Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lochol 20 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 20 mg of Fluvastatin corresponding to 21.06 mg of Fluvastatin Sodium
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

Capsule size #3, blue cap and white body hard shell capsules without imprints

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dyslipidaemia
Treatment of adults with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Secondary prevention in coronary heart disease
Secondary prevention of major adverse cardiac events in adults with coronary heart disease after percutaneous coronary interventions (see section 5.1).

4.2 Posology and method of administration

Adults
Dyslipidaemia
Prior to initiating treatment with Lochol, patients should be placed on a standard cholesterol-lowering diet, which should be continued during treatment.
Starting and maintenance doses should be individualized according to the baseline LDL-C levels and the treatment goal to be accomplished.
The recommended dosing range is 20 to 80 mg/day. For patients requiring LDL-C reduction to a goal of <25% a starting dose of 20 mg may be used as one capsule in the evening. For patients requiring LDL-C reduction to a goal of ≥25%, the recommended starting dose is 40 mg as one capsule in the evening. The dose may be up-titrated to 80 mg daily, administered as a single dose (one 80 mg prolonged release tablet) at any time of the day or as one 40 mg capsule given twice daily (one in the morning and one in the evening).

The maximum lipid-lowering effect with a given dose is achieved within 4 weeks. Dose adjustments should be made at intervals of 4 weeks or more.

Secondary prevention in coronary heart disease
In patients with coronary heart disease after percutaneous coronary interventions the appropriate daily dose is 80 mg. Lochol is efficacious in monotherapy. When Lochol is used in combination with cholestyramine or other resins, it should be administered at least 4 hours after the resin to avoid significant interaction due to binding of the drug to the resin. In cases where coadministration with a fibrate or niacin is necessary, the benefit and the risk of concurrent treatment should be carefully considered (for use with fibrates or niacin see section 4.5).

Paediatric population
Children and adolescents with heterozygous familial hypercholesterolaemia
Prior to initiating treatment with Lochol in children and adolescents aged 9 years and older with heterozygous familial hypercholesterolaemia, the patient should be placed on a standard cholesterol-lowering diet, and continued during treatment.

The recommended starting dose is one 20 mg Lochol capsule. Dose adjustments should be made at 6-week intervals. Doses should be individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum daily dose administered is 80 mg either as one Lochol 40 mg capsule twice daily or as one 80mg prolonged release tablet once daily.

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

Fluvastatin has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia.

Renal Impairment
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 however, due to limited experience with doses >40mg/day in case of severe renal impairment (CrCL <0,5 mL/sec or 30 mL/min), these doses should be initiated with caution.

Hepatic Impairment
Fluvastatin is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see sections 4.3, 4.4 and 5.2).

Elderly population
No dose adjustments are necessary in this population.

Method of administration
Lochol capsules can be taken with or without meals and should be swallowed as whole with a glass of water.

4.3 Contraindications

Fluvastatin is contraindicated:
- in patients with known hypersensitivity to fluvastatin or any of the excipients listed in section 6.1.
- in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see sections 4.2, 4.4 and 4.8).
- during pregnancy and breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Liver function
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.

As with other lipid-lowering agents, it is recommended that liver function tests be performed before the initiation of treatment and at 12 weeks following initiation of treatment or elevation in dose and periodically thereafter in all patients. Should an increase in aspartate aminotransferase or alanine aminotransferase exceed 3 times the upper limit of normal and persist, therapy should be discontinued. In very rare cases, possibly drug-related hepatitis was observed that resolved upon discontinuation of treatment.

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

Skeletal muscle
Myopathy has rarely been reported with fluvastatin. 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 CK or other muscle enzyme levels in asymptomatic patients on statins. If CK 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 treatment
As with all other statins physicians should prescribe fluvastatin with caution in patients with predisposing 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.
- Sepsis.
- Hypotension.
- Excessive exercise of muscle.
- Major surgery.
- Severe metabolic, endocrine or electrolyte disorders.
- 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 (> 5x ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK levels are still significantly elevated (> 5x ULN) at baseline, treatment should not be started.

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

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.

The risk of myopathy has been reported to be increased in patients receiving immunosuppressive agents (including ciclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. Isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with ciclosporin and fluvastatin with colchicines. Fluvastatin should be used with caution in patients receiving such concomitant medicine (see section 4.5).

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). 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.

Diabetes Mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Paediatric population
Children and adolescents with heterozygous familial hypercholesterolaemia
In patients aged < 18 years, efficacy and safety have not been studied for treatment periods longer than two years. No data are available about the physical, intellectual and sexual maturation for prolonged treatment period. The long-term efficacy of fluvastatin 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). In the case of pre-pubertal children, as experience is very limited in this group, the potential risks and benefits should be carefully evaluated before the initiation of treatment.

Homozygous familial hypercholesterolaemia
No data are available for the use of fluvastatin in patients with the very rare condition of homozygous familial hypercholesterolaemia.

4.5 Interaction with other medicinal products and other forms of interaction

Fibrates and niacin
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. Since an increased risk of myopathy and/or rhabdomyolysis has been observed in patients receiving HMG-CoA reductase inhibitors together with any of these molecules, the benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution (see section 4.4).

Colchicines
Myotoxicity, including muscle pain and weakness and rhabdomyolysis, has been reported in isolated cases with concomitant administration of colchicines. The benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution (see section 4.4).

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 in which fluvastatin tablets (80 mg fluvastatin) were administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration (Cmax) were increased 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. Starting and maintenance dose of fluvastatin should be as low as possible when combined with ciclosporin.

Both fluvastatin capsules(40 mg fluvastatin) and fluvastatin tablets (80 mg fluvastatin) had no effect on the bioavailability of ciclosporin when co-administered.

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 increases 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.

Rifampicin
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.

Oral antidiabetic agents
For patients receiving oral sulfonylureas (glibenclamide (glyburide), tolbutamide) for the treatment of non-insulin-dependent (type 2) diabetes mellitus (NIDDM), addition of fluvastatin does not lead to clinically significant changes in glycaemic control. In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean Cmax, AUC, and t½ of glibenclamide by 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.

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.

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 patients pre-treated with fluconazole for 4 days, caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

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.

Phenytoin
The overall magnitude of the changes in phenytoin pharmacokinetics during co-administration with fluvastatin is relatively small and not clinically significant. Thus routine monitoring of phenytoin plasma levels is sufficient during co-administration with fluvastatin.

Cardiovascular agents
No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with propranaolol, digoxin, losartan, clopidogrel or amlodipine. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with these agents.

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.

Grapefruit juice
Based on the lack of interaction of fluvastatin with other CYP3A4 substrates, fluvastatin is not expected to interact with grapefruit juice.

4.6 Fertility, pregnancy and lactation

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

Pregnancy
There is insufficient data on the use of fluvastatin during pregnancy.

Since HMG-CoA reductase inhibitors decrease the synthesis of cholesterol and possibly of other biologically active substances derived from cholesterol, they may cause foetal harm when administered to pregnant women. Therefore, fluvastatin is contraindicated during pregnancy (see section 4.3).

Breast-feeding
Based on preclinical data, it is expected that fluvastatin is excreted into human milk. There is insufficient information on the effects of fluvastatin in newborns / infants.

Fluvastatin is contraindicated in breastfeeding women (see section 4.3).

Fertility
In animal studies no effects on male and female fertility were observed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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

Adverse drug reactions (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category, using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1 Adverse drug reactions

Blood and lymphatic system disorders
Very rare: Thrombocytopenia

Immune system disorders
Rare: Hypersensitivity reactions (rash, urticaria)
Very rare: Anaphylactic reaction

Psychiatric disorders
Common: Insomnia

Nervous system disorders
Common: Headache
Very rare: Paraesthesia, dysaesthesia, hypoaesthesia also known to be associated with the underlying hyperlipidaemic disorders

Vascular disorders
Very rare: Vasculitis

Gastrointestinal disorders
Common: Nausea, abdominal pain, dyspepsia.
Very rare: Pancreatitis

Hepatobiliary disorders
Very rare: Hepatitis

Skin and subcutaneous tissue disorders
Very rare: Angiooedema, face oedema and other skin reactions (e.g. eczema, dermatitis, bullous exanthema).

Musculoskeletal and connective tissue disorders
Rare: Myalgia, muscular weakness, myopathy
Very rare: Rhabdomyolysis, lupus like syndrome, myositis

Reproductive system and breast disorders
Not known*: Erectile dysfunction

Investigations
Common: Blood creatine phosphokinase increased, blood transaminases increased

* Based on 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 categorised as not known.

The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares
- Memory loss
- Sexual dysfunction
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m2, raised triglycerides, history of hypertension).

Paediatric population
Children and adolescents with heterozygous familial hypercholesterolaemia
The safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia assessed in 114 patients aged 9 to17 years treated in two open-label non-comparative 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 low.

Laboratory findings
Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Based on pooled analyses of controlled clinical trials confirmed elevations of alanine aminotransferase or aspartate aminotranferase levels to more than 3 times the upper limit of normal occurred in 0.2% on fluvastatin capsules 20 mg/day, 1.5% to 1.8% on fluvastatin capsules 40 mg/day, 1.9% on fluvastatin tablets 80 mg/day and in 2.7% to 4.9% on twice daily fluvastatin capsules 40 mg. The majority of patients with these abnormal biochemical findings were asymptomatic. Marked elevations of CK levels to more than 5x ULN developed in a very small number of patients (0.3 to 1.0%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via
FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: http://www.imb.ie/
E-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

To date there has been limited experience with overdose of fluvastatin. Specific treatment is not available for fluvastatin overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests and serum CK levels should be monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C10A A04

Fluvastatin, a fully synthetic cholesterol-lowering agent, is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Fluvastatin exerts its main effect in the liver and is mainly a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The ultimate result of these mechanisms is a reduction of the plasma cholesterol concentration.

Fluvastatin reduces total-C, LDL-C, Apo B, and triglycerides, and increases HDL-C in patients with hypercholesterolaemia and mixed dyslipidaemia.

In 12 placebo-controlled studies in patients with Type IIa or IIb hyperlipoproteinaemia, fluvastatin alone was administered to 1,621 patients in daily dose regimens of 20 mg, 40 mg and 80 mg (40 mg twice daily) for at least 6 weeks duration. In a 24-week analysis, daily doses of 20 mg, 40 mg and 80 mg produced dose-related reductions in total-C, LDL-C, Apo B and in triglycerides and increases in HDL-C (see Table 2).

80 mg fluvastatin tablets were administered to over 800 patients in three pivotal trials of 24 weeks active treatment duration and compared to 40 mg fluvastatin once or twice daily. Given as a single daily dose of 80 mg, fluvastatin significantly reduced total-C, LDL-C, triglycerides (TG) and Apo B (see Table 2).

Therapeutic response is well established within two weeks, and a maximum response is achieved within four weeks. After four weeks of therapy, the median decrease in LDL-C was 38% and at week 24 (endpoint) the median LDL-C decrease was 35%. Significant increases in HDL-C were also observed.

Table 2
Median percent change in lipid parameters from baseline to week 24
Placebo-controlled studies (Fluvastatin capsules) and active-controlled trials (Fluvastatin prolonged-release tablets**)**

	Total-C		TG		LDL-C		Apo B		HDL-C	
Dose	**N**	**% Δ**	**N**	**% Δ**	**N**	**% Δ**	**N**	**% Δ**	**N**	**% Δ**
All patients										
Fluvastatin 20 mg[1]	747	-17	747	-12	747	-22	114	-19	747	+3
Fluvastatin 40 mg[1]	748	-19	748	-14	748	-25	125	-18	748	+4
Fluvastatin 40 mg twice daily[1]	257	-27	257	-18	257	-36	232	-28	257	+6
Fluvastatin 80 mg[2]	750	-25	750	-19	748	-35	745	-27	750	+7
Baseline TG ≥ 200 mg/dl										
Fluvastatin 20 mg[1]	148	-16	148	-17	148	-22	23	-19	148	+6
Fluvastatin 40 mg[1]	179	-18	179	-20	179	-24	47	-18	179	+7
Fluvastatin 40 mg twice daily[1]	76	-27	76	-23	76	-35	69	-28	76	+9
Fluvastatin 80 mg[2]	239	-25	239	-25	237	-33	235	-27	239	+11

[1] Data for fluvastatin capsules from 12 placebo-controlled trials
[2] Data for fluvastatin 80 mg prolonged-release tablet from three 24-week controlled trials

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of fluvastatin on coronary atherosclerosis was assessed by quantitative coronary angiography in male and female patients (35 to 75 years old) with coronary artery disease and baseline LDL-C levels of 3.0 to 4.9 mmol/l (115 to 190 mg/dl). In this randomised, double-blind, controlled clinical study, 429 patients were treated with either fluvastatin 40 mg/day or placebo. Quantitative coronary angiograms were evaluated at baseline and after 2.5 years of treatment and were evaluable in 340 out of 429 patients. Fluvastatin treatment slowed the progression of coronary atherosclerosis lesions by 0.072 mm (95% confidence intervals for treatment difference from −0.1222 to −0.022 mm) over 2.5 years as measured by change in minimum lumen diameter (fluvastatin −0.028 mm vs. placebo −0.100 mm). No direct correlation between the angiographic findings and the risk of cardiovascular events has been demonstrated.

In a fluvastatin Intervention Prevention Study, the effect of fluvastatin on major adverse cardiac events (MACE; i.e. cardiac death, non-fatal myocardial infarction and coronary revascularisation) was assessed in patients with coronary heart disease who had first successful percutaneous coronary intervention. The study included male and female patients (18 to 80 years old) and with baseline total-C levels ranging from 3.5 to 7.0 mmol/l (135 to 270 mg/dl).
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). The primary endpoint of MACE occurred in 21.4% of patients treated with fluvastatin vs 26.7% of patients treated with placebo (absolute risk difference: 5.2%; 95% CI: 1.1 to 9.3). These beneficial effects were particularly noteworthy in patients with diabetes mellitus and in patients with multivessel disease.

Paediatric population
Children and adolescents with heterozygous familial hypercholesterolaemia
The safety and efficacy of fluvastatin capsules/prolonged-release tablets in children and adolescent patients aged 9-16 years of age with heterozygous familial hypercholesterolaemia 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 fluvastatin capsules (20 mg/day to 40 mg twice daily) or 80 mg fluvastatin prolonged-release tablets once daily 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 hypercholesterolaemia and either a family history of premature ischaemic 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 fluvastatin capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (40 mg twice daily) to achieve an LDL-C goal of 96.7 to 123.7 mg/dl (2.5 mmol/l to 3.2 mmol/l).

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 4.9 mmol/l) or LDL-C > 160 mg/dl (equivalent to 4.1 mmol/l) and one or more risk factors for coronary heart disease, or LDL-C > 160 mg/dl (equivalent to 4.1 mmol/l) and a proven LDL-receptor defect. The mean baseline LDL-C was 225 mg/dl equivalent to 5,8 mmol/l (range: 148-343 mg/dl equivalent to 3.8-8.9 mmol/l). All patients were started on fluvastatin capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (80 mg fluvastatin prolonged-release tablet) to achieve an LDL-C goal of < 130 mg/dl (3.4 mmol/l). 70 patients were pubertal or postpubertal (n=69 evaluated for efficacy).

In the first study (in prepubertal boys), 20 to 80 mg fluvastatin daily doses decreased plasma levels of total-C and LDL-C 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 1.9-8.7 mmol/l). In the second study (in pubertal or postpubertal girls and boys), 20 to 80 mg fluvastatin daily doses decreased plasma levels of total-C and LDL-C by 22% and 28%, respectively. The mean achieved LDL-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 80 mg. At study endpoint, 26 to 30% of patients in both studies achieved a targeted LDL-C goal 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 80 mg fluvastatin prolonged-release tablets, 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 substance 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 litres. More than 98% of the circulating drug is bound to plasma proteins, and this binding is not affected either by the concentration of fluvastatin, or by warfarin, salicylic acid or glyburide.

Biotransformation
Fluvastatin is mainly metabolised 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. There are multiple, alternative cytochrome P450 (CYP450) pathways for fluvastatin biotransformation and thus fluvastatin metabolism is relatively insensitive to CYP450 inhibition.

Fluvastatin inhibited only the metabolism of compounds that are metabolised 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 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 fluvastatin, the terminal disposition half-life for fluvastatin is 2.3 ± 0.9 hours.

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 presystemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency (see sections 4.3 and 4.4).

Children and adolescents with heterozygous familial hypercholesterolaemia
No pharmacokinetic data in children are available.

5.3 Preclinical safety data

The conventional studies, including safety pharmacology, genotoxicity, repeated dose toxicity, carcinogenicity and toxicity on reproduction studies did not indicate other risks for the patient than those expected due to the pharmacological mechanism of action. A variety of changes were identified in toxicity studies that are common to HMG-CoA reductase inhibitors. Based on clinical observations, liver function tests are already recommended (see section 4.4). Further toxicity seen in animals was either not relevant for human use or occurred at exposure levels sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Despite the theoretical considerations concerning the role of cholesterol in embryo development, animal studies did not suggest an embryotoxic and teratogenic potential of fluvastatin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Pregelatinised starch (maize)
Talc
Sodium lauril sulphate
Magnesium stearate

Capsule shell:
Gelatine
Titanium dioxide (E 171)
Brilliant Blue FCT (E133)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister (Al/Al): 2 years

HDPE bottles: 2 years

6.4 Special precautions for storage

Do not store above 25°C
Store in original package in order to protect from light and moisture

6.5 Nature and contents of container

Blister (Al/Al), pack sizes: 14, 28, 30, 50, 56, 90, 100 hard capsules
Bottle, pack sizes: 30, 50, 100 (2x50) hard capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/171/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th June 2009

Date of last renewal: 6th September 2013

10 DATE OF REVISION OF THE TEXT

October 2013