Muscle):

Rare: myalgia, muscle weakness, myopathy

Very rare: myositis, rhabdomyolysis, lupus erythematosus-like reactions

Hepatobiliary disorders (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Liver enzymes):

Very rare: hepatitis

Investigations:

Common: Blood creatine phosphokinase increased, blood transaminases increased

Other adverse drug reactions from spontaneous reports and literature cases (frequency not known):

The following adverse drug reactions have been derived from post-marketing experience with fluvastatin via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Reproductive system and breast disorders: Erectile dysfunction

Musculoskeletal and connective tissue disorders: Immune-mediated necrotizing myopathy (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Immune mediated necrotizing myopathy).

Musculoskeletal system: Rhabdomyolysis (examples of signs and symptoms are muscle weakness, muscle swelling, muscle pain, dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure, cardiac arrhythmia) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Skeletal Muscle, and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Rhabdomyolysis may be fatal.

Nervous system disorders: Myasthenia gravis

Eye disorders: Ocular myasthenia

Psychiatric disorders: depression

Children and adolescents:

The safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolemia assessed in two open label, uncontrolled studies was similar to the one observed in adults. The most common adverse events observed were influenza and infections.
In these limited, uncontrolled studies, there was no detectable effect on growth or sexual maturation in the adolescent boys or menstrual cycle length in girls (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Precautions in Special Patient Groups, Paediatric Use). The specific effects of fluvastatin on the safety and growth and sexual maturation parameters could not be directly compared between patients receiving fluvastatin and untreated controls, as these were uncontrolled studies.

Laboratory findings:

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Marked elevations of CPK levels to more than 10x ULN developed in a very small number of patients.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In a placebo-controlled study including 40 hypercholesterolaemic 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 treatment of overdosage can be recommended. Should an accidental overdosage occur, treat symptomatically and institute supportive measures as required. Liver function tests and serum CPK levels should be monitored.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

A variety of clinical studies has demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (a membrane transport complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. In multicentre clinical trials, those pharmacologic and/or non-pharmacologic interventions that simultaneously lowered LDL-C and increased HDL-C reduced the rate of cardiovascular events (both fatal and non-fatal myocardial infarctions) in high risk males or in males and females with established coronary artery disease.

In patients with hypercholesterolaemia, treatment with both fluvastatin and Lescol XL tablets reduced total-C, LDL-C and apolipoprotein B. Both fluvastatin and Lescol XL tablets also moderately reduced triglycerides while producing an increase in HDL-C. The agent had no consistent effect on Lp(a) or fibrinogen. Therapeutic response was well established within 2 weeks and maximum response was achieved within 4 weeks from treatment initiation and maintained during chronic therapy. It has not been established what effect fluvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol has on cardiovascular morbidity or mortality, as well as on total mortality.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 the 3R,5S enantiomer exerts the pharmacological activity. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of low density lipoprotein (LDL) receptors and thereby increases the uptake of LDL particles. The ultimate result of these mechanisms is a reduction of the plasma cholesterol concentration.

Clinical trials

The Lipoprotein and Coronary Atherosclerosis Study (LCAS)

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of fluvastatin therapy on coronary atherosclerosis in patients with mild to moderately elevated LDL cholesterol levels (3.0 - 4.9 mmol/L (115 – 190 mg/dL)) and documented coronary artery disease was assessed by quantitative coronary angiography. In this double-blind, placebo-controlled trial in which 429 patients were randomised, angiograms were evaluated in 340 patients at baseline and at 2.5 years, or after at least one year of double-blind treatment. Colestyramine, up to 12 g/day, was administered from week 12 after the beginning of the double-blind treatment to patients with a baseline LDL-C level $\geq$ 4.1 mmol/L (160 mg/dL). Forty-two and 37 patients in the fluvastatin and placebo groups respectively, received colestyramine. The primary endpoint was the change in the minimum lumen diameter (MLD) of qualified lesions of left ventricular epicardial vessels. Restricted maximum likelihood was used to account for correlation amongst lesions in subjects having more than one lesion.

Fluvastatin treatment significantly (p = 0.005) slowed the progression of atherosclerosis as judged from change in MLD. There was a smaller increase in percent stenosis of qualified lesions (p = 0.014) and the number of patients with new lesions was lower (p = 0.032) in the fluvastatin-treated group compared to the placebo group (See table 1 for results). When interpreting angiographic results, it is important to be aware that angiography may underestimate the extent and severity of atherosclerosis and cannot predict the site of future coronary occlusions. Acute ischaemic events tend to occur not at the sites of severe stenosis but at lesser stenotic lesions, which are lipid rich, soft and more prone to rupture. The incidence of any cardiac morbid or any fatal event in the 429 randomised patients was 14.5% in the fluvastatin group and 19.1% in the placebo group (p=0.20). Cardiac morbid events were probable myocardial infarction, acute myocardial infarction requiring hospitalisation, unstable angina pectoris requiring hospitalisation, coronary artery bypass graft and percutaneous transluminal coronary angioplasty.

Table 1: Summary of Results

	Fluvastatin n=171	Placebo n= 169
Minimum lumen diameter (mm) - qualified lesions		
Baseline	1.64$\pm$0.04	1.68$\pm$0.04
Change	-0.03$\pm$0.02	-0.10$\pm$0.02
% Stenosis - qualified lesions		
Baseline	43.2$\pm$0.7	41.3$\pm$0.8
Change	0.6$\pm$0.7	2.8$\pm$0.8

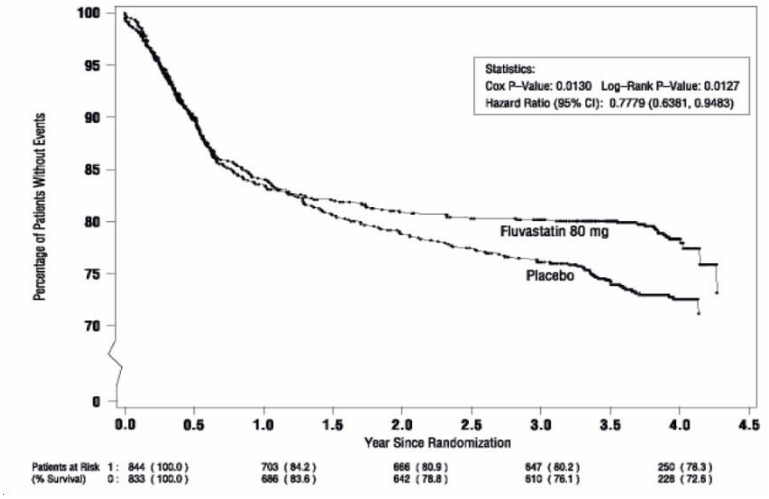
Patients developing new qualified lesions during study		
	22 (12.9%)	37 (21.9%)

The Lescol Intervention Prevention Study (LIPS)

The Lescol Intervention Prevention Study (LIPS) was an international, multicentre, randomised, double-blind, parallel group trial of fluvastatin 80 mg daily or placebo, administered to male and female patients aged 18-80 years with coronary heart disease. All 844 fluvastatin-treated and 833 placebo-treated patients in the trial had undergone successful transcutaneous catheter therapy (TCT) for one or more lesions. These patients had cholesterol levels between 3.5 and 7 mmol/L (135 and 270 mg/dL). In this trial the effect of fluvastatin treatment for approximately 4 years on the risk of developing one of several major cardiac adverse events (MACE) was assessed. The primary endpoint of the trial was the time to a patient suffering their first MACE, defined as either cardiac death, non-fatal acute myocardial infarction (AMI) or new revascularisation procedure (TCT, coronary artery bypass grafting [CABG]).

Fluvastatin significantly reduced the risk of developing one of the cardiac events included as a MACE (p=0.013) over four years (Figure 1). In the fluvastatin group, 181 patients developed a MACE during treatment compared to 222 patients in the placebo group. There was no significant reduction in any specific cardiac adverse event, including cardiac death (p=0.06) and non-fatal AMI (p=0.27).

Figure 1: Primary endpoint – recurrent cardiac events (cardiac death, nonfatal acute myocardial infarction or revascularisation procedure) [ITT population]

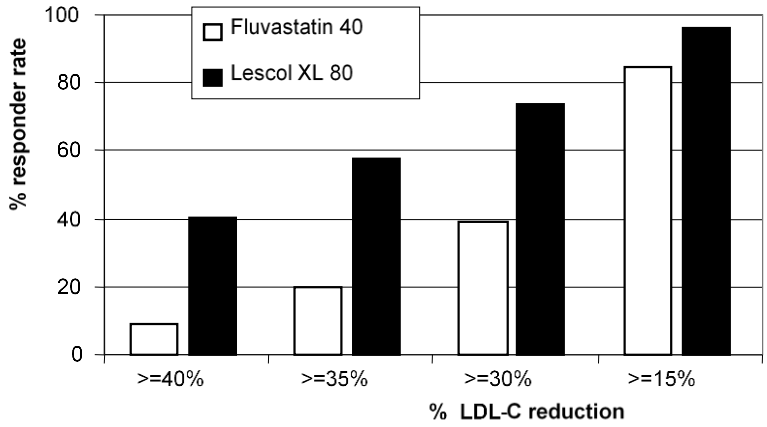


LIPS indicated that, after a median of 3.9 years of treatment, there was a statistically significant reduction in the proportion of patients who had suffered a first MACE. In the fluvastatin group, 78.3% of patients survived 4 years without suffering a MACE compared to 72.6% in the placebo group. There was no statistically significant separation of the effect between fluvastatin and placebo until 3 years. Prescribers should note that the benefit of fluvastatin treatment for periods of less than 4.5 years was not examined in the LIPS trial.

Clinical Trials with Lescol XL

In three multicentre, double-blind, active-controlled studies in nearly 1700 patients with primary hypercholesterolaemia or mixed dyslipidaemia, Lescol XL 80 mg administered at bedtime was compared to fluvastatin 40 mg given at bedtime and to fluvastatin 40 mg given twice daily at breakfast and at bedtime over 24 weeks of therapy. Patients with diabetes and familial hypercholesterolaemia were excluded from these studies. Responder rates at the time when maximum therapeutic response is achieved are illustrated in Figure 2 for the fluvastatin 40 mg (mean LDL-C reduction of 26%) and Lescol XL 80 mg doses (mean LDL-C reduction of 36%).

Figure 2: 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, both fluvastatin 40 mg twice a day and Lescol XL 80 mg once daily reduced total-C, LDL-C, apolipoprotein-B (Apo-B) and triglycerides (TG), and increased HDL-C after 24 weeks of therapy (see Table 2).

Table 2: Mean changes from baseline to 24 weeks for Lescol XL once daily and fluvastatin 40 mg twice a day

	Lescol XL 80 mg/d (n = 857)	fluvastatin 40 mg BD (n = 330)	95% confidence interval for the difference
LDL-C mmol/L (mg/dL)	-1.7 ± 0.8 (-66.6 ± 29.2)	-1.8 ± 0.8 (-67.7 ± 31.7)	-0.14, 0.08 (-5.3, 3.1)
HDL-C mmol/L (mg/dL)	0.1 ± 0.2 (4.2 ± 7.0)	0.1 ± 0.2 (3.6 ± 6.3)	-0.01, 0.04 (-0.5, 1.5)
LDL/HDL ratio	-1.5 ± 0.7	-1.5 ± 0.7	-0.1, 0.1

Total cholesterol mmol/L (mg/dL)	- 1.8 ± 0.8 (-68.2 ± 31.3)	- 1.8 ± 0.9 (-70.4 ± 33.4)	-0.11, 0.12 (-4.3, 4.8)
Triglycerides mmol/l (mg/dL)	- 0.3 ± 0.6 (-28.8 ± 53.8)	-0.3 ± 0.6 (-30.9 ± 51.0)	-0.04, 0.14 (-3.5, 12.0)
Apo A1 mg/dL	11.4 ± 18.8	10.2 ± 17.5	-1.1, 4.4
Apo B mg/dL	-46.6 ± 24.3	-47.4 ± 25.3	-3.8, 3.3

Of the 857 patients randomised to Lescol XL 80 mg, 271 with primary mixed dyslipidaemia (Fredrickson Type IIb) as defined by baseline plasma triglyceride levels ≥ 2.25 mmol/L (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. ≤ 0.9 mmol/L (35 mg/dL)), who had mean increases in HDL-C of 16%. Significant decreases in total-C, LDL-C and Apo-B were also achieved. In these studies, patients with triglycerides > 4.5 mmol/L (400 mg/dL) were excluded.

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients:

Fluvastatin sodium was studied in two open-label, uncontrolled, dose-titration studies (ZA01 and B2301) which enrolled paediatric patients with heterozygous familial hypercholesterolemia. The studies included patients aged 9 years and above with an established diagnosis of heterozygous familial hypercholesterolemia.

The first study (ZA01) 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 premature ischemic heart disease or tendon xanthomas.. All patients were started on fluvastatin 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (40 mg bid) to achieve an LDL-C goal of 2.5 to 3.2 mmol/L (96.7 to 123.7 mg/dL). The mean baseline LDL-C was 5.8 mmol/L (226 mg/dL) (range: 3.6 to 9.2. mmol/L). Endpoint analyses were performed at Year 2. Fluvastatin 20 mg to 80 mg daily doses decreased plasma levels of Total-C and LDL-C by 21% and 27%, respectively (see Table 3). The mean achieved LDL-C (primary endpoint) was 4.2 mmol/L (161 mg/dL) (range: 1.9 to 8.7 mmol/L).

Table 3: Baseline concentrations and percentage change in plasma lipid concentrations at endpoint in paediatric studies (ITT population)

	Study ZA01 (prepubertal)		**Study B2301 (pubertal and postpubertal)**	
	Baseline mean (SD) mmol/L N=29	**Mean % change from baseline (95% CI) N=27**	**Baseline mean (SD) mmol/L N=69**	**Mean % change from baseline (95% CI) N=69**
LDL-C	5.8 (1.4)	-27.0 (- 34.7, -19.4)	5.8 (1.2)	-28.3 (- 33.3, -23.4)

Total-Cholesterol	7.7 (1.4)	-21.1 (- 26.8, -15.4)	7.5 (1.2)	-21.9 (- 26.2, -17.7)
HDL-C	1.4 (0.3)	1.3 (- 8.0, 10.7)	1.2 (0.2)	4.1 (0.1, 8.2)
Triglycerides	0.8 (0.4-2.5)*	-7.0 (- 22.1, 8.0)	0.9 (0.5-3.0)*	-5.5 (- 14.9, 3.9)

**refers to median (range)*

The second study (B2301) enrolled 85 male and female patients, 10 to 16 years of age, who had an LDL-C ≥ 4.9 mmol/L (190 mg/dL) or LDL-C ≥ 4.1 mmol/L (160 mg/dL) and one or more risk factors for coronary heart disease, or LDL-C > 4.1 mmol/L (160 mg/dL) and a proven LDL-receptor defect. The main exclusion criteria were patients with homozygous familial hypercholesterolemia; secondary forms of dyslipoproteinemia; serum triglycerides levels > 6.8 mmol/L (600 mg/dL); ALAT, ASAT or creatinine levels > 1.5 x ULN; serum CK or serum TSH > 2 x ULN; BMI > 30 kg/m2. All patients were started on fluvastatin 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (Lescol 80 mg XL tablet) to achieve an LDL-C goal of ≤ 3.4 mmol/L (130 mg/dL). 70 patients were pubertal or postpubertal (n=69 evaluated for efficacy; see Table 3). The mean baseline LDL-C was 5.8 mmol/L (225 mg/dL) (range 3.8 to 8.9 mmol/L).

Endpoint analyses were performed at Week 114. Fluvastatin 20 mg to 80 mg daily doses decreased plasma levels of Total-C and LDL-C by 22% and 28%, respectively (see Table 3). The mean achieved LDL-C was 4.1 mmol/L (159 mg/dL) (range: 2.3 to 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 80 mg. At study endpoint, 26% to 30% of patients in both studies achieved a targeted LDL-C goal of ≤130 mg/dL. The long term efficacy of fluvastatin or Lescol XL tablets therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 PHARMACOKINETIC PROPERTIES

Absorption:

The following pharmacokinetic information is based on an immediate release formulation of fluvastatin.

Fluvastatin is absorbed rapidly and completely following oral administration of the immediate release formulation, with peak concentrations reached in less than 1 hour. Following administration of a 10 mg dose, the absolute bioavailability is 24% (range 9-50%). Administration with food reduces the rate but not the extent of absorption. At steady-state, administration of fluvastatin with the evening meal results in a two-fold decrease in C_{max} and more than two-fold increase in t_{max} as compared to administration 4 hours after the evening meal. No significant difference in extent of absorption or in lipid-lowering effects were observed between the two administrations. After single or multiple doses above 20 mg, fluvastatin exhibits saturable first-pass metabolism resulting in higher-than-expected plasma fluvastatin concentrations. The inactive enantiomer accounts for about 60% of the increase.

Lescol XL prolonged release tablets: After oral administration of Lescol XL 80 mg, and in comparison with the immediate release formulation, the absorption rate of fluvastatin is almost 60% slower while the mean residence time of fluvastatin is increased by approximately 4 hours.

Distribution*:*

Fluvastatin is 98% bound to plasma proteins. The apparent volume of distribution is estimated at 330 Litres. The parent drug is targeted to the liver and no active metabolites are present systemically.

Metabolism:

Fluvastatin is metabolised in the liver, primarily via hydroxylation of the indole ring at the 5 and 6 positions. N-dealkylation and beta-oxidation of the side-chains also occurs. The major components circulating in the blood are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxy metabolites have some pharmacological activity, but do not circulate in the blood. Both enantiomers of fluvastatin are metabolised in a similar manner.

In vitro data indicate that fluvastatin metabolism involves multiple Cytochrome P450 (CYP) isoenzymes. CYP2C9 isoenzyme is primarily involved in the metabolism of fluvastatin (~75%), while CYP2C8 and CYP3A4 isoenzymes are involved to a much less extent, i.e. ~5% and ~20% respectively. If one pathway is inhibited in the elimination process of fluvastatin, other pathways may compensate. 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.

In an in vitro study with human liver microsomes, fluvastatin inhibited the metabolism of CYP2C9 substrates, diclofenac and tolbutamide with Ki about 0.2 µM (about 86 ng/mL). Therefore, there is potential for competitive interaction between fluvastatin and compounds that are CYP2C9 substrates such as diclofenac, phenytoin, tolbutamide and warfarin and although unlikely, such interactions need to be considered (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Excretion:

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 of fluvastatin, the terminal disposition half-life for fluvastatin is 2.3±0.9 hours.

Pharmacokinetics in special patient groups:

Patients with impaired renal function:

The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency. Therefore, no dose adjustments are necessary in these patients.

Patients with impaired hepatic function:

As fluvastatin is subject to saturable first-pass metabolism/sequestration by the liver and is primarily eliminated via the biliary route, the potential exists for drug accumulation in patients with hepatic insufficiency (see Section 4.3 CONTRAINDICATIONS, and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Special Patient Groups).

Age and gender:

Due to their generally smaller body weight, female patients show higher fluvastatin plasma concentrations after administration of 20 - 40 mg of fluvastatin compared to males.

Paediatric Use:

Pharmacokinetic data in the paediatric population are not available.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity

Animal carcinogenicity studies showed an increased incidence of benign and malignant thyroid follicular tumours in male rats receiving fluvastatin orally at 18 to 24 mg/kg per day, (1.8 to 2.4 times the human daily dose based on body surface area (BSA) comparisons) and a low incidence of squamous papillomas in the forestomach of female mice dosed orally at 0.3 to 30 mg/kg per day (0.01 to 1.5 times the maximum human dose based on BSA comparisons), as well as in rats dosed at 18 to 24 mg/kg per day. The thyroid tumours in rats may be secondary to alterations in thyroid hormone levels. The forestomach tumours in mice and rats appear to be related to the pharmacological activity of the drug, but are not considered relevant to its clinical use. Although there was no evidence of an increase in the incidence of hepatic tumours with fluvastatin, it should be noted that high doses of other HMG-CoA reductase inhibitors have been reported to cause hepatocellular adenomas and carcinomas in mice and rats.

Animal studies have shown that fluvastatin causes the development of cataracts in dogs at oral doses greater than 8 mg/kg per day for 8 weeks or longer, and the development of gallstones in hamsters receiving dietary doses of 5-40 mg/kg per day. Mean plasma levels at the no effect dose for cataract formation in dogs were about 40 times greater than that achieved in humans at the maximum therapeutic dose of 40 mg per day. Clinical trials of fluvastatin have shown no evidence for drug-related development of cataracts or gallstones in humans. Testicular degeneration and aspermatogenesis occurred in hamsters following dietary administration of fluvastatin at 40 mg/kg per day for six months; a no-effect dose level for this toxicity was not established. No evidence of testicular toxicity was seen in chronic toxicity studies in mice, rats, dogs or monkeys at oral doses up to 30, 24, 36 and 40 mg/kg respectively.

Genotoxicity

Fluvastatin demonstrated no evidence of genotoxic activity in a standard battery of assays.

CNS toxicity

Pre-clinical safety data: CNS effects, as evidenced by decreased activity, ataxia, loss of righting reflex and ptosis were seen in the following animal studies: the 18-month mouse carcinogenicity study at 50 mg/kg per day (2.5 times the human daily dose based on BSA), the 6-month dog study at 36 mg/kg per day (12 times the human dose based on BSA), the 6-month hamster study at 40 mg/kg per day (2.7 times the human dose based on BSA), and in acute, high-dose studies in rats and hamsters (50 mg/kg; or 5 (rats) and 3.4 (hamster) times the human dose based on BSA), rabbits (300 mg/kg; 56 times the human dose based on BSA) and mice (1500 mg/kg). CNS toxicity in the acute high-dose studies was characterised (in mice) by conspicuous vacuolation in the ventral white columns of the spinal cord at a dose of 5000 mg/kg and (in rat) by oedema with separation of myelinated fibres of the ventral spinal tracts and sciatic nerve at a dose of 1500 mg/kg. CNS toxicity, characterised by periaxonal vacuolization, was observed in the medulla of dogs that died after treatment for 5 weeks with 48 mg/kg per day; this finding was not observed in the remaining dogs when the dose level was lowered to 36 mg/kg per day. CNS vascular lesions, characterised by perivascular haemorrhages, oedema and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. No CNS lesions have been observed after chronic treatment for up to 2 years with fluvastatin in the mouse (at doses up to 350 mg/kg per day; 17.8 times the maximum human dose based on BSA), rat (up to 24 mg/kg per day; 2.4 times the maximum human dose based on BSA) or dog (up to 16 mg/kg per day; 5.4 times the maximum human dose based on BSA).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, hypromellose, hyprolose, potassium bicarbonate, povidone, magnesium stearate and Opadry complete film coating system 00F22737 Yellow.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Lescol XL tablets should be kept out of the reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Lescol XL prolonged release tablets:

Alu/Alu-blister packs. Blister packs contain 7 or 28 prolonged-release tablets.

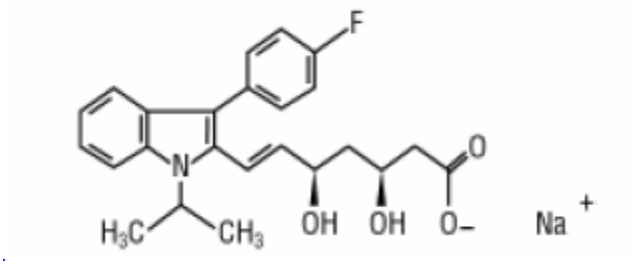
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:



Racemic

Empirical formula: $C_{24}H_{25}FNO_4 \bullet Na$

Chemical name: [R*,S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid monosodium salt

Molecular weight: 433.46

CAS number: 93957-55-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

19 September 1994

10 DATE OF REVISION

10 December 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Addition of depression with unknown adverse events frequency

Internal document code:

les101224i based on CDS dated 14 March 2016.