FLUVASTATIN 20MG AND 40MG CAPSULES  
PL 24668/0015-8, 20-21

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FLUVASTATIN 20MG AND 40MG CAPSULES
PL 24668/0015-8, 20-21

LAY SUMMARY

On 30th December 2008, the MHRA granted Cadeceus Pharma Limited Marketing Authorisations (licences) for Fluvastatin 20 and 40mg Capsules (PL 24668/0015-8, 20-21), to treat raised levels of certain types of fat in the blood. These types of fat include cholesterol and triglycerides. Fluvastatin works by reducing levels of fats in the blood and is to be used if a low fat diet has not reduced these fats sufficiently.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Fluvastatin 20 and 40mg Capsules outweigh the risks; hence Marketing Authorisations have been granted.
FLUVASTATIN 20MG AND 40MG CAPSULES
PL 24668/0015-8, 20-21

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Fluvastatin 20mg and 40mg Capsules (PL 24668/0015-8, 20-21) to Cadeceus Pharma Limited on 30th December 2008. These products are prescription-only medicines for the following indications:

- as an adjunct to diet for the reduction of elevated total-C, LDL-C, apo B and TG levels in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson types IIa and IIb).
- to slow the progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant coronary heart disease who do not adequately respond to dietary control.
- in patients with coronary heart disease for the secondary prevention of coronary events after percutaneous coronary intervention, see Section 5.1.

This application for Fluvastatin 20mg and 40mg Capsules is submitted as an abridged standard application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Lescol Capsules 20mg and 40mg, first authorised to Novartis Pharmaceuticals Limited in August 1993.

The product contains the active substance 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. Unlike the other HMG-CoA reductase inhibitors which are fungal derivatives, fluvastatin is the first synthetic agent of its class.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Fluvastatin Sodium

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

Structure:

\[
\text{CAS registry number: 93957-55-2}
\]

Physical form: A white to pale yellow, brownish – pale yellow or reddish – pale yellow, hygroscopic powder.
Soluble in water, ethanol and methanol.

Molecular formula: \( \text{C}_{24}\text{H}_{25}\text{FNO}_4\cdot\text{Na} \)
Molecular weight: 433.46.

The drug substance is not described in the European Pharmacopoeia but a monograph exists in the USP pharmacopoeia.

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance fluvastatin sodium.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance fluvastatin. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer.

The specifications and typical analytical test reports are provided and are satisfactory.
Satisfactory specifications and certificates of analysis have been provided all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

An appropriate retest period has been proposed based on stability data submitted for the active substance fluvastatin.

**DRUG PRODUCT**

Other ingredients

Other ingredients consist of pharmaceutical excipients mannitol, talc and magnesium stearate. All the ingredients within the body of the capsule comply with their relevant European Pharmacopoeia monographs.

The capsule shell contains: gelatin, water, red iron oxide (E172), titanium dioxide (E171), and yellow iron oxide (E172). Water, titanium dioxide (E171) and gelatin comply with their relevant European Pharmacopoeia monographs. Red iron oxide (E172) and yellow iron oxide (E172) comply with the National Formulary.

With the exception of gelatin and lactose monohydrate, none of the excipients used contain material of animal or human origin. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption. A satisfactory TSE certificate of suitability has been provided for the supplier of gelatin.

**Product development**

The objective of the development programme was to produce a product that could be considered a generic medicinal product of Lescol Capsules 20mg and 40mg (Novartis Pharmaceuticals Limited, August 1993).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative dissolution and impurity profiles have been provided for the finished product versus the reference product Lescol Capsules 40mg (Novartis Pharmaceuticals Limited).

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of finished product and the results appear satisfactory. The applicant has committed to perform process validation on future production-scale batches.

**Finished product specification**

The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis for all working standards used have been provided and are satisfactory.
Container-Closure System
The product is packaged either in blister packs composed of aluminium or bottles composed of white high-density polyethylene (HDPE) with white polyethylene (PE) child-resistant closures and silica gel as desiccant.

Specifications and certificates of analysis for the packaging types used have been provided. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 14, 28, 30, 50, 56, 60, and 100 capsules.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, for the 20 mg capsules a shelf-life of 18 months for the blister packs and 2 years for the bottles has been set, which is satisfactory. For the 40 mg capsules a shelf life of 2 years for the blister packs and bottles has been set, which is satisfactory. Storage conditions are “Do not store above 25°C” and ‘Store in the original package to protect from light and moisture.’

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
These are pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
These are pharmaceutically satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

These applications for Fluvastatin 20mg and 40mg Capsules are submitted as abridged standard applications according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal products of Lescol 20mg and 40mg Capsules, first authorised to Novartis Pharmaceuticals Limited in August 1993.

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, the marketing authorisation holder has included the following study:

A single-centre, laboratory-blinded, randomized, 4-period, 2-sequence, single-dose bioequivalence study comparing the pharmacokinetics of Fluvastatin 40mg Capsules (Test) versus Lescol 40mg Capsules (Reference) in fasted volunteers.

All subjects were in a fasted state before dosing. Blood sampling was performed pre-and up to 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 6 and 8 hours post dose in each treatment period. There was a washout period of 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
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<tr>
<th>(+) -3R,5S-Fluvastatin (active enantiomer):</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng/ml/h)</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng/ml/h)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
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<tbody>
<tr>
<td>Fluvastatin:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>18.6</td>
<td>18.3</td>
<td>33.3</td>
</tr>
<tr>
<td>Reference</td>
<td>20.1</td>
<td>19.8</td>
<td>38.7</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>104</td>
<td>104</td>
<td>105</td>
</tr>
<tr>
<td>(98-110%)</td>
<td>(99-110%)</td>
<td>(95-116%)</td>
<td></td>
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<tr>
<th>(-) -3S,5R-Fluvastatin (in-active enantiomer):</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng/ml/h)</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng/ml/h)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
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<tr>
<td>Fluvastatin:</td>
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<td></td>
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</tr>
<tr>
<td>Test</td>
<td>13.3</td>
<td>13.0</td>
<td>33.4</td>
</tr>
<tr>
<td>Reference</td>
<td>16.2</td>
<td>15.7</td>
<td>39.7</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>106</td>
<td>106</td>
<td>105</td>
</tr>
<tr>
<td>(101-111%)</td>
<td>(101-111%)</td>
<td>(95-116%)</td>
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The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC<sub>0-t</sub> and C<sub>max</sub> for the active and inactive enantiomers lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

EFFICACY
No new data has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.
PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.

DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that Fluvastatin 20mg and 40mg Capsules can be considered as generic medicinal products to the originator products Lescol 20mg and 40mg Capsules (Novartis Pharmaceuticals Limited).

The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Fluvastatin 20mg and 40mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Fluvastatin 40mg Capsules and the reference product Lescol 40mg Capsules (Novartis Pharmaceuticals Limited). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 40mg capsule can be extrapolated to the 20mg capsule.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product Lescol 40mg Capsules.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with fluvastatin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
**FLUVASTATIN 20MG and 40MG CAPSULES**  
**PL 24668/0015-8, 20-21**

**STEPS TAKEN FOR ASSESMENT**

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 4\textsuperscript{th} April 2006.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 2\textsuperscript{nd} May 2006.</td>
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<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information on 26\textsuperscript{th} October 2006.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 23\textsuperscript{rd} October 2007.</td>
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<td>5</td>
<td>The applications were determined on 30\textsuperscript{th} December 2008.</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fluvastatin 20 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 21.06mg fluvastatin sodium corresponding to 20mg fluvastatin.
For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM
Hard gelatine capsule, size 3. The capsule contains pale yellow powder.
Capsule cap: Swedish orange opaque with imprint 20.
Capsule body: Ivory opaque with imprint FST.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Fluvastatin Capsules are indicated as an adjunct to diet for the reduction of elevated total-C, LDL-C, apo B and TG levels in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson types IIa and IIb).

Fluvastatin Capsules are also indicated to slow the progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant coronary heart disease who do not adequately respond to dietary control.

Fluvastatin Capsules are also indicated in patients with coronary heart disease for the secondary prevention of coronary events after percutaneous coronary intervention, see Section 5.1.

4.2 Posology and method of administration
Prior to initiating Fluvastatin Capsules, secondary causes of hypercholesterolaemia should be excluded, and the patient placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

Dose recommendations for lipid lowering effect
The recommended starting dose is 40 mg (One 40 mg capsule) once daily in the evening, although a dose of 20 mg fluvastatin (One 20 mg capsule) once daily may be adequate in mild cases. Most patients will require a dose of 20 mg to 40 mg once daily but the dose may be increased to 80 mg daily (One 40 mg capsule twice daily), individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum recommended daily dose is 80 mg.

The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of Fluvastatin Capsules is maintained with prolonged administration.

Fluvastatin Capsules are efficacious in monotherapy or in combination with bile acid sequestrants. When Fluvastatin Capsules are used in combination with cholestyramine or other resins, they should be administered at least 4 hours after the resin to avoid a significant interaction due to binding of the drug to the resin. Minimal data exist to support the efficacy and safety of Fluvastatin Capsules in combination with nicotinic acid or fibrates (see Section 4.5 Interactions with other medicaments and other forms of interaction).

Dose recommendations for slowing the progression of coronary atherosclerosis
In a study in patients with primary hypercholesterolaemia and concomitant coronary heart disease 40 mg daily slowed the progression of coronary atherosclerosis.
Dose recommendations for the secondary prevention of coronary events after percutaneous coronary intervention
In patients with coronary heart disease after percutaneous coronary intervention, the dose is 80 mg daily.

**Patients with impaired kidney function**
Fluvastatin is cleared by the liver, with less than 6% of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency (creatinine > 260 μmol/L). No dose adjustments are therefore necessary in these patients.

**Patients with impaired liver function**
Fluvastatin Capsules are contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see 4.3 Contraindications and 4.4 Special warnings and precautions for use).

**Use in Elderly**
There is no evidence of reduced tolerability or altered dosage requirements in elderly patients.

**Use in Children**
As there is no experience with the use of Fluvastatin Capsules in individuals less than 18 years of age, its use is contraindicated in this group.

4.3 **Contraindications**
Hypersensitivity to the active substance or to any of the excipients of Fluvastatin Capsules. Patients with active liver disease, hepatic impairment, or unexplained, persistent elevations in serum transaminases. Individuals under 18 years of age.

4.4 **Special warnings and precautions for use**
HMG-CoA reductase inhibitors, including Fluvastatin Capsules, are unlikely to be of benefit in patients with rare homozygous familial hypercholesterolaemia.

As with other lipid-lowering drugs, it is recommended that liver function tests be performed before the initiation of treatment and at 12 weeks following initiation of the treatment or elevation in dose and periodically thereafter in all patients. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 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 Capsules are administered to patients with a history of liver disease or heavy alcohol ingestion.

Since fluvastatin is eliminated primarily via the biliary route and is subject to significant pre-systemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency.

The use of fluvastatin in combination with glibenclamide should be avoided whenever possible (see Section 4.5 Interaction with other medicaments and other forms of interaction).

**Skeletal muscle:**
With Fluvastatin Capsules, myopathy has rarely been reported, whereas myositis and rhabdomyolysis have been reported very rarely. In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked elevation of creatine kinase (CK) values myopathy, myositis or rhabdomyolysis have to be considered. Patients should therefore be advised to report promptly unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.

**Creatine kinase measurement:**
There is no current evidence to require routine monitoring of plasma total creatine kinase or other muscle enzyme levels in asymptomatic patients on statins. If creatine kinase has to be
measured it should not be done following strenuous exercise or in the presence of any plausible alternative cause of CK-increase as this makes the value interpretation difficult.

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

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse
- In elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK-levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated (> 5 x ULN) at baseline, treatment should not be started.

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

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy is known to be increased in patients receiving immunosuppressive drugs (including ciclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. Minimal data exist to support the efficacy or safety of Fluvastatin Capsules in combination with nicotinic acid, its derivatives, fibrates or ciclosporin. Isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with colchicines. Fluvastatin Capsules should be used with caution in patients receiving such concomitant medication (see Section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction
Fluvastatin is substantially metabolised by cytochrome P450 (CYP2C9). Other substrates or inhibitors of CYP2C9 administered concomitantly may therefore potentially result in increased plasma levels of fluvastatin, with a consequent increased risk of myopathy (see section 4.4).

Food interactions
Although AUC and Cmax were lowered and tmax prolonged when Fluvastatin Capsules were taken with food, there was no apparent difference in the lipid-lowering effects whether Fluvastatin Capsules were taken with food or not.

Drug interactions
Effects of other drugs on fluvastatin:
Ciclosporin - In an interaction study concomitant administration of fluvastatin (up to 40mg/day) and ciclosporin resulted in an increase in the bioavailability of fluvastatin by a factor of 1.9. The results from another study where 80mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration were (Cmax) were increased by 2 fold compared to historical data in healthy subjects. The combination of fluvastatin and ciclosporin should be used with caution due to the potential for an increased risk of myopathy and/or rhabdomyolysis. (see section 4.4 Special warning and precautions for use).
Fibric acid derivatives (fibrates) and nicotinic acid:
Bezafibrate - An interaction study between 20mg o.d. fluvastatin and 200mg t.d.s. bezafibrate showed that mean AUC and Cmax values of fluvastatin were increased on average by about 50-60%. No effect was seen on bezafibrate pharmacokinetics. This combination should be used with caution, however, due to the increased risk of developing myopathy and/or rhabdomyolysis when HMG-CoA reductase inhibitors including fluvastatin have been combined with fibrates. Any patient complaining of myalgia should be carefully evaluated.

Gemfibrozil - In an interaction study the concomitant administration of fluvastatin and gemfibrozil had no effect on the pharmacokinetics of either drug. The combination should be used with caution however, due to reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with fibrates.

Ciprofibrate - Concomitant administration of fluvastatin and ciprofibrate has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when ciprofibrate is used in combination with other HMG-CoA reductase inhibitors.

Nicotinic acid - Concomitant administration of fluvastatin and nicotinic acid has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when nicotinic acid is used in combination with other HMG-CoA reductase inhibitors.

Erythromycin - There are reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with erythromycin. The results from an interaction study with a small number of healthy volunteers suggested that erythromycin and fluvastatin were not metabolised by the same isoenzyme, however caution should be exercised when these two drugs are given in combination in view of the interaction seen with other HMG-CoA reductase inhibitors.

Fluconazole – Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor) resulted in an increase in the exposure (AUC) and mean peak concentration (Cmax) of fluvastatin by about 84% and 44% respectively. Caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Itraconazole - No interactions have been seen with itraconazole. Nevertheless patients should be closely monitored.

Antipyrine - Administration of Fluvastatin Capsules does not influence the metabolism and excretion of antipyrine. As antipyrine is a model for drugs metabolised by the microsomal hepatic enzyme systems, interactions with other drugs metabolised by these systems are not expected.

Propranolol - Concomitant administration of Fluvastatin Capsules with propranolol has no effect on the bioavailability of Fluvastatin Capsules.

Bile-acid sequestering agents - Administration of Fluvastatin Capsules 4 hours after cholestyramine results in a clinically significant additive effect compared with that achieved with either drug alone. Fluvastatin Capsules should be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding to the resin.

Digoxin - Concomitant administration of Fluvastatin Capsules with digoxin has no effect on digoxin plasma concentrations.

Amlodipine – No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with amlodipine.
Cimetidine/ranitidine/omeprazole - Concomitant administration of Fluvastatin Capsules with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of Fluvastatin Capsules, which, however, is of no clinical relevance.

Rifampicin - Administration of Fluvastatin Capsules to subjects pre-treated with rifampicin resulted in a reduction of the bioavailability of Fluvastatin Capsules 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.

Phenytoin - In an interaction study concomitant administration of fluvastatin and phenytoin resulted in an increase of fluvastatin mean AUC and Cmax values by 40% and 27% respectively. This combination should be used with caution due to the increased risk of developing myopathy and/or rhabdomyolysis.

Effects of fluvastatin on other drugs:

Ciclosporin – Fluvastatin Capsules had no effect on ciclosporin bioavailability when co-administered (see also Effects of other drugs on fluvastatin).

Colchicine – No information is available on the pharmacokinetic interaction between fluvastatin and colchicine. However, myotoxicity, including muscle pain and weakness and rhabdomyolysis, have been reported anecdotally with concomitant administration of colchicines.

Phenytoin – Co-administration of fluvastatin (40 mg b.i.d. for 5 days) increased the mean Cmax of phenytoin by 5% whereas the mean AUC was increased by 22%. Patients on phenytoin should be carefully monitored when fluvastatin therapy is initiated or when the dose is increased.

Warfarin and other Coumarin derivatives - Co-administration of fluvastatin with warfarin may commonly cause significant increases in prothrombin time. This has resulted very rarely in serious haemorrhage. It is recommended that prothrombin times are monitored when fluvastatin therapy is initiated, discontinued or the dosage changed in patients receiving warfarin or other coumarin derivative.

Glibenclamide - An interaction study between fluvastatin 40mg b.i.d. and glibenclamide was done in diabetic patients stabilised on 5-20mg of glibenclamide. The AUC for glibenclamide increased on average by 1.7 times (range: 0.9 – 3.5), Cmax increased on average by 1.6 times (range: 0.9 -3.0) and the mean t1/2 of glibenclamide increased from 8.5 to 18.8 hours when taken with fluvastatin. In this study there were no significant changes in glucose levels but in view of the increases seen in glibenclamide levels there remains a potential for serious hypoglycaemia and this combination should be avoided whenever possible.

Other concomitant therapy - In clinical studies in which Fluvastatin Capsules were used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, salicylic acid, H2-blockers and non-steroidal anti-inflammatory drugs (NSAIDs), no clinically significant adverse interactions occurred.

4.6 Pregnancy and lactation

Animal studies have indicated that fluvastatin is devoid of embryotoxic and teratogenic potential. However, 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, HMG-CoA reductase inhibitors are contraindicated during pregnancy and 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.
As small amounts of fluvastatin have been found in rat milk, Fluvastatin Capsules are contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines
No data exist on the effects of Fluvastatin Capsules on the ability to drive and use machines.

4.8 Undesirable effects
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

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

Table 1

| Blood and lymphatic system disorders | Very rare: Thrombocytopenia |
| Psychiatric disorders               | Common: Insomnia.           |
| Nervous system disorders            | Common: Headache.           |
| Very rare: Paraesthesia, dyseaesthesia, hypoaesthesia and peripheral neuropathy also known to be associated with the underlying hyperlipidemic disorders. |
| Vascular disorders                  | Very rare: Vasculitis.      |
| Gastrointestinal disorders          | Common: Dyspepsia, abdominal pain, nausea. |
| Very rare: Pancreatitis             |
| Hepatobiliary disorders             | Very rare: Hepatitis.       |
| Skin and subcutaneous tissue disorders | Rare: Hypersensitivity reactions such as rash, urticaria. |
| Very rare: Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema |
| Musculoskeletal and connective tissue disorders | Rare: Myalgia, muscle weakness, myopathy. |
| Very rare: Rhabdomyolysis, myositis, lupus erythematosus-like reactions. |

Laboratory Findings
Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in a small number of patients (less than or equal to 1%). Marked elevations of CK levels to more than 5 x ULN developed 0.3 - 1.0% of patients receiving licensed doses of fluvastatin in clinical trials.

4.9 Overdose
The experience with overdoses of Fluvastatin Capsules is very limited. Should an accidental overdosage occur, administration of activated charcoal is recommended. In the case of a very recent oral intake gastric lavage may be considered. Treatment should be symptomatic.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitor, ATC code: C01 AA01
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. 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.

A variety of clinical studies has demonstrated that elevated levels of total cholesterol (total-C), 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. Epidemiologic 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). The overall cholesterol profile is improved with the principal effects being the reduction of total-C and LDL-C. Fluvastatin also produces a moderate reduction in triglycerides and a moderate increase in HDL-C.

In a pooled analysis of all placebo-controlled studies, patients with primary mixed dyslipidaemia (Type IIb) defined as baseline TG levels ≥200 mg/dL, treatment with Fluvastatin in daily doses ranging from 20 mg to 80 mg (40 mg b.i.d.) demonstrated consistent and significant decreases in total-C, LDL-C, and apo-B, TG, and a modest increase in HDL-C.

In the Lescol Intervention Prevention Study (LIPS), the effect of fluvastatin on major adverse cardiac events (MACE) was assessed in patients with coronary heart disease who had first successful transcathether therapy (TCT). The study included male and female patients (18-80 years old) and with baseline total cholesterol levels ranging from 3.5-7.0 mmol/L. In this randomised, double-blind, placebo-controlled trial, a total of 1677 patients were recruited (844 in fluvastatin group and 833 in placebo group). The MACE was defined as cardiac death, non fatal MI and re-intervention (including CABG, repeat TCT, or TCT of a new lesion). The dose of fluvastatin used in this study was 80 mg daily over 4 years. Although the overall composite endpoint showed significant reduction in MACE (22%) compared to placebo (p=0.013), the individual components (cardiac death, non fatal MI and re-intervention) failed to reach statistical significance. There was however a trend in favour of fluvastatin. Therapy with fluvastatin reduced the risk of cardiac death and/or myocardial infarction by 31% (p=0.065).

5.2 Pharmacokinetic properties
Fluvastatin is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. Fluvastatin is absorbed rapidly and completely (98%) following oral administration to fasted volunteers. In a fed state, the drug is absorbed at a reduced rate. 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 (Vzf) for the drug is 330 L. More than 98% of the circulating drug is bound to plasma proteins, and this binding is unaffected by drug concentration.

The major circulating blood components are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate systemically.

The hepatic metabolic pathways of fluvastatin in humans have been characterised. There are multiple, alternative cytochrome P450 (CYP450) pathways involved. However, the major pathway is mediated by CYP2C9 and this pathway is subject to potential interactions with other CYP2C9 substrates or inhibitors. In addition there are several minor pathways (e.g. CYP3A4).
Several detailed in vitro studies have addressed the inhibitory potential of fluvastatin on common CYP isoenzymes. Fluvastatin inhibited only the metabolism of compounds that are metabolized by CYP2C9.

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 $1.8 \pm 0.8$ L/min. Steady-state plasma concentrations show no evidence of fluvastatin accumulation following administration of 40 mg daily. Following oral administration of 40 mg of Fluvastatin Capsules, the terminal disposition half-life for fluvastatin is $2.3 \pm 0.9$ hours.

Food: Although AUC and Cmax were lowered and tmax prolonged when fluvastatin was taken with food, there was no apparent difference in the lipid-lowering effect whether fluvastatin was taken with food or not.

Plasma concentrations of fluvastatin do not vary as a function of either age or gender in the general population.

5.3 Preclinical safety data

The safety of fluvastatin was extensively investigated in toxicity studies in rats, dogs, monkeys, mice and hamsters. A variety of changes were identified that are common to HMG-CoA reductase inhibitors, viz. hyperplasia and hyperkeratosis of the rodent non-glandular stomach, cataracts in dogs, myopathy in rodents, mild liver changes in most laboratory animals with gall bladder changes in dog, monkey and hamster, thyroid weight increases in the rat and testicular degeneration in the hamster. Fluvastatin is devoid of the CNS vascular and degenerative changes recorded in dogs with other members of this class of compound.

A carcinogenicity study was performed in rats at dose levels of 6, 9 and 18 mg/kg a day (escalated to 24 mg/kg a day after 1 year) to establish a clear maximum tolerated dose. These treatment levels yielded plasma drug levels approximately 9, 13 and 26 to 35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and one carcinoma of the forestomach was observed at the 24 mg/kg a day dose level. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded in male rats treated with 18 to 24 mg/kg a day.

The forestomach neoplasms observed in rats and mice reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug. The increased incidence of thyroid follicular cell neoplasms in male rats given fluvastatin appears to be consistent with species-specific findings with other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no treatment-related increases in the incidences of hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg a day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg a day and in females at 15 mg/kg a day. These treatment levels yielded plasma drug levels approximately 0.2, 10 and 21 times the mean human plasma drug concentration after a 40-mg oral dose.

No evidence of mutagenicity was observed in vitro, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of Salmonella typhimurium or Escherichia coli; malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese hamster cells; HGPRT V79 Chinese hamster cells. In addition, there was no evidence of mutagenicity in vivo in either a rat or mouse micronucleus test.

In a study in rats at dose levels in females of 0.6, 2 and 6 mg/kg a day and in males of 2, 10 and 20 mg/kg a day, Fluvastatin had no adverse effects on the fertility or reproductive performance. Teratology studies in rats and rabbits showed maternal toxicity at high dose levels, but there was no evidence of embryotoxic or teratogenic potential. A study in which
female rats were dosed at 12 and 24 mg/kg a day during late gestation until weaning of the pups resulted in maternal mortality at or near term and post partum accompanied by foetal and neonatal lethality. No effects on the pregnant females or foetuses occurred at the low dose level of 2 mg/kg a day.

A second study at levels of 2, 6, 12 and 24 mg/kg a day during late gestation and early lactation showed similar effects at 6 mg/kg a day and above caused by cardiotoxicity. In a third study, pregnant rats were administered 12 or 24 mg/kg a day during late gestation until weaning of pups with or without the presence of concurrent supplementation with mevalonic acid, a derivative of HMG-CoA that is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the cardiotoxicity and the maternal and neonatal mortality. Therefore, the maternal and neonatal lethality observed with fluvastatin reflects its exaggerated pharmacologic effect during pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol
Talc
Magnesium Stearate
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Packed in Alu/Alu Blisters: 18 months
Packed in plastic bottles: 24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons
2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.
Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
8th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/12/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fluvastatin 40 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 42.12mg fluvastatin sodium corresponding to 40mg fluvastatin.
For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM
Hard gelatine capsule, size 1. The capsule contains pale yellow powder.
Capsule cap: Swedish orange opaque with imprint 40.
Capsule body: Rich yellow opaque with imprint FST.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Fluvastatin Capsules are indicated as an adjunct to diet for the reduction of elevated total-C, LDL-C, apo B and TG levels in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson types IIa and IIb).

Fluvastatin Capsules are also indicated to slow the progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant coronary heart disease who do not adequately respond to dietary control.

Fluvastatin Capsules are also indicated in patients with coronary heart disease for the secondary prevention of coronary events after percutaneous coronary intervention, see Section 5.1.

4.2 Posology and method of administration
Prior to initiating Fluvastatin Capsules, secondary causes of hypercholesterolaemia should be excluded, and the patient placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

Dose recommendations for lipid lowering effect
The recommended starting dose is 40 mg (One 40 mg capsule) once daily in the evening, although a dose of 20 mg fluvastatin (One 20 mg capsule) once daily may be adequate in mild cases. Most patients will require a dose of 20 mg to 40 mg once daily but the dose may be increased to 80 mg daily (One 40 mg capsule twice daily), individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum recommended daily dose is 80 mg.

The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of Fluvastatin Capsules is maintained with prolonged administration.

Fluvastatin Capsules are efficacious in monotherapy or in combination with bile acid sequestrants. When Fluvastatin Capsules are used in combination with cholestyramine or other resins, they should be administered at least 4 hours after the resin to avoid a significant interaction due to binding of the drug to the resin. Minimal data exist to support the efficacy and safety of Fluvastatin Capsules in combination with nicotinic acid or fibrates (see Section 4.5 Interactions with other medicaments and other forms of interaction).

Dose recommendations for slowing the progression of coronary atherosclerosis
In a study in patients with primary hypercholesterolaemia and concomitant coronary heart disease 40 mg daily slowed the progression of coronary atherosclerosis.
Dose recommendations for the secondary prevention of coronary events after percutaneous coronary intervention
In patients with coronary heart disease after percutaneous coronary intervention, the dose is 80 mg daily.

Patients with impaired kidney function
Fluvastatin is cleared by the liver, with less than 6% of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency (creatinine > 260 μmol/L). No dose adjustments are therefore necessary in these patients.

Patients with impaired liver function
Fluvastatin Capsules are contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Use in Elderly
There is no evidence of reduced tolerability or altered dosage requirements in elderly patients.

Use in Children
As there is no experience with the use of Fluvastatin Capsules in individuals less than 18 years of age, its use is contraindicated in this group.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients of Fluvastatin Capsules. Patients with active liver disease, hepatic impairment, or unexplained, persistent elevations in serum transaminases. Individuals under 18 years of age.

4.4 Special warnings and precautions for use
HMG-CoA reductase inhibitors, including Fluvastatin Capsules, are unlikely to be of benefit in patients with rare homozygous familial hypercholesterolaemia.

As with other lipid-lowering drugs, it is recommended that liver function tests be performed before the initiation of treatment and at 12 weeks following initiation of the treatment or elevation in dose and periodically thereafter in all patients. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 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 Capsules are administered to patients with a history of liver disease or heavy alcohol ingestion.

Since fluvastatin is eliminated primarily via the biliary route and is subject to significant pre-systemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency.

The use of fluvastatin in combination with glibenclamide should be avoided whenever possible (see Section 4.5 Interaction with other medicaments and other forms of interaction).

Skeletal muscle:
With Fluvastatin Capsules, myopathy has rarely been reported, whereas myositis and rhabdomyolysis have been reported very rarely. In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked elevation of creatine kinase (CK) values myopathy, myositis or rhabdomyolysis have to be considered. Patients should therefore be advised to report promptly unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.
Creatine kinase measurement:
There is no current evidence to require routine monitoring of plasma total creatine kinase or other muscle enzyme levels in asymptomatic patients on statins. If creatine kinase has to be measured it should not be done following strenuous exercise or in the presence of any plausible alternative cause of CK-increase as this makes the value interpretation difficult.

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

• Renal impairment
• Hypothyroidism
• Personal or familial history of hereditary muscular disorders
• Previous history of muscular toxicity with a statin or fibrate
• Alcohol abuse
• In elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK-levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated (> 5 x ULN) at baseline, treatment should not be started.

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

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy is known to be increased in patients receiving immunosuppressive drugs (including ciclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. Minimal data exist to support the efficacy or safety of Fluvastatin Capsules in combination with nicotinic acid, its derivatives, fibrates or ciclosporin. Isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with colchicines. Fluvastatin Capsules should be used with caution in patients receiving such concomitant medication (see Section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction
Fluvastatin is substantially metabolised by cytochrome P450 (CYP2C9). Other substrates or inhibitors of CYP2C9 administered concomitantly may therefore potentially result in increased plasma levels of fluvastatin, with a consequent increased risk of myopathy (see section 4.4).

Food interactions
Although AUC and Cmax were lowered and tmax prolonged when Fluvastatin Capsules were taken with food, there was no apparent difference in the lipid-lowering effects whether Fluvastatin Capsules were taken with food or not.

Drug interactions
Effects of other drugs on fluvastatin:
Ciclosporin - In an interaction study concomitant administration of fluvastatin (up to 40mg/day) and ciclosporin resulted in an increase in the bioavailability of fluvastatin by a factor of 1.9. The results from another study where 80mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration were (Cmax) were increased by 2 fold compared to
historical data in healthy subjects. The combination of fluvastatin and ciclosporin should be used with caution due to the potential for an increased risk of myopathy and/or rhabdomyolysis. (see section 4.4 Special warning and precautions for use).

Fibric acid derivatives (fibrates) and nicotinic acid:

Bezafibrate - An interaction study between 20mg o.d. fluvastatin and 200mg t.d.s. bezafibrate showed that mean AUC and Cmax values of fluvastatin were increased on average by about 50-60%. No effect was seen on bezafibrate pharmacokinetics. This combination should be used with caution, however, due to the increased risk of developing myopathy and/or rhabdomyolysis when HMG-CoA reductase inhibitors including fluvastatin have been combined with fibrates. Any patient complaining of myalgia should be carefully evaluated.

Gemfibrozil - In an interaction study the concomitant administration of fluvastatin and gemfibrozil had no effect on the pharmacokinetics of either drug. The combination should be used with caution however, due to reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with fibrates.

Ciprofibrate - Concomitant administration of fluvastatin and ciprofibrate has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when ciprofibrate is used in combination with other HMG-CoA reductase inhibitors.

Nicotinic acid - Concomitant administration of fluvastatin and nicotinic acid has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when nicotinic acid is used in combination with other HMG-CoA reductase inhibitors.

Erythromycin - There are reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with erythromycin. The results from an interaction study with a small number of healthy volunteers suggested that erythromycin and fluvastatin were not metabolised by the same isoenzyme, however caution should be exercised when these two drugs are given in combination in view of the interaction seen with other HMG-CoA reductase inhibitors.

Fluconazole – Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor) resulted in an increase in the exposure (AUC) and mean peak concentration (Cmax) of fluvastatin by about 84% and 44% respectively. Caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Itraconazole - No interactions have been seen with itraconazole. Nevertheless patients should be closely monitored.

Antipyrine - Administration of Fluvastatin Capsules does not influence the metabolism and excretion of antipyrine. As antipyrine is a model for drugs metabolised by the microsomal hepatic enzyme systems, interactions with other drugs metabolised by these systems are not expected.

Propranolol - Concomitant administration of Fluvastatin Capsules with propranolol has no effect on the bioavailability of Fluvastatin Capsules.

Bile-acid sequestering agents - Administration of Fluvastatin Capsules 4 hours after cholestyramine results in a clinically significant additive effect compared with that achieved with either drug alone. Fluvastatin Capsules should be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding to the resin.

Digoxin - Concomitant administration of Fluvastatin Capsules with digoxin has no effect on digoxin plasma concentrations.
Amlodipine – No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with amlodipine.

Cimetidine/ranitidine/omeprazole - Concomitant administration of Fluvastatin Capsules with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of Fluvastatin Capsules, which, however, is of no clinical relevance.

Rifampicin - Administration of Fluvastatin Capsules to subjects pre-treated with rifampicin resulted in a reduction of the bioavailability of Fluvastatin Capsules 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.

Phenytoin - In an interaction study concomitant administration of fluvastatin and phenytoin resulted in an increase of fluvastatin mean AUC and Cmax values by 40% and 27% respectively. This combination should be used with caution due to the increased risk of developing myopathy and/or rhabdomyolysis.

Effects of fluvastatin on other drugs:
Ciclosporin – Fluvastatin Capsules had no effect on ciclosporin bioavailability when co-administered (see also Effects of other drugs on fluvastatin).

Colchicine – No information is available on the pharmacokinetic interaction between fluvastatin and colchicine. However, myotoxicity, including muscle pain and weakness and rhabdomyolysis, have been reported anecdotally with concomitant administration of colchicines.

Phenytoin – Co-administration of fluvastatin (40 mg b.i.d. for 5 days) increased the mean Cmax of phenytoin by 5% whereas the mean AUC was increased by 22%. Patients on phenytoin should be carefully monitored when fluvastatin therapy is initiated or when the dose is increased.

Warfarin and other Coumarin derivatives - Co-administration of fluvastatin with warfarin may commonly cause significant increases in prothrombin time. This has resulted very rarely in serious haemorrhage. It is recommended that prothrombin times are monitored when fluvastatin therapy is initiated, discontinued or the dosage changed in patients receiving warfarin or other coumarin derivative.

Glibenclamide - An interaction study between fluvastatin 40mg b.i.d. and glibenclamide was done in diabetic patients stabilised on 5-20mg of glibenclamide. The AUC for glibenclamide increased on average by 1.7 times (range: 0.9 – 3.5), Cmax increased on average by 1.6 times (range: 0.9 -3.0) and the mean t1/2 of glibenclamide increased from 8.5 to 18.8 hours when taken with fluvastatin. In this study there were no significant changes in glucose levels but in view of the increases seen in glibenclamide levels there remains a potential for serious hypoglycaemia and this combination should be avoided whenever possible.

Other concomitant therapy - In clinical studies in which Fluvastatin Capsules were used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, salicylic acid, H2-blockers and non-steroidal anti-inflammatory drugs (NSAIDs), no clinically significant adverse interactions occurred.

4.6 Pregnancy and lactation
Animal studies have indicated that fluvastatin is devoid of embryotoxic and teratogenic potential. However, 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, HMG-CoA reductase inhibitors are contraindicated during pregnancy and 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.
As small amounts of fluvastatin have been found in rat milk, Fluvastatin Capsules are contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines
No data exist on the effects of Fluvastatin Capsules on the ability to drive and use machines.

4.8 Undesirable effects
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

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

Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very rare</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Very rare</td>
<td>Paraesthesia, dysaesthesia, hypoesthesia and peripheral neuropathy also known to be associated with the underlying hyperlipidemic disorders.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very rare</td>
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<tr>
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<td>Hepatitis</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rare</td>
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<tr>
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</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Rare</td>
<td>Myalgia, muscle weakness, myopathy.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Rhabdomyolysis, myositis, lupus erythematosus-like reactions.</td>
</tr>
</tbody>
</table>

Laboratory Findings
Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in a small number of patients (less than or equal to 1%). Marked elevations of CK levels to more than 5 x ULN developed 0.3 - 1.0% of patients receiving licensed doses of fluvastatin in clinical trials.

4.9 Overdose
The experience with overdoses of Fluvastatin Capsules is very limited. Should an accidental overdosage occur, administration of activated charcoal is recommended. In the case of a very recent oral intake gastric lavage may be considered. Treatment should be symptomatic.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitor, ATC code: C01 AA01

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. 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.

A variety of clinical studies has demonstrated that elevated levels of total cholesterol (total-C), 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. Epidemiologic 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). The overall cholesterol profile is improved with the principal effects being the reduction of total-C and LDL-C. Fluvastatin also produces a moderate reduction in triglycerides and a moderate increase in HDL-C.

In a pooled analysis of all placebo-controlled studies, patients with primary mixed dyslipidaemia (Type IIb) defined as baseline TG levels ≥200 mg/dL, treatment with Fluvastatin in daily doses ranging from 20 mg to 80 mg (40 mg b.i.d.) demonstrated consistent and significant decreases in total-C, LDL-C, and apo-B, TG, and a modest increase in HDL-C.

In the Lescol Intervention Prevention Study (LIPS), the effect of fluvastatin on major adverse cardiac events (MACE) was assessed in patients with coronary heart disease who had first successful transcathether therapy (TCT). The study included male and female patients (18-80 years old) and with baseline total cholesterol levels ranging from 3.5-7.0 mmol/L. In this randomised, double-blind, placebo-controlled trial, a total of 1677 patients were recruited (844 in fluvastatin group and 833 in placebo group). The MACE was defined as cardiac death, non fatal MI and re-intervention (including CABG, repeat TCT, or TCT of a new lesion). The dose of fluvastatin used in this study was 80 mg daily over 4 years. Although the overall composite endpoint showed significant reduction in MACE (22%) compared to placebo (p=0.013), the individual components (cardiac death, non fatal MI and re-intervention) failed to reach statistical significance. There was however a trend in favour of fluvastatin. Therapy with fluvastatin reduced the risk of cardiac death and/or myocardial infarction by 31% (p=0.065).

5.2 Pharmacokinetic properties

Fluvastatin is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. Fluvastatin is absorbed rapidly and completely (98%) following oral administration to fasted volunteers. In a fed state, the drug is absorbed at a reduced rate. 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 (Vzf) for the drug is 330 L. More than 98% of the circulating drug is bound to plasma proteins, and this binding is unaffected by drug concentration.

The major circulating blood components are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate systemically.

The hepatic metabolic pathways of fluvastatin in humans have been characterised. There are multiple, alternative cytochrome P450 (CYP450) pathways involved. However, the major pathway is mediated by CYP2C9 and this pathway is subject to potential interactions with other CYP2C9 substrates or inhibitors. In addition there are several minor pathways (e.g. CYP3A4).
Several detailed in vitro studies have addressed the inhibitory potential of fluvastatin on common CYP isoenzymes. Fluvastatin inhibited only the metabolism of compounds that are metabolized by CYP2C9.

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 40 mg daily. Following oral administration of 40 mg of Fluvastatin Capsules, the terminal disposition half-life for fluvastatin is 2.3 ± 0.9 hours.

Food: Although AUC and Cmax were lowered and tmax prolonged when fluvastatin was taken with food, there was no apparent difference in the lipid-lowering effect whether fluvastatin was taken with food or not.

Plasma concentrations of fluvastatin do not vary as a function of either age or gender in the general population.

5.3 Preclinical safety data

The safety of fluvastatin was extensively investigated in toxicity studies in rats, dogs, monkeys, mice and hamsters. A variety of changes were identified that are common to HMG-CoA reductase inhibitors, viz. hyperplasia and hyperkeratosis of the rodent non-glandular stomach, cataracts in dogs, myopathy in rodents, mild liver changes in most laboratory animals with gall bladder changes in dog, monkey and hamster, thyroid weight increases in the rat and testicular degeneration in the hamster. Fluvastatin is devoid of the CNS vascular and degenerative changes recorded in dogs with other members of this class of compound.

A carcinogenicity study was performed in rats at dose levels of 6, 9 and 18 mg/kg a day (escalated to 24 mg/kg a day after 1 year) to establish a clear maximum tolerated dose. These treatment levels yielded plasma drug levels approximately 9, 13 and 26 to 35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and one carcinoma of the forestomach was observed at the 24 mg/kg a day dose level. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded in male rats treated with 18 to 24 mg/kg a day.

The forestomach neoplasms observed in rats and mice reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug. The increased incidence of thyroid follicular cell neoplasms in male rats given fluvastatin appears to be consistent with species-specific findings with other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no treatment-related increases in the incidences of hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg a day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg a day and in females at 15 mg/kg a day. These treatment levels yielded plasma drug levels approximately 0.2, 10 and 21 times the mean human plasma drug concentration after a 40-mg oral dose.

No evidence of mutagenicity was observed in vitro, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of Salmonella typhimurium or Escherichia coli: malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese hamster cells; HGPRT V79 Chinese hamster cells. In addition, there was no evidence of mutagenicity in vivo in either a rat or mouse micronucleus test.

In a study in rats at dose levels in females of 0.6, 2 and 6 mg/kg a day and in males of 2, 10 and 20 mg/kg a day, Fluvastatin had no adverse effects on the fertility or reproductive performance. Teratology studies in rats and rabbits showed maternal toxicity at high dose levels, but there was no evidence of embryotoxic or teratogenic potential. A study in which
female rats were dosed at 12 and 24 mg/kg a day during late gestation until weaning of the pups resulted in maternal mortality at or near term and post partum accompanied by foetal and neonatal lethality. No effects on the pregnant females or foetuses occurred at the low dose level of 2 mg/kg a day.

A second study at levels of 2, 6, 12 and 24 mg/kg a day during late gestation and early lactation showed similar effects at 6 mg/kg a day and above caused by cardiotoxicity. In a third study, pregnant rats were administered 12 or 24 mg/kg a day during late gestation until weaning of pups with or without the presence of concurrent supplementation with mevalonic acid, a derivative of HMG-CoA that is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the cardiotoxicity and the maternal and neonatal mortality. Therefore, the maternal and neonatal lethality observed with fluvastatin reflects its exaggerated pharmacologic effect during pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol
Talc
Magnesium Stearate
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons
2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.
Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
8th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/12/2008

10 DATE OF REVISION OF THE TEXT
30/12/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fluvastatin 20 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 21.06mg fluvastatin sodium corresponding to 20mg fluvastatin.
For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM
Hard gelatine capsule, size 3. The capsule contains pale yellow powder.
Capsule cap: Swedish orange opaque with imprint 20.
Capsule body: Ivory opaque with imprint FST.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Fluvastatin Capsules are indicated as an adjunct to diet for the reduction of elevated total-C, LDL-C, apo B and TG levels in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson types IIa and IIb).

Fluvastatin Capsules are also indicated to slow the progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant coronary heart disease who do not adequately respond to dietary control.

Fluvastatin Capsules are also indicated in patients with coronary heart disease for the secondary prevention of coronary events after percutaneous coronary intervention, see Section 5.1.

4.2 Posology and method of administration
Prior to initiating Fluvastatin Capsules, secondary causes of hypercholesterolaemia should be excluded, and the patient placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

Dose recommendations for lipid lowering effect
The recommended starting dose is 40 mg (One 40 mg capsule) once daily in the evening, although a dose of 20 mg fluvastatin (One 20 mg capsule) once daily may be adequate in mild cases. Most patients will require a dose of 20 mg to 40 mg once daily but the dose may be increased to 80 mg daily (One 40 mg capsule twice daily), individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum recommended daily dose is 80 mg.

The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of Fluvastatin Capsules is maintained with prolonged administration.

Fluvastatin Capsules are efficacious in monotherapy or in combination with bile acid sequestrants. When Fluvastatin Capsules are used in combination with cholestyramine or other resins, they should be administered at least 4 hours after the resin to avoid a significant interaction due to binding of the drug to the resin. Minimal data exist to support the efficacy and safety of Fluvastatin Capsules in combination with nicotinic acid or fibrates (see Section 4.5 Interactions with other medicaments and other forms of interaction).

Dose recommendations for slowing the progression of coronary atherosclerosis
In a study in patients with primary hypercholesterolaemia and concomitant coronary heart disease 40 mg daily slowed the progression of coronary atherosclerosis.

Dose recommendations for the secondary prevention of coronary events after percutaneous coronary intervention

31
In patients with coronary heart disease after percutaneous coronary intervention, the dose is 80 mg daily.

**Patients with impaired kidney function**
Fluvastatin is cleared by the liver, with less than 6% of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency (creatinine > 260 μmol/L). No dose adjustments are therefore necessary in these patients.

**Patients with impaired liver function**
Fluvastatin Capsules are contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see 4.3 Contraindications and 4.4 Special warnings and precautions for use).

**Use in Elderly**
There is no evidence of reduced tolerability or altered dosage requirements in elderly patients.

**Use in Children**
As there is no experience with the use of Fluvastatin Capsules in individuals less than 18 years of age, its use is contraindicated in this group.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients of Fluvastatin Capsules. Patients with active liver disease, hepatic impairment, or unexplained, persistent elevations in serum transaminases. Individuals under 18 years of age.

4.4 Special warnings and precautions for use
HMG-CoA reductase inhibitors, including Fluvastatin Capsules, are unlikely to be of benefit in patients with rare homozygous familial hypercholesterolaemia.

As with other lipid-lowering drugs, it is recommended that liver function tests be performed before the initiation of treatment and at 12 weeks following initiation of the treatment or elevation in dose and periodically thereafter in all patients. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 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 Capsules are administered to patients with a history of liver disease or heavy alcohol ingestion.

Since fluvalastatin is eliminated primarily via the biliary route and is subject to significant pre-systemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency.

The use of fluvalastatin in combination with glibenclamide should be avoided whenever possible (see Section 4.5 Interaction with other medicaments and other forms of interaction).

**Skeletal muscle:**
With Fluvastatin Capsules, myopathy has rarely been reported, whereas myositis and rhabdomyolysis have been reported very rarely. In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked elevation of creatine kinase (CK) values myopathy, myositis or rhabdomyolysis have to be considered. Patients should therefore be advised to report promptly unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.
**Creatine kinase measurement:**
There is no current evidence to require routine monitoring of plasma total creatine kinase or other muscle enzyme levels in asymptomatic patients on statins. If creatine kinase has to be measured it should not be done following strenuous exercise or in the presence of any plausible alternative cause of CK-increase as this makes the value interpretation difficult.

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

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse
- In elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis. In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK-levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated (> 5 x ULN) at baseline, treatment should not be started.

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

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to < 5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy is known to be increased in patients receiving immunosuppressive drugs (including ciclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. Minimal data exist to support the efficacy or safety of Fluvastatin Capsules in combination with nicotinic acid, its derivatives, fibrates or ciclosporin. Isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with colchicines. Fluvastatin Capsules should be used with caution in patients receiving such concomitant medication (see Section 4.5).

**4.5 Interaction with other medicinal products and other forms of interaction**
Fluvastatin is substantially metabolised by cytochrome P450 (CYP2C9). Other substrates or inhibitors of CYP2C9 administered concomitantly may therefore potentially result in increased plasma levels of fluvastatin, with a consequent increased risk of myopathy (see section 4.4).

**Food interactions**
Although AUC and Cmax were lowered and tmax prolonged when Fluvastatin Capsules were taken with food, there was no apparent difference in the lipid-lowering effects whether Fluvastatin Capsules were taken with food or not.

**Drug interactions**
Effects of other drugs on fluvastatin:
Ciclosporin - In an interaction study concomitant administration of fluvastatin (up to 40mg/day) and ciclosporin resulted in an increase in the bioavailability of fluvastatin by a factor of 1.9. The results from another study where 80mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration were (Cmax) were increased by 2 fold compared to
historical data in healthy subjects. The combination of fluvastatin and ciclosporin should be used with caution due to the potential for an increased risk of myopathy and/or rhabdomyolysis. (see section 4.4 Special warning and precautions for use).

Fibric acid derivatives (fibrates) and nicotinic acid:
Bezafibrate - An interaction study between 20mg o.d. fluvastatin and 200mg t.d.s. bezafibrate showed that mean AUC and Cmax values of fluvastatin were increased on average by about 50-60%. No effect was seen on bezafibrate pharmacokinetics. This combination should be used with caution, however, due to the increased risk of developing myopathy and/or rhabdomyolysis when HMG-CoA reductase inhibitors including fluvastatin have been combined with fibrates. Any patient complaining of myalgia should be carefully evaluated.

Gemfibrozil - In an interaction study the concomitant administration of fluvastatin and gemfibrozil had no effect on the pharmacokinetics of either drug. The combination should be used with caution however, due to reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with fibrates.

Ciprofibrate - Concomitant administration of fluvastatin and ciprofibrate has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when ciprofibrate is used in combination with other HMG-CoA reductase inhibitors.

Nicotinic acid - Concomitant administration of fluvastatin and nicotinic acid has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when nicotinic acid is used in combination with other HMG-CoA reductase inhibitors.

Erythromycin - There are reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with erythromycin. The results from an interaction study with a small number of healthy volunteers suggested that erythromycin and fluvastatin were not metabolised by the same isoenzyme, however caution should be exercised when these two drugs are given in combination in view of the interaction seen with other HMG-CoA reductase inhibitors.

Fluconazole – Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor) resulted in an increase in the exposure (AUC) and mean peak concentration (Cmax) of fluvastatin by about 84% and 44% respectively. Caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Itraconazole - No interactions have been seen with itraconazole. Nevertheless patients should be closely monitored.

Antipyrine - Administration of Fluvastatin Capsules does not influence the metabolism and excretion of antipyrine. As antipyrine is a model for drugs metabolised by the microsomal hepatic enzyme systems, interactions with other drugs metabolised by these systems are not expected.

Propranolol - Concomitant administration of Fluvastatin Capsules with propranolol has no effect on the bioavailability of Fluvastatin Capsules.

Bile-acid sequestering agents - Administration of Fluvastatin Capsules 4 hours after cholestyramine results in a clinically significant additive effect compared with that achieved with either drug alone. Fluvastatin Capsules should be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding to the resin.

Digoxin - Concomitant administration of Fluvastatin Capsules with digoxin has no effect on digoxin plasma concentrations.
Amlodipine – No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with amlodipine.

Cimetidine/ranitidine/omeprazole - Concomitant administration of Fluvastatin Capsules with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of Fluvastatin Capsules, which, however, is of no clinical relevance.

Rifampicin - Administration of Fluvastatin Capsules to subjects pre-treated with rifampicin resulted in a reduction of the bioavailability of Fluvastatin Capsules 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.

Phenytoin - In an interaction study concomitant administration of fluvastatin and phenytoin resulted in an increase of fluvastatin mean AUC and Cmax values by 40% and 27% respectively. This combination should be used with caution due to the increased risk of developing myopathy and/or rhabdomyolysis.

Effects of fluvastatin on other drugs:

Ciclosporin – Fluvastatin Capsules had no effect on ciclosporin bioavailability when co-administered (see also Effects of other drugs on fluvastatin).

Colchicin – No information is available on the pharmacokinetic interaction between fluvastatin and colchicine. However, myotoxicity, including muscle pain and weakness and rhabdomyolysis, have been reported anecdotally with concomitant administration of colchicines.

Phenytoin – Co-administration of fluvastatin (40 mg b.i.d. for 5 days) increased the mean Cmax of phenytoin by 5% whereas the mean AUC was increased by 22%. Patients on phenytoin should be carefully monitored when fluvastatin therapy is initiated or when the dose is increased.

Warfarin and other Coumarin derivatives - Co-administration of fluvastatin with warfarin may commonly cause significant increases in prothrombin time. This has resulted very rarely in serious haemorrhage. It is recommended that prothrombin times are monitored when fluvastatin therapy is initiated, discontinued or the dosage changed in patients receiving warfarin or other coumarin derivative.

Glibenclamide - An interaction study between fluvastatin 40mg b.i.d. and glibenclamide was done in diabetic patients stabilised on 5-20mg of glibenclamide. The AUC for glibenclamide increased on average by 1.7 times (range: 0.9 – 3.5), Cmax increased on average by 1.6 times (range: 0.9 -3.0) and the mean t1/2 of glibenclamide increased from 8.5 to 18.8 hours when taken with fluvastatin. In this study there were no significant changes in glucose levels but in view of the increases seen in glibenclamide levels there remains a potential for serious hypoglycaemia and this combination should be avoided whenever possible.

Other concomitant therapy - In clinical studies in which Fluvastatin Capsules were used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, salicylic acid, H2-blockers and non-steroidal anti-inflammatory drugs (NSAIDs), no clinically significant adverse interactions occurred.

### 4.6 Pregnancy and lactation

Animal studies have indicated that fluvastatin is devoid of embryotoxic and teratogenic potential. However, 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, HMG-CoA reductase inhibitors are contraindicated during pregnancy and 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.

As small amounts of fluvastatin have been found in rat milk, Fluvastatin Capsules are contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines
No data exist on the effects of Fluvastatin Capsules on the ability to drive and use machines.

4.8 Undesirable effects
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.
The most commonly reported adverse drug reactions are minor gastrointestinal symptoms, insomnia and headache.

Table 1
| Blood and lymphatic system disorders | Very rare:       |
|                                    | Thrombocytopenia |
| Psychiatric disorders              |                 |
| Common:                            | Insomnia.       |
| Nervous system disorders           |                 |
| Common:                            | Headache.       |
| Very rare:                         | Paraesthesia, dyasaesthesia, hypoaesthesia and peripheral neuropathy also known to be associated with the underlying hyperlipidemic disorders. |
| Vascular disorders                 |                 |
| Very rare:                         | Vasculitis.     |
| Gastrointestinal disorders         |                 |
| Common:                            | Dyspepsia, abdominal pain, nausea. |
| Very rare:                         | Pancreatitis    |
| Hepatobiliary disorders            |                 |
| Very rare:                         | Hepatitis.      |
| Skin and subcutaneous tissue disorders |         |
| Rare:                              | Hypersensitivity reactions such as rash, urticaria. |
| Very rare:                         | Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema |
| Musculoskeletal and connective tissue disorders |       |
| Rare:                              | Myalgia, muscle weakness, myopathy. |
| Very rare:                         | Rhabdomyolysis, myositis, lupus erythematosus-like reactions. |

Laboratory Findings
Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in a small number of patients (less than or equal to 1%). Marked elevations of CK levels to more than 5 x ULN developed 0.3 - 1.0% of patients receiving licensed doses of fluvastatin in clinical trials.

4.9 Overdose
The experience with overdoses of Fluvastatin Capsules is very limited. Should an accidental overdose occur, administration of activated charcoal is recommended. In the case of a very recent oral intake gastric lavage may be considered. Treatment should be symptomatic.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitor, ATC code: C01 AA01
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. 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.

A variety of clinical studies has demonstrated that elevated levels of total cholesterol (total-C), 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. Epidemiologic 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). The overall cholesterol profile is improved with the principal effects being the reduction of total-C and LDL-C. Fluvastatin also produces a moderate reduction in triglycerides and a moderate increase in HDL-C.

In a pooled analysis of all placebo-controlled studies, patients with primary mixed dyslipidaemia (Type IIb) defined as baseline TG levels \( \geq \) 200 mg/dL, treatment with Fluvastatin in daily doses ranging from 20 mg to 80 mg (40 mg b.i.d.) demonstrated consistent and significant decreases in total-C, LDL-C, and apo-B, TG, and a modest increase in HDL-C.

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Fluvastatin is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. Fluvastatin is absorbed rapidly and completely (98%) following oral administration to fasted volunteers. In a fed state, the drug is absorbed at a reduced rate. 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 (Vzf) for the drug is 330 L. More than 98% of the circulating drug is bound to plasma proteins, and this binding is unaffected by drug concentration.

The major circulating blood components are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate systemically.

The hepatic metabolic pathways of fluvastatin in humans have been characterised. There are multiple, alternative cytochrome P450 (CYP450) pathways involved. However, the major pathway is mediated by CYP2C9 and this pathway is subject to potential interactions with other CYP2C9 substrates or inhibitors. In addition there are several minor pathways (e.g. CYP3A4).
Several detailed in vitro studies have addressed the inhibitory potential of fluvastatin on common CYP isoenzymes. Fluvastatin inhibited only the metabolism of compounds that are metabolized by CYP2C9.

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 $1.8 \pm 0.8 \text{ L/min}$. Steady-state plasma concentrations show no evidence of fluvastatin accumulation following administration of 40 mg daily. Following oral administration of 40 mg of Fluvastatin Capsules, the terminal disposition half-life for fluvastatin is $2.3 \pm 0.9 \text{ hours}$.

Food: Although AUC and Cmax were lowered and tmax prolonged when fluvastatin was taken with food, there was no apparent difference in the lipid-lowering effect whether fluvastatin was taken with food or not.

Plasma concentrations of fluvastatin do not vary as a function of either age or gender in the general population.

5.3 Preclinical safety data

The safety of fluvastatin was extensively investigated in toxicity studies in rats, dogs, monkeys, mice and hamsters. A variety of changes were identified that are common to HMG-CoA reductase inhibitors, viz. hyperplasia and hyperkeratosis of the rodent non-glandular stomach, cataracts in dogs, myopathy in rodents, mild liver changes in most laboratory animals with gall bladder changes in dog, monkey and hamster, thyroid weight increases in the rat and testicular degeneration in the hamster. Fluvastatin is devoid of the CNS vascular and degenerative changes recorded in dogs with other members of this class of compound.

A carcinogenicity study was performed in rats at dose levels of 6, 9 and 18 mg/kg a day (escalated to 24 mg/kg a day after 1 year) to establish a clear maximum tolerated dose. These treatment levels yielded plasma drug levels approximately 9, 13 and 26 to 35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and one carcinoma of the forestomach was observed at the 24 mg/kg a day dose level. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded in male rats treated with 18 to 24 mg/kg a day.

The forestomach neoplasms observed in rats and mice reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug. The increased incidence of thyroid follicular cell neoplasms in male rats given fluvastatin appears to be consistent with species-specific findings with other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no treatment-related increases in the incidences of hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg a day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg a day and in females at 15 mg/kg a day. These treatment levels yielded plasma drug levels approximately 0.2, 10 and 21 times the mean human plasma drug concentration after a 40-mg oral dose.

No evidence of mutagenicity was observed in vitro, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of Salmonella typhimurium or Escherichia coli: malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese hamster cells; HGPRT V79 Chinese hamster cells. In addition, there was no evidence of mutagenicity in vivo in either a rat or mouse micronucleus test.

In a study in rats at dose levels in females of 0.6, 2 and 6 mg/kg a day and in males of 2, 10 and 20 mg/kg a day, Fluvastatin had no adverse effects on the fertility or reproductive performance. Teratology studies in rats and rabbits showed maternal toxicity at high dose levels, but there was no evidence of embryotoxic or teratogenic potential. A study in which
female rats were dosed at 12 and 24 mg/kg a day during late gestation until weaning of the pups resulted in maternal mortality at or near term and post partum accompanied by foetal and neonatal lethality. No effects on the pregnant females or foetuses occurred at the low dose level of 2 mg/kg a day.

A second study at levels of 2, 6, 12 and 24 mg/kg a day during late gestation and early lactation showed similar effects at 6 mg/kg a day and above caused by cardiotoxicity. In a third study, pregnant rats were administered 12 or 24 mg/kg a day during late gestation until weaning of pups with or without the presence of concurrent supplementation with mevalonic acid, a derivative of HMG-CoA that is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the cardiotoxicity and the maternal and neonatal mortality. Therefore, the maternal and neonatal lethality observed with fluvastatin reflects its exaggerated pharmacologic effect during pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol
Talc
Magnesium Stearate
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Packed in Alu/Alu Blisters: 18 months
Packed in plastic bottles: 24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons
2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.
Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
8th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/12/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fluvastatin 40 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 42.12mg fluvastatin sodium corresponding to 40mg fluvastatin.
For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM
Hard gelatine capsule, size 1. The capsule contains pale yellow powder.
Capsule cap: Swedish orange opaque with imprint 40.
Capsule body: Rich yellow opaque with imprint FST.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Fluvastatin Capsules are indicated as an adjunct to diet for the reduction of elevated total-C, LDL-C, apo B and TG levels in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson types IIa and IIb).

Fluvastatin Capsules are also indicated to slow the progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant coronary heart disease who do not adequately respond to dietary control.

Fluvastatin Capsules are also indicated in patients with coronary heart disease for the secondary prevention of coronary events after percutaneous coronary intervention, see Section 5.1.

4.2 Posology and method of administration
Prior to initiating Fluvastatin Capsules, secondary causes of hypercholesterolaemia should be excluded, and the patient placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

Dose recommendations for lipid lowering effect
The recommended starting dose is 40 mg (One 40 mg capsule) once daily in the evening, although a dose of 20 mg fluvastatin (One 20 mg capsule) once daily may be adequate in mild cases. Most patients will require a dose of 20 mg to 40 mg once daily but the dose may be increased to 80 mg daily (One 40 mg capsule twice daily), individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum recommended daily dose is 80 mg.

The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of Fluvastatin Capsules is maintained with prolonged administration.

Fluvastatin Capsules are efficacious in monotherapy or in combination with bile acid sequestrants. When Fluvastatin Capsules are used in combination with cholestyramine or other resins, they should be administered at least 4 hours after the resin to avoid a significant interaction due to binding of the drug to the resin. Minimal data exist to support the efficacy and safety of Fluvastatin Capsules in combination with nicotinic acid or fibrates (see Section 4.5 Interactions with other medicaments and other forms of interaction).

Dose recommendations for slowing the progression of coronary atherosclerosis
In a study in patients with primary hypercholesterolaemia and concomitant coronary heart disease 40 mg daily slowed the progression of coronary atherosclerosis.
Dose recommendations for the secondary prevention of coronary events after percutaneous coronary intervention
In patients with coronary heart disease after percutaneous coronary intervention, the dose is 80 mg daily.

**Patients with impaired kidney function**
Fluvastatin is cleared by the liver, with less than 6% of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency (creatinine > 260 μmol/L). No dose adjustments are therefore necessary in these patients.

**Patients with impaired liver function**
Fluvastatin Capsules are contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see 4.3 Contraindications and 4.4 Special warnings and precautions for use).

**Use in Elderly**
There is no evidence of reduced tolerability or altered dosage requirements in elderly patients.

**Use in Children**
As there is no experience with the use of Fluvastatin Capsules in individuals less than 18 years of age, its use is contraindicated in this group.

### 4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients of Fluvastatin Capsules. Patients with active liver disease, hepatic impairment, or unexplained, persistent elevations in serum transaminases. Individuals under 18 years of age.

### 4.4 Special warnings and precautions for use
HMG-CoA reductase inhibitors, including Fluvastatin Capsules, are unlikely to be of benefit in patients with rare homozygous familial hypercholesterolaemia.

As with other lipid-lowering drugs, it is recommended that liver function tests be performed before the initiation of treatment and at 12 weeks following initiation of the treatment or elevation in dose and periodically thereafter in all patients. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 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 Capsules are administered to patients with a history of liver disease or heavy alcohol ingestion.

Since fluvastatin is eliminated primarily via the biliary route and is subject to significant pre-systemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency.

The use of fluvastatin in combination with glibenclamide should be avoided whenever possible (see Section 4.5 Interaction with other medicaments and other forms of interaction).

**Skeletal muscle:**
With Fluvastatin Capsules, myopathy has rarely been reported, whereas myositis and rhabdomyolysis have been reported very rarely. In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked elevation of creatine kinase (CK) values myopathy, myositis or rhabdomyolysis have to be considered. Patients should therefore be advised to report promptly unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.
Creatine kinase measurement:
There is no current evidence to require routine monitoring of plasma total creatine kinase or other muscle enzyme levels in asymptomatic patients on statins. If creatine kinase has to be measured it should not be done following strenuous exercise or in the presence of any plausible alternative cause of CK-increase as this makes the value interpretation difficult.

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

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse
- In elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK-levels are significantly elevated at baseline (>5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated (>5 x ULN) at baseline, treatment should not be started.

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

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to ≤5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy is known to be increased in patients receiving immunosuppressive drugs (including ciclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. Minimal data exist to support the efficacy or safety of Fluvastatin Capsules in combination with nicotinic acid, its derivatives, fibrates or ciclosporin. Isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with colchicines. Fluvastatin Capsules should be used with caution in patients receiving such concomitant medication (see Section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction
Fluvastatin is substantially metabolised by cytochrome P450 (CYP2C9). Other substrates or inhibitors of CYP2C9 administered concomitantly may therefore potentially result in increased plasma levels of fluvastatin, with a consequent increased risk of myopathy (see section 4.4).

Food interactions
Although AUC and Cmax were lowered and tmax prolonged when Fluvastatin Capsules were taken with food, there was no apparent difference in the lipid-lowering effects whether Fluvastatin Capsules were taken with food or not.

Drug interactions
Effects of other drugs on fluvastatin:
Ciclosporin - In an interaction study concomitant administration of fluvastatin (up to 40mg/day) and ciclosporin resulted in an increase in the bioavailability of fluvastatin by a factor of 1.9. The results from another study where 80mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration were (Cmax) were increased by 2 fold compared to
historical data in healthy subjects. The combination of fluvastatin and ciclosporin should be used with caution due to the potential for an increased risk of myopathy and/or rhabdomyolysis. (see section 4.4 Special warning and precautions for use).

Fibric acid derivatives (fibrates) and nicotinic acid:
Bezafibrate - An interaction study between 20mg o.d. fluvastatin and 200mg t.d.s. bezafibrate showed that mean AUC and Cmax values of fluvastatin were increased on average by about 50-60%. No effect was seen on bezafibrate pharmacokinetics. This combination should be used with caution, however, due to the increased risk of developing myopathy and/or rhabdomyolysis when HMG-CoA reductase inhibitors including fluvastatin have been combined with fibrates. Any patient complaining of myalgia should be carefully evaluated.

Gemfibrozil - In an interaction study the concomitant administration of fluvastatin and gemfibrozil had no effect on the pharmacokinetics of either drug. The combination should be used with caution however, due to reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with fibrates.

Ciprofibrate - Concomitant administration of fluvastatin and ciprofibrate has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when ciprofibrate is used in combination with other HMG-CoA reductase inhibitors.

Nicotinic acid - Concomitant administration of fluvastatin and nicotinic acid has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when nicotinic acid is used in combination with other HMG-CoA reductase inhibitors.

Erythromycin - There are reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with erythromycin. The results from an interaction study with a small number of healthy volunteers suggested that erythromycin and fluvastatin were not metabolised by the same isoenzyme, however caution should be exercised when these two drugs are given in combination in view of the interaction seen with other HMG-CoA reductase inhibitors.

Fluconazole – Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor) resulted in an increase in the exposure (AUC) and mean peak concentration (Cmax) of fluvastatin by about 84% and 44% respectively. Caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Itraconazole - No interactions have been seen with itraconazole. Nevertheless patients should be closely monitored.

Antipyrine - Administration of Fluvastatin Capsules does not influence the metabolism and excretion of antipyrine. As antipyrine is a model for drugs metabolised by the microsomal hepatic enzyme systems, interactions with other drugs metabolised by these systems are not expected.

Propranolol - Concomitant administration of Fluvastatin Capsules with propranolol has no effect on the bioavailability of Fluvastatin Capsules.

Bile-acid sequestering agents - Administration of Fluvastatin Capsules 4 hours after cholestyramine results in a clinically significant additive effect compared with that achieved with either drug alone. Fluvastatin Capsules should be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding to the resin.

Digoxin - Concomitant administration of Fluvastatin Capsules with digoxin has no effect on digoxin plasma concentrations.
Amlodipine – No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with amlodipine.

Cimetidine/ranitidine/omeprazole - Concomitant administration of Fluvastatin Capsules with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of Fluvastatin Capsules, which, however, is of no clinical relevance.

Rifampicin - Administration of Fluvastatin Capsules to subjects pre-treated with rifampicin resulted in a reduction of the bioavailability of Fluvastatin Capsules 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.

Phenytoin - In an interaction study concomitant administration of fluvastatin and phenytoin resulted in an increase of fluvastatin mean AUC and Cmax values by 40% and 27% respectively. This combination should be used with caution due to the increased risk of developing myopathy and/or rhabdomyolysis.

Effects of fluvastatin on other drugs:

Ciclosporin – Fluvastatin Capsules had no effect on ciclosporin bioavailability when co-administered (see also Effects of other drugs on fluvastatin).

Colchicine – No information is available on the pharmacokinetic interaction between fluvastatin and colchicine. However, myotoxicity, including muscle pain and weakness and rhabdomyolysis, have been reported anecdotally with concomitant administration of colchicines.

Phenytoin – Co-administration of fluvastatin (40 mg b.i.d. for 5 days) increased the mean Cmax of phenytoin by 5% whereas the mean AUC was increased by 22%. Patients on phenytoin should be carefully monitored when fluvastatin therapy is initiated or when the dose is increased.

Warfarin and other Coumarin derivatives - Co-administration of fluvastatin with warfarin may commonly cause significant increases in prothrombin time. This has resulted very rarely in serious haemorrhage. It is recommended that prothrombin times are monitored when fluvastatin therapy is initiated, discontinued or the dosage changed in patients receiving warfarin or other coumarin derivative.

Glibenclamide - An interaction study between fluvastatin 40mg b.i.d. and glibenclamide was done in diabetic patients stabilised on 5-20mg of glibenclamide. The AUC for glibenclamide increased on average by 1.7 times (range: 0.9 – 3.5), Cmax increased on average by 1.6 times (range: 0.9 -3.0) and the mean t1/2 of glibenclamide increased from 8.5 to 18.8 hours when taken with fluvastatin. In this study there were no significant changes in glucose levels but in view of the increases seen in glibenclamide levels there remains a potential for serious hypoglycaemia and this combination should be avoided whenever possible.

Other concomitant therapy - In clinical studies in which Fluvastatin Capsules were used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, salicylic acid, H2-blockers and non-steroidal anti-inflammatory drugs (NSAIDs), no clinically significant adverse interactions occurred.

4.6 Pregnancy and lactation

Animal studies have indicated that fluvastatin is devoid of embryotoxic and teratogenic potential. However, 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, HMG-CoA reductase inhibitors are contraindicated during pregnancy and 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.

As small amounts of fluvastatin have been found in rat milk, Fluvastatin Capsules are contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines
No data exist on the effects of Fluvastatin Capsules on the ability to drive and use machines.

4.8 Undesirable effects
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1,000, < 1/100); rare (≥1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.
The most commonly reported adverse drug reactions are minor gastrointestinal symptoms, insomnia and headache.

Table 1

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
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<tbody>
<tr>
<td>Very rare:</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
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</thead>
<tbody>
<tr>
<td>Common:</td>
</tr>
<tr>
<td>Insomnia.</td>
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<table>
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<tr>
<th>Nervous system disorders</th>
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<tbody>
<tr>
<td>Common:</td>
</tr>
<tr>
<td>Headache.</td>
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</table>

<table>
<thead>
<tr>
<th>Very rare:</th>
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</thead>
<tbody>
<tr>
<td>Paraesthesia, dyseaesthesia, hypoaesthesia and peripheral neuropathy also known to be associated with the underlying hyperlipidemic disorders.</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Vascular disorders</th>
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<tbody>
<tr>
<td>Very rare:</td>
</tr>
<tr>
<td>Vasculitis.</td>
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<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
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<tbody>
<tr>
<td>Common:</td>
</tr>
<tr>
<td>Dyspepsia, abdominal pain, nausea.</td>
</tr>
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</table>

| Very rare:                     |
| Pancreatitis                   |

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
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<tbody>
<tr>
<td>Very rare:</td>
</tr>
<tr>
<td>Hepatitis.</td>
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<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
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<tbody>
<tr>
<td>Rare:</td>
</tr>
<tr>
<td>Hypersensitivity reactions such as rash, urticaria.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare:</td>
</tr>
<tr>
<td>Myalgia, muscle weakness, myopathy.</td>
</tr>
</tbody>
</table>

| Very rare:                              |
| Rhabdomyolysis, myositis, lupus erythmatosus-like reactions. |

Laboratory Findings
Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in a small number of patients (less than or equal to 1%). Marked elevations of CK levels to more than 5 x ULN developed 0.3 - 1.0% of patients receiving licensed doses of fluvastatin in clinical trials.

4.9 Overdose
The experience with overdoses of Fluvastatin Capsules is very limited. Should an accidental overdosage occur, administration of activated charcoal is recommended. In the case of a very recent oral intake gastric lavage may be considered. Treatment should be symptomatic.
5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitor, ATC code: C01 AA01
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. 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.

A variety of clinical studies has demonstrated that elevated levels of total cholesterol (total-C), 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. Epidemiologic 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). The overall cholesterol profile is improved with the principal effects being the reduction of total-C and LDL-C. Fluvastatin also produces a moderate reduction in triglycerides and a moderate increase in HDL-C.

In a pooled analysis of all placebo-controlled studies, patients with primary mixed dyslipidaemia (Type IIb) defined as baseline TG levels ≥ 200 mg/dL, treatment with Fluvastatin in daily doses ranging from 20 mg to 80 mg (40 mg b.i.d.) demonstrated consistent and significant decreases in total-C, LDL-C, and apo-B, TG, and a modest increase in HDL-C.

In the Lescol Intervention Prevention Study (LIPS), the effect of fluvastatin on major adverse cardiac events (MACE) was assessed in patients with coronary heart disease who had first successful transcatheter therapy (TCT). The study included male and female patients (18-80 years old) and with baseline total cholesterol levels ranging from 3.5-7.0 mmol/L. In this randomised, double-blind, placebo-controlled trial, a total of 1677 patients were recruited (844 in fluvastatin group and 833 in placebo group). The MACE was defined as cardiac death, non fatal MI and re-intervention (including CABG, repeat TCT, or TCT of a new lesion). The dose of fluvastatin used in this study was 80 mg daily over 4 years. Although the overall composite endpoint showed significant reduction in MACE (22%) compared to placebo (p=0.013), the individual components (cardiac death, non fatal MI and re-intervention) failed to reach statistical significance. There was however a trend in favour of fluvastatin. Therapy with fluvastatin reduced the risk of cardiac death and/or myocardial infarction by 31% (p=0.065).

5.2 Pharmacokinetic properties
Fluvastatin is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. Fluvastatin is absorbed rapidly and completely (98%) following oral administration to fasted volunteers. In a fed state, the drug is absorbed at a reduced rate. 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 (Vzf) for the drug is 330 L. More than 98% of the circulating drug is bound to plasma proteins, and this binding is unaffected by drug concentration.

The major circulating blood components are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate systemically.

The hepatic metabolic pathways of fluvastatin in humans have been characterised. There are multiple, alternative cytochrome P450 (CYP450) pathways involved. However, the major pathway is mediated by CYP2C9 and this pathway is subject to potential interactions with other CYP2C9 substrates or inhibitors. In addition there are several minor pathways (e.g. CYP3A4).
Several detailed in vitro studies have addressed the inhibitory potential of fluvastatin on common CYP isoenzymes. Fluvastatin inhibited only the metabolism of compounds that are metabolized by CYP2C9.

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 $1.8 \pm 0.8 \text{ L/min}$. Steady-state plasma concentrations show no evidence of fluvastatin accumulation following administration of 40 mg daily. Following oral administration of 40 mg of Fluvastatin Capsules, the terminal disposition half-life for fluvastatin is $2.3 \pm 0.9 \text{ hours}$.

Food: Although AUC and Cmax were lowered and tmax prolonged when fluvastatin was taken with food, there was no apparent difference in the lipid-lowering effect whether fluvastatin was taken with food or not.

Plasma concentrations of fluvastatin do not vary as a function of either age or gender in the general population.

5.3 Preclinical safety data

The safety of fluvastatin was extensively investigated in toxicity studies in rats, dogs, monkeys, mice and hamsters. A variety of changes were identified that are common to HMG-CoA reductase inhibitors, viz. hyperplasia and hyperkeratosis of the rodent non-glandular stomach, cataracts in dogs, myopathy in rodents, mild liver changes in most laboratory animals with gall bladder changes in dog, monkey and hamster, thyroid weight increases in the rat and testicular degeneration in the hamster. Fluvastatin is devoid of the CNS vascular and degenerative changes recorded in dogs with other members of this class of compound.

A carcinogenicity study was performed in rats at dose levels of 6, 9 and 18 mg/kg a day (escalated to 24 mg/kg a day after 1 year) to establish a clear maximum tolerated dose. These treatment levels yielded plasma drug levels approximately 9, 13 and 26 to 35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and one carcinoma of the forestomach was observed at the 24 mg/kg a day dose level. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded in male rats treated with 18 to 24 mg/kg a day.

The forestomach neoplasms observed in rats and mice reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug. The increased incidence of thyroid follicular cell neoplasms in male rats given fluvastatin appears to be consistent with species-specific findings with other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no treatment-related increases in the incidences of hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg a day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg a day and in females at 15 mg/kg a day. These treatment levels yielded plasma drug levels approximately 0.2, 10 and 21 times the mean human plasma drug concentration after a 40-mg oral dose.

No evidence of mutagenicity was observed in vitro, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of Salmonella typhimurium or Escherichia coli: malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese hamster cells; HGPRT V79 Chinese hamster cells. In addition, there was no evidence of mutagenicity in vivo in either a rat or mouse micronucleus test.

In a study in rats at dose levels in females of 0.6, 2 and 6 mg/kg a day and in males of 2, 10 and 20 mg/kg a day, Fluvastatin had no adverse effects on the fertility or reproductive performance. Teratology studies in rats and rabbits showed maternal toxicity at high dose levels, but there was no evidence of embryotoxic or teratogenic potential. A study in which
female rats were dosed at 12 and 24 mg/kg a day during late gestation until weaning of the pups resulted in maternal mortality at or near term and post partum accompanied by foetal and neonatal lethality. No effects on the pregnant females or foetuses occurred at the low dose level of 2 mg/kg a day.

A second study at levels of 2, 6, 12 and 24 mg/kg a day during late gestation and early lactation showed similar effects at 6 mg/kg a day and above caused by cardiotoxicity. In a third study, pregnant rats were administered 12 or 24 mg/kg a day during late gestation until weaning of pups with or without the presence of concurrent supplementation with mevalonic acid, a derivative of HMG-CoA that is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the cardiotoxicity and the maternal and neonatal mortality. Therefore, the maternal and neonatal lethality observed with fluvastatin reflects its exaggerated pharmacologic effect during pregnancy.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Mannitol
Talc
Magnesium Stearate
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons
2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.
Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
8th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/12/2008

10 DATE OF REVISION OF THE TEXT
30/12/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fluvastatin 20 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 21.06mg fluvastatin sodium corresponding to 20mg fluvastatin. For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Fluvastatin Capsules are indicated as an adjunct to diet for the reduction of elevated total-C, LDL-C, apo B and TG levels in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson types IIa and IIb).

Fluvastatin Capsules are also indicated to slow the progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant coronary heart disease who do not adequately respond to dietary control.

Fluvastatin Capsules are also indicated in patients with coronary heart disease for the secondary prevention of coronary events after percutaneous coronary intervention, see Section 5.1.

4.2 Posology and method of administration
Prior to initiating Fluvastatin Capsules, secondary causes of hypercholesterolaemia should be excluded, and the patient placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

Dose recommendations for lipid lowering effect
The recommended starting dose is 40 mg (One 40 mg capsule) once daily in the evening, although a dose of 20 mg fluvastatin (One 20 mg capsule) once daily may be adequate in mild cases. Most patients will require a dose of 20 mg to 40 mg once daily but the dose may be increased to 80 mg daily (One 40 mg capsule twice daily), individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum recommended daily dose is 80 mg.

The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of Fluvastatin Capsules is maintained with prolonged administration.

Fluvastatin Capsules are efficacious in monotherapy or in combination with bile acid sequestrants. When Fluvastatin Capsules are used in combination with cholestyramine or other resins, they should be administered at least 4 hours after the resin to avoid a significant interaction due to binding of the drug to the resin. Minimal data exist to support the efficacy and safety of Fluvastatin Capsules in combination with nicotinic acid or fibrates (see Section 4.5 Interactions with other medicaments and other forms of interaction).

Dose recommendations for slowing the progression of coronary atherosclerosis
In a study in patients with primary hypercholesterolaemia and concomitant coronary heart disease 40 mg daily slowed the progression of coronary atherosclerosis.

Dose recommendations for the secondary prevention of coronary events after percutaneous coronary intervention
In patients with coronary heart disease after percutaneous coronary intervention, the dose is 80 mg daily.

**Patients with impaired kidney function**
Fluvastatin is cleared by the liver, with less than 6% of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency (creatinine > 260 μmol/L). No dose adjustments are therefore necessary in these patients.

**Patients with impaired liver function**
Fluvastatin Capsules are contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see 4.3 Contraindications and 4.4 Special warnings and precautions for use).

**Use in Elderly**
There is no evidence of reduced tolerability or altered dosage requirements in elderly patients.

**Use in Children**
As there is no experience with the use of Fluvastatin Capsules in individuals less than 18 years of age, its use is contraindicated in this group.

### 4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients of Fluvastatin Capsules. Patients with active liver disease, hepatic impairment, or unexplained, persistent elevations in serum transaminases. Individuals under 18 years of age.

### 4.4 Special warnings and precautions for use
HMG-CoA reductase inhibitors, including Fluvastatin Capsules, are unlikely to be of benefit in patients with rare homozygous familial hypercholesterolaemia.

As with other lipid-lowering drugs, it is recommended that liver function tests be performed before the initiation of treatment and at 12 weeks following initiation of the treatment or elevation in dose and periodically thereafter in all patients. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 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 Capsules are administered to patients with a history of liver disease or heavy alcohol ingestion.

Since fluvastatin is eliminated primarily via the biliary route and is subject to significant pre-systemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency.

The use of fluvastatin in combination with glibenclamide should be avoided whenever possible (see Section 4.5 Interaction with other medicaments and other forms of interaction).

**Skeletal muscle:**
With Fluvastatin Capsules, myopathy has rarely been reported, whereas myositis and rhabdomyolysis have been reported very rarely. In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked elevation of creatine kinase (CK) values myopathy, myositis or rhabdomyolysis have to be considered. Patients should therefore be advised to report promptly unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.
Creatine kinase measurement:
There is no current evidence to require routine monitoring of plasma total creatine kinase or other muscle enzyme levels in asymptomatic patients on statins. If creatine kinase has to be measured it should not be done following strenuous exercise or in the presence of any plausible alternative cause of CK-increase as this makes the value interpretation difficult.

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

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse
- In elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK-levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated (> 5 x ULN) at baseline, treatment should not be started.

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

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy is known to be increased in patients receiving immunosuppressive drugs (including ciclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. Minimal data exist to support the efficacy or safety of Fluvastatin Capsules in combination with nicotinic acid, its derivatives, fibrates or ciclosporin. Isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with colchicines. Fluvastatin Capsules should be used with caution in patients receiving such concomitant medication (see Section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction
Fluvastatin is substantially metabolised by cytochrome P450 (CYP2C9). Other substrates or inhibitors of CYP2C9 administered concomitantly may therefore potentially result in increased plasma levels of fluvastatin, with a consequent increased risk of myopathy (see section 4.4).

Food interactions
Although AUC and Cmax were lowered and tmax prolonged when Fluvastatin Capsules were taken with food, there was no apparent difference in the lipid-lowering effects whether Fluvastatin Capsules were taken with food or not.

Drug interactions
Effects of other drugs on fluvastatin:
Ciclosporin - In an interaction study concomitant administration of fluvastatin (up to 40mg/day) and ciclosporin resulted in an increase in the bioavailability of fluvastatin by a factor of 1.9. The results from another study where 80mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration were (Cmax) were increased by 2 fold compared to
historical data in healthy subjects. The combination of fluvastatin and ciclosporin should be used with caution due to the potential for an increased risk of myopathy and/or rhabdomyolysis. (see section 4.4 Special warning and precautions for use).

Fibric acid derivatives (fibrates) and nicotinic acid:
Bezafibrate - An interaction study between 20mg o.d. fluvastatin and 200mg t.d.s. bezafibrate showed that mean AUC and Cmax values of fluvastatin were increased on average by about 50-60%. No effect was seen on bezafibrate pharmacokinetics. This combination should be used with caution, however, due to the increased risk of developing myopathy and/or rhabdomyolysis when HMG-CoA reductase inhibitors including fluvastatin have been combined with fibrates. Any patient complaining of myalgia should be carefully evaluated.

Gemfibrozil - In an interaction study the concomitant administration of fluvastatin and gemfibrozil had no effect on the pharmacokinetics of either drug. The combination should be used with caution however, due to reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with fibrates.

Ciprofibrate - Concomitant administration of fluvastatin and ciprofibrate has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when ciprofibrate is used in combination with other HMG-CoA reductase inhibitors.

Nicotinic acid - Concomitant administration of fluvastatin and nicotinic acid has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when nicotinic acid is used in combination with other HMG-CoA reductase inhibitors.

Erythromycin - There are reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with erythromycin. The results from an interaction study with a small number of healthy volunteers suggested that erythromycin and fluvastatin were not metabolised by the same isoenzyme, however caution should be exercised when these two drugs are given in combination in view of the interaction seen with other HMG-CoA reductase inhibitors.

Fluconazole – Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor) resulted in an increase in the exposure (AUC) and mean peak concentration (Cmax) of fluvastatin by about 84% and 44% respectively. Caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Itraconazole - No interactions have been seen with itraconazole. Nevertheless patients should be closely monitored.

Antipyrine - Administration of Fluvastatin Capsules does not influence the metabolism and excretion of antipyrine. As antipyrine is a model for drugs metabolised by the microsomal hepatic enzyme systems, interactions with other drugs metabolised by these systems are not expected.

Propranolol - Concomitant administration of Fluvastatin Capsules with propranolol has no effect on the bioavailability of Fluvastatin Capsules.

Bile-acid sequestering agents - Administration of Fluvastatin Capsules 4 hours after cholestyramine results in a clinically significant additive effect compared with that achieved with either drug alone. Fluvastatin Capsules should be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding to the resin.

Digoxin - Concomitant administration of Fluvastatin Capsules with digoxin has no effect on digoxin plasma concentrations.
Amlodipine – No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with amlodipine.

Cimetidine/ranitidine/omeprazole - Concomitant administration of Fluvastatin Capsules with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of Fluvastatin Capsules, which, however, is of no clinical relevance.

Rifampicin - Administration of Fluvastatin Capsules to subjects pre-treated with rifampicin resulted in a reduction of the bioavailability of Fluvastatin Capsules 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.

Phenytoin - In an interaction study concomitant administration of fluvastatin and phenytoin resulted in an increase of fluvastatin mean AUC and Cmax values by 40% and 27% respectively. This combination should be used with caution due to the increased risk of developing myopathy and/or rhabdomyolysis.

Effects of fluvastatin on other drugs:
Ciclosporin – Fluvastatin Capsules had no effect on ciclosporin bioavailability when co-administered (see also Effects of other drugs on fluvastatin).

Colchicine – No information is available on the pharmacokinetic interaction between fluvastatin and colchicine. However, myotoxicity, including muscle pain and weakness and rhabdomyolysis, have been reported anecdotally with concomitant administration of colchicines.

Phenytoin – Co-administration of fluvastatin (40 mg b.i.d. for 5 days) increased the mean Cmax of phenytoin by 5% whereas the mean AUC was increased by 22%. Patients on phenytoin should be carefully monitored when fluvastatin therapy is initiated or when the dose is increased.

Warfarin and other Coumarin derivatives - Co-administration of fluvastatin with warfarin may commonly cause significant increases in prothrombin time. This has resulted very rarely in serious haemorrhage. It is recommended that prothrombin times are monitored when fluvastatin therapy is initiated, discontinued or the dosage changed in patients receiving warfarin or other coumarin derivative.

Glibenclamide - An interaction study between fluvastatin 40mg b.i.d. and glibenclamide was done in diabetic patients stabilised on 5-20mg of glibenclamide. The AUC for glibenclamide increased on average by 1.7 times (range: 0.9 – 3.5), Cmax increased on average by 1.6 times (range: 0.9 -3.0) and the mean t1/2 of glibenclamide increased from 8.5 to 18.8 hours when taken with fluvastatin. In this study there were no significant changes in glucose levels but in view of the increases seen in glibenclamide levels there remains a potential for serious hypoglycaemia and this combination should be avoided whenever possible.

Other concomitant therapy - In clinical studies in which Fluvastatin Capsules were used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, salicylic acid, H2-blockers and non-steroidal anti-inflammatory drugs (NSAIDs), no clinically significant adverse interactions occurred.

### 4.6 Pregnancy and lactation

Animal studies have indicated that fluvastatin is devoid of embryotoxic and teratogenic potential. However, 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, HMG-CoA reductase inhibitors are contraindicated during pregnancy and 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.
As small amounts of fluvastatin have been found in rat milk, Fluvastatin Capsules are contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines
No data exist on the effects of Fluvastatin Capsules on the ability to drive and use machines.

4.8 Undesirable effects
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness. The most commonly reported adverse drug reactions are minor gastrointestinal symptoms, insomnia and headache.

Table 1

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare:</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td>Common: Insomnia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
</tr>
<tr>
<td>Common: Headache</td>
</tr>
<tr>
<td>Very rare:</td>
</tr>
<tr>
<td>Vascular disorders</td>
</tr>
<tr>
<td>Very rare:</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Common: Dyspepsia, abdominal pain, nausea.</td>
</tr>
<tr>
<td>Very rare:</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
</tr>
<tr>
<td>Very rare:</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
</tr>
<tr>
<td>Rare:</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
</tr>
<tr>
<td>Rare: Myalgia, muscle weakness, myopathy.</td>
</tr>
<tr>
<td>Very rare:</td>
</tr>
</tbody>
</table>

Laboratory Findings
Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in a small number of patients (less than or equal to 1%). Marked elevations of CK levels to more than 5 x ULN developed 0.3 - 1.0% of patients receiving licensed doses of fluvastatin in clinical trials.

4.9 Overdose
The experience with overdoses of Fluvastatin Capsules is very limited. Should an accidental overdosage occur, administration of activated charcoal is recommended. In the case of a very recent oral intake gastric lavage may be considered. Treatment should be symptomatic.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotheerapeutic group: HMG-CoA reductase inhibitor, ATC code: C01 AA01

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. 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.

A variety of clinical studies has demonstrated that elevated levels of total cholesterol (total-C), 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. Epidemiologic 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). The overall cholesterol profile is improved with the principal effects being the reduction of total-C and LDL-C. Fluvastatin also produces a moderate reduction in triglycerides and a moderate increase in HDL-C.

In a pooled analysis of all placebo-controlled studies, patients with primary mixed dyslipidaemia (Type IIb) defined as baseline TG levels ≥200 mg/dL, treatment with Fluvastatin in daily doses ranging from 20 mg to 80 mg (40 mg b.i.d.) demonstrated consistent and significant decreases in total-C, LDL-C, and apo-B, TG, and a modest increase in HDL-C.

In the Lescol Intervention Prevention Study (LIPS), the effect of fluvastatin on major adverse cardiac events (MACE) was assessed in patients with coronary heart disease who had first successful transcathether therapy (TCT). The study included male and female patients (18-80 years old) and with baseline total cholesterol levels ranging from 3.5-7.0 mmol/L.

In this randomised, double-blind, placebo-controlled trial, a total of 1677 patients were recruited (844 in fluvastatin group and 833 in placebo group). The MACE was defined as cardiac death, non fatal MI and re-intervention (including CABG, repeat TCT, or TCT of a new lesion). The dose of fluvastatin used in this study was 80 mg daily over 4 years. Although the overall composite endpoint showed significant reduction in MACE (22%) compared to placebo (p=0.013), the individual components (cardiac death, non fatal MI and re-intervention) failed to reach statistical significance. There was however a trend in favour of fluvastatin. Therapy with fluvastatin reduced the risk of cardiac death and/or myocardial infarction by 31% (p=0.065).

5.2 Pharmacokinetic properties

Fluvastatin is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. Fluvastatin is absorbed rapidly and completely (98%) following oral administration to fasted volunteers. In a fed state, the drug is absorbed at a reduced rate. 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 (VzF) for the drug is 330 L. More than 98% of the circulating drug is bound to plasma proteins, and this binding is unaffected by drug concentration.

The major circulating blood components are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate systemically.

The hepatic metabolic pathways of fluvastatin in humans have been characterised. There are multiple, alternative cytochrome P450 (CYP450) pathways involved. However, the major pathway is mediated by CYP2C9 and this pathway is subject to potential interactions with other CYP2C9 substrates or inhibitors. In addition there are several minor pathways (e.g. CYP3A4).
Several detailed in vitro studies have addressed the inhibitory potential of fluvastatin on common CYP isoenzymes. Fluvastatin inhibited only the metabolism of compounds that are metabolized by CYP2C9.

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 40 mg daily. Following oral administration of 40 mg of Fluvastatin Capsules, the terminal disposition half-life for fluvastatin is 2.3 ± 0.9 hours.

Food: Although AUC and Cmax were lowered and tmax prolonged when fluvastatin was taken with food, there was no apparent difference in the lipid-lowering effect whether fluvastatin was taken with food or not.

Plasma concentrations of fluvastatin do not vary as a function of either age or gender in the general population.

5.3 Preclinical safety data

The safety of fluvastatin was extensively investigated in toxicity studies in rats, dogs, monkeys, mice and hamsters. A variety of changes were identified that are common to HMG-CoA reductase inhibitors, viz. hyperplasia and hyperkeratosis of the rodent non-glandular stomach, cataracts in dogs, myopathy in rodents, mild liver changes in most laboratory animals with gall bladder changes in dog, monkey and hamster, thyroid weight increases in the rat and testicular degeneration in the hamster. Fluvastatin is devoid of the CNS vascular and degenerative changes recorded in dogs with other members of this class of compound.

A carcinogenicity study was performed in rats at dose levels of 6, 9 and 18 mg/kg a day (escalated to 24 mg/kg a day after 1 year) to establish a clear maximum tolerated dose. These treatment levels yielded plasma drug levels approximately 9, 13 and 26 to 35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and one carcinoma of the forestomach was observed at the 24 mg/kg a day dose level. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded in male rats treated with 18 to 24 mg/kg a day.

The forestomach neoplasms observed in rats and mice reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug. The increased incidence of thyroid follicular cell neoplasms in male rats given fluvastatin appears to be consistent with species-specific findings with other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no treatment-related increases in the incidences of hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg a day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg a day and in females at 15 mg/kg a day. These treatment levels yielded plasma drug levels approximately 0.2, 10 and 21 times the mean human plasma drug concentration after a 40-mg oral dose.

No evidence of mutagenicity was observed in vitro, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of Salmonella typhimurium or Escherichia coli; malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese hamster cells; HGPRT V79 Chinese hamster cells. In addition, there was no evidence of mutagenicity in vivo in either a rat or mouse micronucleus test.

In a study in rats at dose levels in females of 0.6, 2 and 6 mg/kg a day and in males of 2, 10 and 20 mg/kg a day, Fluvastatin had no adverse effects on the fertility or reproductive performance. Teratology studies in rats and rabbits showed maternal toxicity at high dose levels, but there was no evidence of embryotoxic or teratogenic potential. A study in which
female rats were dosed at 12 and 24 mg/kg a day during late gestation until weaning of the pups resulted in maternal mortality at or near term and post partum accompanied by foetal and neonatal lethality. No effects on the pregnant females or foetuses occurred at the low dose level of 2 mg/kg a day.

A second study at levels of 2, 6, 12 and 24 mg/kg a day during late gestation and early lactation showed similar effects at 6 mg/kg a day and above caused by cardiotoxicity. In a third study, pregnant rats were administered 12 or 24 mg/kg a day during late gestation until weaning of pups with or without the presence of concurrent supplementation with mevalonic acid, a derivative of HMG-CoA that is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the cardiotoxicity and the maternal and neonatal mortality. Therefore, the maternal and neonatal lethality observed with fluvastatin reflects its exaggerated pharmacologic effect during pregnancy.

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Gelatin
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Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Packed in Alu/Alu Blisters: 18 months
Packed in plastic bottles: 24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons
2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.
Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
8th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/12/2008
SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT
Fluvastatin 40 mg Capsules

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 42.12mg fluvastatin sodium corresponding to 40mg fluvastatin.
For a full list of excipients, see Section 6.1

PHARMACEUTICAL FORM
Hard gelatine capsule, size 1. The capsule contains pale yellow powder.
Capsule cap: Swedish orange opaque with imprint 40.
Capsule body: Rich yellow opaque with imprint FST.

CLINICAL PARTICULARS

Therapeutic indications
Fluvastatin Capsules are indicated as an adjunct to diet for the reduction of elevated total-C, LDL-C, apo B and TG levels in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson types IIa and IIb).
Fluvastatin Capsules are also indicated to slow the progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant coronary heart disease who do not adequately respond to dietary control.
Fluvastatin Capsules are also indicated in patients with coronary heart disease for the secondary prevention of coronary events after percutaneous coronary intervention, see Section 5.1.

Posology and method of administration
Prior to initiating Fluvastatin Capsules, secondary causes of hypercholesterolaemia should be excluded, and the patient placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

Dose recommendations for lipid lowering effect
The recommended starting dose is 40 mg (One 40 mg capsule) once daily in the evening, although a dose of 20 mg fluvastatin (One 20 mg capsule) once daily may be adequate in mild cases. Most patients will require a dose of 20 mg to 40 mg once daily but the dose may be increased to 80 mg daily (One 40 mg capsule twice daily), individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum recommended daily dose is 80 mg.

The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of Fluvastatin Capsules is maintained with prolonged administration.

Fluvastatin Capsules are efficacious in monotherapy or in combination with bile acid sequestrants. When Fluvastatin Capsules are used in combination with cholestyramine or other resins, they should be administered at least 4 hours after the resin to avoid a significant interaction due to binding of the drug to the resin. Minimal data exist to support the efficacy and safety of Fluvastatin Capsules in combination with nicotinic acid or fibrates (see Section 4.5 Interactions with other medicaments and other forms of interaction).

Dose recommendations for slowing the progression of coronary atherosclerosis
In a study in patients with primary hypercholesterolaemia and concomitant coronary heart disease 40 mg daily slowed the progression of coronary atherosclerosis.
Dose recommendations for the secondary prevention of coronary events after percutaneous coronary intervention
In patients with coronary heart disease after percutaneous coronary intervention, the dose is 80 mg daily.

**Patients with impaired kidney function**
Fluvastatin is cleared by the liver, with less than 6% of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency (creatinine > 260 μmol/L). No dose adjustments are therefore necessary in these patients.

**Patients with impaired liver function**
Fluvastatin Capsules are contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see 4.3 Contraindications and 4.4 Special warnings and precautions for use).

**Use in Elderly**
There is no evidence of reduced tolerability or altered dosage requirements in elderly patients.

**Use in Children**
As there is no experience with the use of Fluvastatin Capsules in individuals less than 18 years of age, its use is contraindicated in this group.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients of Fluvastatin Capsules. Patients with active liver disease, hepatic impairment, or unexplained, persistent elevations in serum transaminases. Individuals under 18 years of age.

4.4 Special warnings and precautions for use
HMG-CoA reductase inhibitors, including Fluvastatin Capsules, are unlikely to be of benefit in patients with rare homozygous familial hypercholesterolaemia.

As with other lipid-lowering drugs, it is recommended that liver function tests be performed before the initiation of treatment and at 12 weeks following initiation of the treatment or elevation in dose and periodically thereafter in all patients. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 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 Capsules are administered to patients with a history of liver disease or heavy alcohol ingestion.

Since fluvastatin is eliminated primarily via the biliary route and is subject to significant pre-systemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency.

The use of fluvastatin in combination with glibenclamide should be avoided whenever possible (see Section 4.5 Interaction with other medicaments and other forms of interaction).

**Skeletal muscle:**
With Fluvastatin Capsules, myopathy has rarely been reported, whereas myositis and rhabdomyolysis have been reported very rarely. In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked elevation of creatine kinase (CK) values myopathy, myositis or rhabdomyolysis have to be considered. Patients should therefore be advised to report promptly unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.
Creatine kinase measurement:
There is no current evidence to require routine monitoring of plasma total creatine kinase or other muscle enzyme levels in asymptomatic patients on statins. If creatine kinase has to be measured it should not be done following strenuous exercise or in the presence of any plausible alternative cause of CK-increase as this makes the value interpretation difficult.

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

• Renal impairment
• Hypothyroidism
• Personal or familial history of hereditary muscular disorders
• Previous history of muscular toxicity with a statin or fibrate
• Alcohol abuse
• In elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK-levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated (> 5 x ULN) at baseline, treatment should not be started.

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

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy is known to be increased in patients receiving immunosuppressive drugs (including ciclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. Minimal data exist to support the efficacy or safety of Fluvastatin Capsules in combination with nicotinic acid, its derivatives, fibrates or ciclosporin. Isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with colchicines. Fluvastatin Capsules should be used with caution in patients receiving such concomitant medication (see Section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction
Fluvastatin is substantially metabolised by cytochrome P450 (CYP2C9). Other substrates or inhibitors of CYP2C9 administered concomitantly may therefore potentially result in increased plasma levels of fluvastatin, with a consequent increased risk of myopathy (see section 4.4).

Food interactions
Although AUC and Cmax were lowered and tmax prolonged when Fluvastatin Capsules were taken with food, there was no apparent difference in the lipid-lowering effects whether Fluvastatin Capsules were taken with food or not.

Drug interactions
Effects of other drugs on fluvastatin:
Ciclosporin - In an interaction study concomitant administration of fluvastatin (up to 40mg/day) and ciclosporin resulted in an increase in the bioavailability of fluvastatin by a factor of 1.9. The results from another study where 80mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration were (Cmax) were increased by 2 fold compared to
historical data in healthy subjects. The combination of fluvastatin and ciclosporin should be used with caution due to the potential for an increased risk of myopathy and/or rhabdomyolysis. (see section 4.4 Special warning and precautions for use).

Fibric acid derivatives (fibrates) and nicotinic acid:
Bezafibrate - An interaction study between 20mg o.d. fluvastatin and 200mg t.d.s. bezafibrate showed that mean AUC and Cmax values of fluvastatin were increased on average by about 50-60%. No effect was seen on bezafibrate pharmacokinetics. This combination should be used with caution, however, due to the increased risk of developing myopathy and/or rhabdomyolysis when HMG-CoA reductase inhibitors including fluvastatin have been combined with fibrates. Any patient complaining of myalgia should be carefully evaluated.

Gemfibrozil - In an interaction study the concomitant administration of fluvastatin and gemfibrozil had no effect on the pharmacokinetics of either drug. The combination should be used with caution however, due to reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with fibrates.

Ciprofibrate - Concomitant administration of fluvastatin and ciprofibrate has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when ciprofibrate is used in combination with other HMG-CoA reductase inhibitors.

Nicotinic acid - Concomitant administration of fluvastatin and nicotinic acid has no effect on the bioavailability of fluvastatin. However, the combination should be used with caution due to reports of an increased risk of myopathy and/or rhabdomyolysis when nicotinic acid is used in combination with other HMG-CoA reductase inhibitors.

Erythromycin - There are reports of an increased risk of myopathy and/or rhabdomyolysis when other HMG-CoA reductase inhibitors have been combined with erythromycin. The results from an interaction study with a small number of healthy volunteers suggested that erythromycin and fluvastatin were not metabolised by the same isoenzyme, however caution should be exercised when these two drugs are given in combination in view of the interaction seen with other HMG-CoA reductase inhibitors.

Fluconazole – Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor) resulted in an increase in the exposure (AUC) and mean peak concentration (Cmax) of fluvastatin by about 84% and 44% respectively. Caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Itraconazole - No interactions have been seen with itraconazole. Nevertheless patients should be closely monitored.

Antipyrine - Administration of Fluvastatin Capsules does not influence the metabolism and excretion of antipyrine. As antipyrine is a model for drugs metabolised by the microsomal hepatic enzyme systems, interactions with other drugs metabolised by these systems are not expected.

Propranolol - Concomitant administration of Fluvastatin Capsules with propranolol has no effect on the bioavailability of Fluvastatin Capsules.

Bile-acid sequestering agents - Administration of Fluvastatin Capsules 4 hours after cholestyramine results in a clinically significant additive effect compared with that achieved with either drug alone. Fluvastatin Capsules should be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding to the resin.

Digoxin - Concomitant administration of Fluvastatin Capsules with digoxin has no effect on digoxin plasma concentrations.
Amlodipine – No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with amlodipine.

Cimetidine/ranitidine/omeprazole - Concomitant administration of Fluvastatin Capsules with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of Fluvastatin Capsules, which, however, is of no clinical relevance.

Rifampicin - Administration of Fluvastatin Capsules to subjects pre-treated with rifampicin resulted in a reduction of the bioavailability of Fluvastatin Capsules 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.

Phenytoin - In an interaction study concomitant administration of fluvastatin and phenytoin resulted in an increase of fluvastatin mean AUC and Cmax values by 40% and 27% respectively. This combination should be used with caution due to the increased risk of developing myopathy and/or rhabdomyolysis.

Effects of fluvastatin on other drugs:
Ciclosporin – Fluvastatin Capsules had no effect on ciclosporin bioavailability when co-administered (see also Effects of other drugs on fluvastatin).

Colchicine – No information is available on the pharmacokinetic interaction between fluvastatin and colchicine. However, myotoxicity, including muscle pain and weakness and rhabdomyolysis, have been reported anecdotally with concomitant administration of colchicines.

Phenytoin – Co-administration of fluvastatin (40 mg b.i.d. for 5 days) increased the mean Cmax of phenytoin by 5% whereas the mean AUC was increased by 22%. Patients on phenytoin should be carefully monitored when fluvastatin therapy is initiated or when the dose is increased.

Warfarin and other Coumarin derivatives - Co-administration of fluvastatin with warfarin may commonly cause significant increases in prothrombin time. This has resulted very rarely in serious haemorrhage. It is recommended that prothrombin times are monitored when fluvastatin therapy is initiated, discontinued or the dosage changed in patients receiving warfarin or other coumarin derivative.

Glibenclamide - An interaction study between fluvastatin 40mg b.i.d. and glibenclamide was done in diabetic patients stabilised on 5-20mg of glibenclamide. The AUC for glibenclamide increased on average by 1.7 times (range: 0.9 – 3.5), Cmax increased on average by 1.6 times (range: 0.9 -3.0) and the mean t1/2 of glibenclamide increased from 8.5 to 18.8 hours when taken with fluvastatin. In this study there were no significant changes in glucose levels but in view of the increases seen in glibenclamide levels there remains a potential for serious hypoglycaemia and this combination should be avoided whenever possible.

Other concomitant therapy - In clinical studies in which Fluvastatin Capsules were used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, salicylic acid, H2-blockers and non-steroidal anti-inflammatory drugs (NSAIDs), no clinically significant adverse interactions occurred.

### 4.6 Pregnancy and lactation

Animal studies have indicated that fluvastatin is devoid of embryotoxic and teratogenic potential. However, 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, HMG-CoA reductase inhibitors are contraindicated during pregnancy and 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.
As small amounts of fluvastatin have been found in rat milk, Fluvastatin Capsules are contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines
No data exist on the effects of Fluvastatin Capsules on the ability to drive and use machines.

4.8 Undesirable effects
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

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

Table 1

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Very rare:</td>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Insomnia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Headache</td>
</tr>
</tbody>
</table>

| Very rare: | Paraesthesia, dyseaesthesia, hypoaesthesia and peripheral neuropathy also known to be associated with the underlying hyperlipidemic disorders. |

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Very rare:</td>
<td>Vasculitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Dyspepsia, abdominal pain, nausea</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Pancreatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare:</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare:</td>
<td>Hypersensitivity reactions such as rash, urticaria</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare:</td>
<td>Myalgia, muscle weakness, myopathy</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Rhabdomyolysis, myositis, lupus erythematosus-like reactions</td>
</tr>
</tbody>
</table>

Laboratory Findings
Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in a small number of patients (less than or equal to 1%). Marked elevations of CK levels to more than 5 x ULN developed 0.3 - 1.0% of patients receiving licensed doses of fluvastatin in clinical trials.

4.9 Overdose
The experience with overdoses of Fluvastatin Capsules is very limited. Should an accidental overdosage occur, administration of activated charcoal is recommended. In the case of a very recent oral intake gastric lavage may be considered. Treatment should be symptomatic.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitor, ATC code: C01 AA01
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. 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.

A variety of clinical studies has demonstrated that elevated levels of total cholesterol (total-C), 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. Epidemiologic 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). The overall cholesterol profile is improved with the principal effects being the reduction of total-C and LDL-C. Fluvastatin also produces a moderate reduction in triglycerides and a moderate increase in HDL-C.

In a pooled analysis of all placebo-controlled studies, patients with primary mixed dyslipidaemia (Type IIb) defined as baseline TG levels >200 mg/dL, treatment with Fluvastatin in daily doses ranging from 20 mg to 80 mg (40 mg b.i.d.) demonstrated consistent and significant decreases in total-C, LDL-C, and apo-B, TG, and a modest increase in HDL-C.

In the Lescol Intervention Prevention Study (LIPS), the effect of fluvastatin on major adverse cardiac events (MACE) was assessed in patients with coronary heart disease who had first successful transcathether therapy (TCT). The study included male and female patients (18-80 years old) and with baseline total cholesterol levels ranging from 3.5-7.0 mmol/L. In this randomised, double-blind, placebo-controlled trial, a total of 1677 patients were recruited (844 in fluvastatin group and 833 in placebo group). The MACE was defined as cardiac death, non fatal MI and re-intervention (including CABG, repeat TCT, or TCT of a new lesion). The dose of fluvastatin used in this study was 80 mg daily over 4 years. Although the overall composite endpoint showed significant reduction in MACE (22%) compared to placebo (p=0.013), the individual components (cardiac death, non fatal MI and re-intervention) failed to reach statistical significance. There was however a trend in favour of fluvastatin. Therapy with fluvastatin reduced the risk of cardiac death and/or myocardial infarction by 31% (p=0.065).

5.2 Pharmacokinetic properties

Fluvastatin is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. Fluvastatin is absorbed rapidly and completely (98%) following oral administration to fasted volunteers. In a fed state, the drug is absorbed at a reduced rate. 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 (Vzf) for the drug is 330 L. More than 98% of the circulating drug is bound to plasma proteins, and this binding is unaffected by drug concentration.

The major circulating blood components are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate systemically.

The hepatic metabolic pathways of fluvastatin in humans have been characterised. There are multiple, alternative cytochrome P450 (CYP450) pathways involved. However, the major pathway is mediated by CYP2C9 and this pathway is subject to potential interactions with
other CYP2C9 substrates or inhibitors. In addition there are several minor pathways (e.g. CYP3A4).

Several detailed in vitro studies have addressed the inhibitory potential of fluvastatin on common CYP isoenzymes. Fluvastatin inhibited only the metabolism of compounds that are metabolized by CYP2C9.

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 40 mg daily. Following oral administration of 40 mg of Fluvastatin Capsules, the terminal disposition half-life for fluvastatin is 2.3 ± 0.9 hours.

Food: Although AUC and Cmax were lowered and tmax prolonged when fluvastatin was taken with food, there was no apparent difference in the lipid-lowering effect whether fluvastatin was taken with food or not.

Plasma concentrations of fluvastatin do not vary as a function of either age or gender in the general population.

5.3 Preclinical safety data

The safety of fluvastatin was extensively investigated in toxicity studies in rats, dogs, monkeys, mice and hamsters. A variety of changes were identified that are common to HMG-CoA reductase inhibitors, viz. hyperplasia and hyperkeratosis of the rodent non-glandular stomach, cataracts in dogs, myopathy in rodents, mild liver changes in most laboratory animals with gall bladder changes in dog, monkey and hamster, thyroid weight increases in the rat and testicular degeneration in the hamster. Fluvastatin is devoid of the CNS vascular and degenerative changes recorded in dogs with other members of this class of compound.

A carcinogenicity study was performed in rats at dose levels of 6, 9 and 18 mg/kg a day (escalated to 24 mg/kg a day after 1 year) to establish a clear maximum tolerated dose. These treatment levels yielded plasma drug levels approximately 9, 13 and 26 to 35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and one carcinoma of the forestomach was observed at the 24 mg/kg a day dose level. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded in male rats treated with 18 to 24 mg/kg a day.

The forestomach neoplasms observed in rats and mice reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug. The increased incidence of thyroid follicular cell neoplasms in male rats given fluvastatin appears to be consistent with species-specific findings with other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no treatment-related increases in the incidences of hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg a day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg a day and in females at 15 mg/kg a day. These treatment levels yielded plasma drug levels approximately 0.2, 10 and 21 times the mean human plasma drug concentration after a 40-mg oral dose.

No evidence of mutagenicity was observed in vitro, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of Salmonella typhimurium or Escherichia coli: malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese hamster cells; HGPRT V79 Chinese hamster cells. In addition, there was no evidence of mutagenicity in vivo in either a rat or mouse micronucleus test.
In a study in rats at dose levels in females of 0.6, 2 and 6 mg/kg a day and in males of 2, 10 and 20 mg/kg a day, Fluvastatin had no adverse effects on the fertility or reproductive performance. Teratology studies in rats and rabbits showed maternal toxicity at high dose levels, but there was no evidence of embryotoxic or teratogenic potential. A study in which female rats were dosed at 12 and 24 mg/kg a day during late gestation until weaning of the pups resulted in maternal mortality at or near term and post partum accompanied by foetal and neonatal lethality. No effects on the pregnant females or foetuses occurred at the low dose level of 2 mg/kg a day.

A second study at levels of 2, 6, 12 and 24 mg/kg a day during late gestation and early lactation showed similar effects at 6 mg/kg a day and above caused by cardiotoxicity. In a third study, pregnant rats were administered 12 or 24 mg/kg a day during late gestation until weaning of pups with or without the presence of concurrent supplementation with mevalonic acid, a derivative of HMG-CoA that is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the cardiotoxicity and the maternal and neonatal mortality. Therefore, the maternal and neonatal lethality observed with fluvastatin reflects its exaggerated pharmacologic effect during pregnancy.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Mannitol
Talc
Magnesium Stearate
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons
2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.
Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

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9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   30/12/2008

10 DATE OF REVISION OF THE TEXT
    30/12/2008
Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Fluvastatin Capsules are and what they are used for
2. Before you take Fluvastatin Capsules
3. How to take Fluvastatin Capsules
4. Possible side effects
5. How to store Fluvastatin Capsules
6. Further information

1. WHAT FLUVASTATIN CAPSULES ARE AND WHAT THEY ARE USED FOR

From the results of your blood tests, your doctor has found that despite your low fat diet you still have too much of one type of fat in your blood. This fat is known as cholesterol. In some people, this increase in cholesterol might also be accompanied by an increase in another type of fat called triglyceride. Although cholesterol and triglycerides are vital to the health of your body, too much of them can make the blood become one of the important causes of heart disease.

Your doctor has prescribed Fluvastatin Capsules together with your diet to help lower cholesterol levels and so reduce your risk of heart problems. Your doctor may also have prescribed Fluvastatin Capsules to help slow down the hardening of the arteries or the rate of heart disease caused by high cholesterol. Fluvastatin is one of a group of cholesterol-lowering drugs called "statins" and exerts its main effect in the liver where cholesterol is made.

If you have had a previous coronary intervention procedure (insertion of catheter tubes through the skin and into the heart to widen narrowed arteries), Fluvastatin Capsules may be used to reduce the risk of having a further heart attack or of having a further heart attack if you have already experienced one.

2. BEFORE YOU TAKE FLUVASTATIN CAPSULES

Do not take Fluvastatin Capsules if:
- you are allergic (hypersensitive) to the active substance or any of the ingredients in Fluvastatin Capsules. These are listed below in the section headed "Further Information".
- you have any liver problems, or you have had a disease that may have affected your liver. Your doctor will usually carry out liver function tests before you start therapy.
- you are pregnant, or planning to become pregnant. If you do become pregnant whilst taking Fluvastatin, tell your doctor.
- you are breast-feeding.
- you are less than 18 years of age.

Tell your doctor before you start taking Fluvastatin if:
- you have a history of high blood pressure.
- you have any kidney problems, an endocrine thyroid gland (hypothyroidism), any muscular disorders (affecting either yourself or other members of your family), previous muscular problems during treatment with other lipid-lowering medicines (eg, other "statin" or "fibrate" medicines).
- your doctor will need to carry out a blood test before and possibly during your treatment. These blood tests will be used to determine whether you may be at risk of muscle-related side effects. A blood test may also be required if you are older than 70 years in order to determine whether you may be at risk of muscle-related side effects.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including other medicines obtained without a prescription. Some medicines can interfere with your treatment or alter blood levels of those drugs you are currently taking. In particular tell your doctor if you are taking any of the following:
- ciclosporin (an immunosuppressive drug), the combination of Fluvastatin and ciclosporin may result in an increased risk of developing muscle problems,
- drugs to prevent blood clotting (such as warfarin), the combination may lead to an increase in the effects of warfarin and cause bleeding,
- other cholesterol lowering drugs (eg, gemfibrozil) or nicotinic acid, the combination may result in an increased risk of developing muscle problems,
- erythromycin (antibiotic), as it may increase the risk of developing muscle problems.

- rifampicin (antibactericidal drug), as it may reduce the effects of Fluvastatin,
- phenytoin (antiepileptic medication), as Fluvastatin may increase the amount of phenytoin in the blood which may cause side effects from the phenytoin. In addition the combination may result in increased blood levels of Fluvastatin which increases the risk of developing muscle problems,
- Fluvastatin is not usually prescribed with glibenclamide (antidiabetic drug). However, if your doctor thinks this is necessary you should be aware that the combination may result in an increase in the amount of glibenclamide in the bloodstream, which may in turn lead to an increased risk of low blood sugar.
- Fluconazole or itraconazole (antifungal),
- Colchicine (a medicine used to treat gout).

Pregnancy and breast-feeding
- Do not take Fluvastatin Capsules if you are pregnant, planning to become pregnant, or breast-feeding. If you do become pregnant whilst taking Fluvastatin, tell your doctor.
- Taking Fluvastatin Capsules with food and drink
Fluvastatin Capsules can be taken with or without food.

3. HOW TO TAKE FLUVASTATIN CAPSULES

Always take Fluvastatin Capsules exactly as your doctor has told you. Your doctor will have chosen the right dose for you but you should check with your doctor or pharmacist if you are not sure.

The usual starting dose is 40 mg Fluvastatin once a day taken in the evening. However, in some cases, 20 mg may be a sufficient starting dose. Your doctor will periodically check your cholesterol levels and may adjust your dose up to a maximum of 40 mg twice a day, depending on what the levels are. If this is the case you should take one capsule in the morning and one in the evening.

If you have undergone a percutaneous coronary intervention procedure in the past you may be prescribed 40 mg twice a day (see section "What Fluvastatin Capsules are and what are they used for").

Follow your doctor's instructions exactly and never change the dosage yourself.

In addition to Fluvastatin, your doctor may also prescribe you a resin type drug like cholestyramine which also helps to lower your cholesterol. As this type of drug can interfere with the way Fluvastatin is taken up in the body, you should take Fluvastatin at least four hours after the resin.

It is important to continue with your low fat diet while you are taking Fluvastatin Capsules.

To take Fluvastatin capsules, place the capsule in your mouth, and swallow whole with a glass of water.

If you take more Fluvastatin than you should
If you accidentally take too much of your medicine, tell your doctor immediately or go to your nearest accident and emergency department.

If you forget to take Fluvastatin Capsules
If you forget to take a dose, take one as soon as you remember, unless it is almost time for your next dose. Then go on as before. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fluvastatin can cause side effects, although not everybody gets them.

Common side effects (estimated frequency is less than 1 person out of 10 but more than 1 out of 100) are:
- indigestion
- feeling sick
- abdominal pain
- headache
- difficulty sleeping

Rarely (estimated frequency is less than 1 person out of 1,000 but more than 1 out of 10,000), patients have
UKPAR Fluvastatin 20 and 40mg Capsules

- Fluvastatin 20 and 40mg Capsules (PL 24668/0015-8, 20-21)

Developed muscle wasting (pain, tenderness, or weakness) and very rarely, inflammation. In very rare cases (less than 1 person out of 10,000), this has progressed to become a serious and potentially life-threatening condition (called "rhabdomyolysis"). If you experience muscle weakness, tenderness, or pain and particularly if, at the same time, you feel unwell or have a high temperature, stop taking Fluvastatin and tell your doctor immediately.

Other rare effects (estimated frequency is less than 1 person out of 1,000 but more than 1 out of 10,000) include skin rashes and urticaria. There are also several very rare reports (less than 1 person out of 10,000) of pins and needles or changes in touch sensations (this may indicate injury or damage to nerve endings), skin reactions such as eczema and dermatitis, and hypersensitivity reactions including any of the following conditions: swelling of the face or neck, muscle and joint pains, joint and blood vessel inflammation, skin rash and swelling. If this happens, you should see your doctor immediately.

In a small number of patients (estimated frequency is less than 1 person out of 100 but more than 1 out of 1,000) slight increases in liver enzymes have occurred and most patients did not develop any symptoms. In these patients the enzyme levels returned to normal or became more normal when therapy was stopped. Your doctor will usually carry out liver function tests before you start therapy and periodically thereafter. Very rarely (less than 1 person out of 10,000), Fluvastatin has caused inflammation of the liver. If you experience yellowing of the skin and eyes and dark-coloured urine, tell your doctor immediately. Also very rarely (less than 1 person out of 10,000), Fluvastatin has caused inflammation of the pancreas.

A reduction in the number of certain types of blood cells (thrombocytopenia) has also been reported in a small number of patients (less than 1 person out of 10,000).

If you are already taking a medicine, or you are taking any other medication, please tell your doctor or pharmacist.

5. HOW TO STORE FLUVASTATIN CAPSULES

Keep out of the reach and sight of children.

Do not use Fluvastatin Capsules after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not store above 25°C.

Store in the original package to protect from light and moisture.

Leave your capsules in the original packaging, and only remove them when it is time for you to take your medicine.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Fluvastatin Capsules contain

The active substance is Fluvastatin sodium.

The other ingredients are:
- Capsule contents — Macrogol, Talc, Magnesium stearate
- Capsule shell — Gelatin. Titanium dioxide (E171), Red iron oxide (E172), Yellow iron oxide (E172)

What Fluvastatin capsules look like and contents of the pack

The Capsules are available in two strengths providing either 20 mg or 40 mg Fluvastatin. The 20mg capsules contain pale yellow powders. One half of the capsule is orange and has the number “20” has been printed on it. The other half of the capsule is ivory coloured and has the letters “FST” printed on it.

The 40mg capsules contain pale yellow powders. One half of the capsule is orange and has the number “40” has been printed on it. The other half of the capsule is yellow and has the letters “FST” printed on it.

Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 160 Capsules. Only marketed pack sizes will be printed on the leaflet.

The Marketing Authorisation Holder

Cadeceus Pharma Limited,
16th Floor,
94 Wigmore Street,
London.
W1U 3HR

The Manufacturer

Actavis hf.
Reykytaravagar 70.
152 – 220 Hofnafjordur.
Iceland

REMEMBER: This medicine is only for you. Only a doctor
Each capsule contains 20 mg fluvastatin as fluvastatin sodium. For oral use only. To be taken as directed by your doctor. Read the package leaflet before use. Swallow whole; do not chew.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Do not store above 25°C. Store in the original package to protect from light and moisture.

Marketing Authorisation Holder:
Caduceus Pharma Limited
6th Floor, 94 Wigmore Street
London, W1U 3RF
Fluvasatin 40 mg Capsules
Do not store above 25°C. Store in the original package to protect from light and moisture.

Marketing Authorisation Holder:
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF

14 capsules

Fluvasatin 40 mg Capsules
Each capsule contains 40 mg fluvasatin as fluvasatin sodium. For oral use only.
To be taken as directed by your doctor.
Read the package leaflet before use.
Swallow whole, do not chew.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
PL 24668/0016

14 capsules

Expiry Date:
Batch Number:
Fluvastatin 20 mg Capsules

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

Marketing Authorisation Holder: Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF

14 capsules

Each capsule contains 20 mg Fluvastatin as Fluvastatin sodium. For oral use only. To be taken as directed by your doctor. Read the package leaflet before use. Swallow whole, do not chew. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

PL 24668/0017

Expiry Date:

Batch Number:
UKPAR Fluvasatin 20 and 40mg Capsules

Each capsule contains 40 mg fluvasatin as fluvasatin sodium. For oral use only. To be taken as directed by your doctor. Read the package leaflet before use. Swallow whole, do not chew.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Do not store above 25°C. Store in the original package to protect from light and moisture.

Marketing Authorisation Holder: Caduceus Pharma Limited
6th Floor, 94 Wigmore Street
London, W1U 3RF

14 capsules

PL 24668/0015-8, 20-21
Fluvastatin 40 mg Capsules

28 Capsules

Each capsule contains 40 mg fluvastatin as fluvastatin sodium

For oral use only.
To be taken as directed by your doctor.
Read the package leaflet before use.
Swallow whole, do not chew.
Do not store above 25°C.
Store in the original package to protect from light and moisture.

OFFICIAL

Marketing Authorisation Holder:
Caduceus Pharma Ltd
68 Thame
54 Highworth
London
W1U 3RF
Each capsule contains 20 mg fluvastatin as fluvastatin sodium. For oral use only. To be taken as directed by your doctor. Read the package leaflet before use. Swallow whole, do not chew. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Do not store above 25°C. Store in the original package to protect from light and moisture.

Marketing Authorisation Holder:
Caduceus Pharma Limited
6th Floor, 94 Wigmore Street
London, W1U 3RF
Each capsule contains 40 mg fluvastatin as fluvastatin sodium. For oral use only.
To be taken as directed by your doctor.
Read the package leaflet before use.
Swallow whole, do not chew.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Do not store above 25°C.
Store in the original package to protect from light and moisture.
Marketing Authorisation Holder:
Caduceus Pharma Limited
6th Floor, 94 Wigmore Street
London, W1U 3RF

14 capsules
Fluvastatin 40 mg Capsules

Do not store above 25°C. Store in the original packaging to protect from light and moisture.

Marketing Authorisation Holder: Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1J 3RF

Each capsule contains 40 mg Fluvastatin as Fluvastatin sodium. For oral use only. To be taken as directed by your doctor. Read the package leaflet before use. Swallow whole, do not chew. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

PL 24668/0021

14 capsules

Barcode position

Expiry Date:
Batch Number:
Fluvastatin 40 mg Capsules

28 Capsules

Each capsule contains 40 mg fluvastatin as fluvastatin sodium

For oral use only.
To be taken as directed by your doctor.
Read the package leaflet before use.
Swallow whole, do not chew.
Do not store above 25 ºC.
Store in the original package to protect from light and moisture.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

PL 24668/0021
FLUVASTATIN 20MG and 40MG CAPSULES

PL 24668/0015-8, 20-21

STEPS TAKEN AFTER AUTHORISATION – SUMMARY

The following table lists non-safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been incorporated into the text of this Public Assessment Report (PAR) or added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

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<th>Scope</th>
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<td>To update sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, and 5.3 of the SPC following completion of an Article 30 of Directive 2001/83/EC concerning fluvastatin.</td>
<td>Approved 03/06/2011</td>
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Annex 1

Variation applications to update SmPC sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, and 5.3 following completion of an Article 30 of Directive 2001/83/EC concerning Fluvastatin on 15-03-2010. Changes were made to the Patient Information Leaflet (PIL) for these products as a consequence of the SmPC updates. The product shall not be marketed in the UK until prior approval of the product leaflet mock-ups has been obtained.

These variations were approved on 3rd June 2011 and the following updated SmPCs and PIL have been incorporated into these Marketing Authorisations.
Summary of Product Characteristics - updated

PL 24668/0015

1 NAME OF THE MEDICINAL PRODUCT
Fluvastatin 20 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 21.06mg fluvastatin sodium corresponding to 20mg fluvastatin.

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM
Hard gelatine capsule, size 3. The capsule contains pale yellow powder.
Capsule cap: Swedish orange opaque with imprint 20.
Capsule body: Ivory opaque with imprint FST.

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 Fluvastatin, 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 uptitrated to 80 mg daily, administered as a single dose 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.

Fluvastatin is efficacious in monotherapy. When Fluvastatin is used in combination with cholesteryamine 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 Fluvastatin 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 Fluvastatin 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 Fluvastatin capsules 40 mg twice daily or as one 80 mg 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
Fluvastatin 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 soya oil, peanut oil or any of the excipients.
• 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 lactation (see section 4.6).

4.4 Special warnings and precautions for use
Liver function
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.
- 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 (> 5 x ULN).

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy has been reported to be increased in patients receiving immunosuppressive 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.

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.

**Lecithin:**
If a patient is hypersensitive to peanut or soya, this medicine should not be used.

### 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 HMGCoA 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 80 mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration (C\text{max}) 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 40 mg fluvastatin and 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 changes 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 noninsulin-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 C\text{max}, AUC, and t½ of glibenclamide by approximately 50%, 69%, and 121%, respectively. Glibenclamide (5 to 20 mg daily) increased the mean C\text{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin, and C-peptide levels. However, patients on
concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 80 mg per day.

*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 pretreated 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 propranolol, digoxin, losartan or amlodipine. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with these agents.

*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 Pregnancy and lactation

**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).

Women of childbearing potential have to use effective contraception.

If a patient becomes pregnant while taking Fluvastatin, therapy should be discontinued.

**Lactation**
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.
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 reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions

Blood and lymphatic system disorders
Very rare: Thrombocytopenia

Immune system disorders
Very rare: Anaphylactic reaction

Psychiatric disorders
Common: Insomnia

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

Vascular disorders
Very rare: Vasculitis

Gastrointestinal disorders
Common: Dyspepsia, abdominal pain, nausea
Very rare: Pancreatitis

Hepatobiliary disorders
Very rare: Hepatitis

Skin and subcutaneous tissue disorders
Rare: Hypersensitivity reactions such as rash, urticaria
Very rare: Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema

Musculoskeletal and connective tissue disorders
Rare: Myalgia, muscle weakness, myopathy
Very rare: Rhabdomyolysis, myositis, lupus erythematosus-like reactions

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)

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 to 17 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 aminotransferase 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 Lescol 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%).

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.

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

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

Lescol/Lescol XL reduces total-C, LDL-C, Apo B, and 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, Lescol 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).

Lescol XL was administered to over 800 patients in three pivotal trials of 24 weeks active treatment duration and compared to Lescol 40 mg once or twice daily. Given as a single daily dose of 80 mg, Lescol XL 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**

<table>
<thead>
<tr>
<th>Placebo-controlled studies (Lescol) and active-controlled trials (Lescol XL)</th>
<th>Total-C</th>
<th>TG</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>N</td>
<td>% Δ</td>
<td>N</td>
<td>% Δ</td>
<td>N</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lescol 20 mg (^1)</td>
<td>747</td>
<td>-17</td>
<td>747</td>
<td>-12</td>
<td>747</td>
</tr>
<tr>
<td>Lescol 40 mg (^1)</td>
<td>748</td>
<td>-19</td>
<td>748</td>
<td>-14</td>
<td>748</td>
</tr>
</tbody>
</table>
UKPAR Fluvastatin 20 and 40mg Capsules                                            PL 24668/0015-8, 20-21

| Lescol 40 mg twice daily¹ | 257 -27 257 -18 257 -36 232 -28 257 +6 |
| Lescol XL 80 mg²         | 750 -25 750 -19 748 -35 745 -27 750 +7 |

**Baseline TG 200 mg/dl**

| Lescol 20 mg¹           | 148 -16 148 -17 148 -22 23 -19 148 +6 |
| Lescol 40 mg¹           | 179 -18 179 -20 179 -24 47 -18 179 +7 |
| Lescol 40 mg twice daily¹ | 76 -27 76 -23 76 -35 69 -28 76 +9 |
| Lescol XL 80 mg²         | 239 -25 239 -25 237 -33 235 -27 239 +11 |

¹ Data for Lescol from 12 placebo-controlled trials
² Data for Lescol XL 80 mg 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 the Lescol Intervention Prevention Study (LIPS), 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 Lescol and Lescol XL 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 Lescol capsules (20 mg/day to 40 mg twice daily) or Lescol XL 80 mg 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 Lescol 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 Lescol capsules 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 < 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), Lescol 20 to 80 mg 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), Lescol 20 to 80 mg 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 target 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 Fluvastatin 80 mg, 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
Mannitol
Talc
Magnesium Stearate
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

Printing ink:
White ink on capsule cap:
Shellac
Titanium dioxide (E171)
Soya lecithin
Antifoam DC 1510

Brown ink on capsule body:
Shellac
Iron oxide red (E172)
Iron oxide black (E172)
Titanium dioxide (E171)
Propylene glycol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Packed in Alu/Alu Blisters: 18 months
Packed in plastic bottles: 24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons

2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.

Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/12/2008

10 DATE OF REVISION OF THE TEXT
03/06/2011
SUMMARY OF PRODUCT CHARACTERISTICS

1  NAME OF THE MEDICINAL PRODUCT
Fluvastatin 40mg capsules

2  QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 42.12mg fluvastatin sodium corresponding to 40mg fluvastatin.

For a full list of excipients, see Section 6.1

3  PHARMACEUTICAL FORM
Hard gelatine capsule, size 1. The capsule contains pale yellow powder.
Capsule cap: Swedish orange opaque with imprint 40.
Capsule body: Rich yellow opaque with imprint FST.

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 Fluvastatin, 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 uptitrated to 80 mg daily, administered as a single dose 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.

Fluvastatin is efficacious in monotherapy. When Fluvastatin 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 Fluvastatin 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 Fluvastatin 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 Fluvastatin capsules 40 mg twice daily or as one 80 mg 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
Fluvastatin 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 soya oil, peanut oil or any of the excipients.
• 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 lactation (see section 4.6).

4.4 Special warnings and precautions for use
Liver function
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.
• In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK levels are still significantly elevated (> 5 x ULN) at baseline, treatment should not be started.

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

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy has been reported to be increased in patients receiving immunosuppressive 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.

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.

Lecithin:
If a patient is hypersensitive to peanut or soya, this medicine should not be used.

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 HMGCoA 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 80 mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration (Cmax) were increased 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 40 mg fluvastatin and 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 changes 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 noninsulin-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 pretreated 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 propranolol, digoxin, losartan or amlodipine. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with these agents.

**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 Pregnancy and lactation

**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).

Women of childbearing potential have to use effective contraception.

If a patient becomes pregnant while taking Fluvastatin, therapy should be discontinued.

**Lactation**
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.
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 reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions

Blood and lymphatic system disorders
Very rare: Thrombocytopenia

Immune system disorders
Very rare: Anaphylactic reaction

Psychiatric disorders
Common: Insomnia

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

Vascular disorders
Very rare: Vasculitis

Gastrointestinal disorders
Common: Dyspepsia, abdominal pain, nausea
Very rare: Pancreatitis

Hepatobiliary disorders
Very rare: Hepatitis

Skin and subcutaneous tissue disorders
Rare: Hypersensitivity reactions such as rash, urticaria
Very rare: Other skin reactions (e.g. eczema, dermatitis, bullous xanthema), face oedema, angioedema

Musculoskeletal and connective tissue disorders
Rare: Myalgia, muscle weakness, myopathy
Very rare: Rhabdomyolysis, myositis, lupus erythematosus-like reactions

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)

Paediatric population
Children and adolescents with heterozygous familial hypercholesterolaemia
The safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia has not been established.
hypercholesterolaemia assessed in 114 patients aged 9 to 17 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 aminotransferase 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 Lescol 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%).

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 in the plasma cholesterol concentration.

Lescol/Lescol XL 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, Lescol 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).

Lescol XL was administered to over 800 patients in three pivotal trials of 24 weeks active treatment duration and compared to Lescol 40 mg once or twice daily. Given as a single daily dose of 80 mg, Lescol XL 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 (Lescol) and active-controlled trials (Lescol XL) |
|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                      | Total-C N | % Δ | TG N | % Δ | LDL-C N | % Δ | Apo B N | % Δ | HDL-C N | % Δ |
| Dose                                 |           |     |      |     |           |     |         |     |           |     |
| All patients                          |           |     |      |     |           |     |         |     |           |     |
| Lescol 20 mg¹                         | 747       | -17 | 747   | -12 | 747       | -22 | 114      | -19 | 747       | +3  |
| Lescol 40 mg²                         | 748       | -19 | 748   | -14 | 748       | -25 | 125      | -18 | 748       | +4  |
Lescol 40 mg twice daily

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1 Data for Lescol from 12 placebo-controlled trials
2 Data for Lescol XL 80 mg 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 the Lescol Intervention Prevention Study (LIPS), 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 Lescol and Lescol XL 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 Lescol capsules (20 mg/day to 40 mg twice daily) or Lescol XL 80 mg 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 Lescol 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 Lescol capsules 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 < 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), Lescol 20 to 80 mg 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), Lescol 20 to 80 mg 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 Fluvastatin 80 mg, 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
Mannitol
Talc
Magnesium Stearate
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

Printing ink:
White ink on capsule cap:
Shellac
Titanium dioxide (E171)
Soya lecithin
Antifoam DC 1510

Brown ink on capsule body:
Shellac
Iron oxide red (E172)
Iron oxide black (E172)
Titanium dioxide (E171)
Propylene glycol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons

2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.

Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0016

9 DATE OF FIRST AUTHORIZATON/RENEWAL OF THE AUTHORISATION
30/12/2008

10 DATE OF REVISION OF THE TEXT
03/06/2011
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fluvastatin 20 mg Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 21.06mg fluvastatin sodium corresponding to 20mg fluvastatin.

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM
Hard gelatine capsule, size 3. The capsule contains pale yellow powder.
Capsule cap: Swedish orange opaque with imprint 20.
Capsule body: Ivory opaque with imprint FST.

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 Fluvastatin, 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 uptitrated to 80 mg daily, administered as a single dose 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.

Fluvastatin is efficacious in monotherapy. When Fluvastatin 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 Fluvastatin 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 Fluvastatin 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 Fluvastatin capsules 40 mg twice daily or as one 80 mg 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
Fluvastatin 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 soya oil, peanut oil or any of the excipients.
  • 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 lactation (see section 4.6).

4.4 Special warnings and precautions for use
Liver function
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.

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 (> 5 x ULN).

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy has been reported to be increased in patients receiving immunosuppressive 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.

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.

Lecithin:
If a patient is hypersensitive to peanut or soya, this medicine should not be used.

4.5 Interaction with other medicinal products and other forms of interaction

Fluvastatin 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 HMGCoA 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 80 mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration (Cmax) were increased 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 40 mg fluvastatin and 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 changes 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 noninsulin-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 pretreated 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 propranolol, digoxin, losartan or amlodipine. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with these agents.

**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 Pregnancy and lactation

**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).

Women of childbearing potential have to use effective contraception.

If a patient becomes pregnant while taking Fluvastatin, therapy should be discontinued.

**Lactation**
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.
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 reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions

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<th>Very rare: Thrombocytopenia</th>
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<tbody>
<tr>
<td>Immune system disorders</td>
<td>Very rare: Anaphylactic reaction</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common: Insomnia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very rare: Headache</td>
</tr>
<tr>
<td></td>
<td>Very rare: Paraesthesia, dyasaesthesia, hypoaesthesia also known to be associated with the underlying hyperlipidaemic disorders</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Very rare: Vasculitis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common: Dyspepsia, abdominal pain, nausea</td>
</tr>
<tr>
<td></td>
<td>Very rare: Pancreatitis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very rare: Hepatitis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rare: Hypersensitivity reactions such as rash, urticaria</td>
</tr>
<tr>
<td></td>
<td>Very rare: Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Rare: Myalgia, muscle weakness, myopathy</td>
</tr>
<tr>
<td></td>
<td>Very rare: Rhabdomyolysis, myositis, lupus erythematosus-like reactions</td>
</tr>
</tbody>
</table>

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)

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 to 17 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 aminotransferase 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 Lescol 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%).

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 in the plasma cholesterol concentration.

Lescol/Lescol XL 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, Lescol 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).

Lescol XL was administered to over 800 patients in three pivotal trials of 24 weeks active treatment duration and compared to Lescol 40 mg once or twice daily. Given as a single daily dose of 80 mg, Lescol XL 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

<table>
<thead>
<tr>
<th>Placebo-controlled studies (Lescol) and active-controlled trials (Lescol XL)</th>
<th>Total-C</th>
<th>TG</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>N</td>
<td>% Δ</td>
<td>N</td>
<td>% Δ</td>
<td>N</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lescol 20 mg</td>
<td>747</td>
<td>-17</td>
<td>747</td>
<td>-12</td>
<td>747</td>
</tr>
<tr>
<td>Lescol 40 mg</td>
<td>748</td>
<td>-19</td>
<td>748</td>
<td>-14</td>
<td>748</td>
</tr>
<tr>
<td>Lescol 40 mg twice daily</td>
<td>257</td>
<td>-27</td>
<td>257</td>
<td>-18</td>
<td>257</td>
</tr>
</tbody>
</table>
Lescol XL 80 mg\(^2\)  
Baseline TG ≥200 mg/dl  
| Lescol 20 mg\(^1\) | 148 | -16 | 148 | -17 | 148 | -22 | 23 | -19 | 148 | +6 |
| Lescol 40 mg\(^1\) | 179 | -18 | 179 | -20 | 179 | -24 | 47 | -18 | 179 | +7 |
| Lescol 40 mg twice daily\(^1\) | 76 | -27 | 76 | -23 | 76 | -35 | 69 | -28 | 76 | +9 |
| Lescol XL 80 mg\(^2\) | 239 | -25 | 239 | -25 | 237 | -33 | 235 | -27 | 239 | +11 |

\(^1\) Data for Lescol from 12 placebo-controlled trials  
\(^2\) Data for Lescol XL 80 mg 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 the Lescol Intervention Prevention Study (LIPS), 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 Lescol and Lescol XL 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 Lescol capsules (20 mg/day to 40 mg twice daily) or Lescol XL 80 mg 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 Lescol 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 Lescol capsules 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 < 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), Lescol 20 to 80 mg 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), Lescol 20 to 80 mg 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 Fluvastatin 80 mg, 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
Mannitol
Talc
Magnesium Stearate
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

Printing ink:
White ink on capsule cap:
Shellac
Titanium dioxide (E171)
Soya lecithin
Antifoam DC 1510

Brown ink on capsule body:
Shellac
Iron oxide red (E172)
Iron oxide black (E172)
Titanium dioxide (E171)
Propylene glycol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Packed in Alu/Alu Blisters: 18 months
Packed in plastic bottles: 24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons

2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.

Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor,
94 Wigmore Street,
London
W1U 3RF
NAME OF THE MEDICINAL PRODUCT
Fluvastatin 40mg capsules.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 42.12mg fluvastatin sodium corresponding to 40mg fluvastatin.

For a full list of excipients, see Section 6.1

PHARMACEUTICAL FORM
Hard gelatine capsule, size 1. The capsule contains pale yellow powder.
Capsule cap: Swedish orange opaque with imprint 40.
Capsule body: Rich yellow opaque with imprint FST.

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 Fluvastatin, 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 uptitrated to 80 mg daily, administered as a single dose 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.

Fluvastatin is efficacious in monotherapy. When Fluvastatin 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 Fluvastatin 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 Fluvastatin 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 Fluvastatin capsules 40 mg twice daily or as one 80 mg 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*
Fluvastatin 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 soya oil, peanut oil or any of the excipients.
- 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 lactation (see section 4.6).

### 4.4 Special warnings and precautions for use

**Liver function**
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.
- 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 (> 5 x ULN).

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy has been reported to be increased in patients receiving immunosuppressive 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.

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.

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

Lecithin:
If a patient is hypersensitive to peanut or soya, this medicine should not be used.

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 HMGCoA 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 80 mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration (C\text{max}) 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 40 mg fluvastatin and 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 changes 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 noninsulin-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 C\text{max}, AUC, and t\text{1/2} of glibenclamide by approximately 50%, 69%, and 121%, respectively. Glibenclamide (5 to 20 mg daily) increased the mean C\text{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin, and C-peptide levels. However, patients on concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 80 mg per day.

**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 pretreated 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 propranolol, digoxin, losartan or amlodipine. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with these agents.

**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 Pregnancy and lactation

**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).

Women of childbearing potential have to use effective contraception.

If a patient becomes pregnant while taking Fluvastatin, therapy should be discontinued.

**Lactation**

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.

### 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 reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 1 Adverse reactions**

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Very rare: Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Very rare: Anaphylactic reaction</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common: Insomnia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
</tbody>
</table>
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: Dyspepsia, abdominal pain, nausea  
Very rare: Pancreatitis

Hepatobiliary disorders  
Very rare: Hepatitis

Skin and subcutaneous tissue disorders  
Rare: Hypersensitivity reactions such as rash, urticaria  
Very rare: Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema

Musculoskeletal and connective tissue disorders  
Rare: Myalgia, muscle weakness, myopathy  
Very rare: Rhabdomyolysis, myositis, lupus erythematosus-like reactions

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)

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 to 17 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 aminotransferase 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 Lescol 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%).

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 in the plasma cholesterol concentration.

Lescol/Lescol XL 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 hyperlipoproteinemia, Lescol 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).

Lescol XL was administered to over 800 patients in three pivotal trials of 24 weeks active treatment duration and compared to Lescol 40 mg once or twice daily. Given as a single daily dose of 80 mg, Lescol XL 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 (Lescol) and active-controlled trials (Lescol XL)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Total-C</th>
<th>TG</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%Δ</td>
<td>N</td>
<td>%Δ</td>
<td>N</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lescol 20 mg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>747</td>
<td>-17</td>
<td>747</td>
<td>-12</td>
<td>747</td>
</tr>
<tr>
<td>Lescol 40 mg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>748</td>
<td>-19</td>
<td>748</td>
<td>-14</td>
<td>748</td>
</tr>
<tr>
<td>Lescol 40 mg twice daily&lt;sup&gt;1&lt;/sup&gt;</td>
<td>257</td>
<td>-27</td>
<td>257</td>
<td>-18</td>
<td>257</td>
</tr>
<tr>
<td>Lescol XL 80 mg&lt;sup&gt;2&lt;/sup&gt;</td>
<td>750</td>
<td>-25</td>
<td>750</td>
<td>-19</td>
<td>748</td>
</tr>
<tr>
<td>Baseline TG ≥200 mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lescol 20 mg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>148</td>
<td>-16</td>
<td>148</td>
<td>-17</td>
<td>148</td>
</tr>
<tr>
<td>Lescol 40 mg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>179</td>
<td>-18</td>
<td>179</td>
<td>-20</td>
<td>179</td>
</tr>
<tr>
<td>Lescol 40 mg twice daily&lt;sup&gt;1&lt;/sup&gt;</td>
<td>76</td>
<td>-27</td>
<td>76</td>
<td>-23</td>
<td>76</td>
</tr>
<tr>
<td>Lescol XL 80 mg&lt;sup&gt;2&lt;/sup&gt;</td>
<td>239</td>
<td>-25</td>
<td>239</td>
<td>-25</td>
<td>237</td>
</tr>
</tbody>
</table>

<sup>1</sup> Data for Lescol from 12 placebo-controlled trials

<sup>2</sup> Data for Lescol XL 80 mg 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.

Table 2: Median percent change in lipid parameters from baseline to week 24
Placebo-controlled studies (Lescol) and active-controlled trials (Lescol XL)
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 −0.122 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 the Lescol Intervention Prevention Study (LIPS), 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 Lescol and Lescol XL 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 Lescol capsules (20 mg/day to 40 mg twice daily) or Lescol XL 80 mg 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 Lescol 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 Lescol capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (Ledol 80 mg XL 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), Lescol 20 to 80 mg 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), Lescol 20 to 80 mg 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 Fluvastatin 80 mg, 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

- Mannitol
- Talc
- Magnesium Stearate
- Gelatin
- Titanium dioxide (E171)
- Red iron oxide (E172)
- Yellow iron oxide (E172)
Printing ink:
White ink on capsule cap:
Shellac
Titanium dioxide (E171)
Soya lecithin
Antifoam DC 1510

Brown ink on capsule body:
Shellac
Iron oxide red (E172)
Iron oxide black (E172)
Titanium dioxide (E171)
Propylene glycol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons

2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.

Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/12/2008

10 DATE OF REVISION OF THE TEXT
03/06/2011
1 NAME OF THE MEDICINAL PRODUCT
Fluvastatin 20 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 21.06mg fluvastatin sodium corresponding to 20mg fluvastatin.

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM
Hard gelatine capsule, size 3. The capsule contains pale yellow powder.
Capsule cap: Swedish orange opaque with imprint 20.
Capsule body: Ivory opaque with imprint FST

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 Fluvastatin, 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 uptitrated to 80 mg daily, administered as a single dose 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.

Fluvastatin is efficacious in monotherapy. When Fluvastatin 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 Fluvastatin 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 Fluvastatin 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 Fluvastatin capsules 40 mg twice daily or as one 80 mg 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
Fluvastatin 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 soya oil, peanut oil or any of the excipients.
• 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 lactation (see section 4.6).

4.4 Special warnings and precautions for use
Liver function
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.
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK levels are still significantly elevated (> 5 x ULN) at baseline, treatment should not be started.

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

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to > 5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy has been reported to be increased in patients receiving immunosuppressive 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.

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.

Lecithin:
If a patient is hypersensitive to peanut or soya, this medicine should not be used.

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 HMGCoA 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 80 mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration (C_max) were increased 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 40 mg fluvastatin and 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 changes 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 noninsulin-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 C_max, AUC, and t½ of glibenclamide by approximately 50%, 69%, and 121%, respectively. Glibenclamide (5 to 20 mg daily) increased the mean C_max and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin, and C-peptide levels. However, patients on
concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 80 mg per day.

**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 pretreated 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 propranolol, digoxin, losartan or amlodipine. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with these agents.

**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 Pregnancy and lactation

**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).

Women of childbearing potential have to use effective contraception.

If a patient becomes pregnant while taking Fluvastatin, therapy should be discontinued.

**Lactation**
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.
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 reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions

Blood and lymphatic system disorders
Very rare: Thrombocytopenia

Immune system disorders
Very rare: Anaphylactic reaction

Psychiatric disorders
Common: Insomnia

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

Vascular disorders
Very rare: Vasculitis

Gastrointestinal disorders
Common: Dyspepsia, abdominal pain, nausea
Very rare: Pancreatitis

Hepatobiliary disorders
Very rare: Hepatitis

Skin and subcutaneous tissue disorders
Rare: Hypersensitivity reactions such as rash, urticaria
Very rare: Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema

Musculoskeletal and connective tissue disorders
Rare: Myalgia, muscle weakness, myopathy
Very rare: Rhabdomyolysis, myositis, lupus erythematosus-like reactions

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)

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 to 17 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 aminotransferase 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 Lescol 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%).

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 in the plasma cholesterol concentration.

Lescol/Lescol XL 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, Lescol 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).

Lescol XL was administered to over 800 patients in three pivotal trials of 24 weeks active treatment duration and compared to Lescol 40 mg once or twice daily. Given as a single daily dose of 80 mg, Lescol XL 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 (Lescol) and active-controlled trials (Lescol XL)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Total-C</th>
<th>TG</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% Δ</td>
<td>N</td>
<td>% Δ</td>
<td>N</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lescol 20 mg¹</td>
<td>747</td>
<td>-17</td>
<td>747</td>
<td>-12</td>
<td>747</td>
</tr>
<tr>
<td>Lescol 40 mg¹</td>
<td>748</td>
<td>-19</td>
<td>748</td>
<td>-14</td>
<td>748</td>
</tr>
<tr>
<td>Lescol 40 mg twice daily¹</td>
<td>257</td>
<td>-27</td>
<td>257</td>
<td>-18</td>
<td>257</td>
</tr>
</tbody>
</table>

¹ Lescol 20 mg once daily and Lescol 40 mg twice daily.
Lescol XL 80 mg$^{2}$

| Baseline TG | 750 | -25 | 750 | -19 | 748 | -35 | 745 | -27 | 750 | +7 |

Lescol 20 mg$^{1}$

| 148 | -16 | 148 | -17 | 148 | -22 | 23 | -19 | 148 | +6 |

Lescol 40 mg$^{1}$

| 179 | -18 | 179 | -20 | 179 | -24 | 47 | -18 | 179 | +7 |

Lescol 40 mg twice daily$^{1}$

| 76 | -27 | 76 | -23 | 76 | -35 | 69 | -28 | 76 | +9 |

Lescol XL 80 mg$^{2}$

| 239 | -25 | 239 | -25 | 237 | -33 | 235 | -27 | 239 | +11 |

$^{1}$ Data for Lescol from 12 placebo-controlled trials

$^{2}$ Data for Lescol XL 80 mg 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 $-0.122$ 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 the Lescol Intervention Prevention Study (LIPS), 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 Lescol and Lescol XL 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 Lescol capsules (20 mg/day to 40 mg twice daily) or Lescol XL 80 mg 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 Lescol 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 Lescol capsules 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 < 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), Lescol 20 to 80 mg 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), Lescol 20 to 80 mg 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 Fluvastatin 80 mg, 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
Mannitol
Talc
Magnesium Stearate
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

Printing ink:
White ink on capsule cap:
Shellac
Titanium dioxide (E171)
Soya lecithin
Antifoam DC 1510

Brown ink on capsule body:
Shellac
Iron oxide red (E172)
Iron oxide black (E172)
Titanium dioxide (E171)
Propylene glycol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Packed in Alu/Alu Blisters: 18 months
Packed in plastic bottles: 24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons

2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.

Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor,
94 Wigmore Street,
London
W1U 3RF
NAME OF THE MEDICINAL PRODUCT
Fluvastatin 40mg capsules

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 42.12mg fluvastatin sodium corresponding to 40mg fluvastatin.

For a full list of excipients, see Section 6.1

PHARMACEUTICAL FORM
Hard gelatine capsule, size 1. The capsule contains pale yellow powder.
Capsule cap: Swedish orange opaque with imprint 40.
Capsule body: Rich yellow opaque with imprint FST.

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 Fluvastatin, 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 uptitrated to 80 mg daily, administered as a single dose 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.

Fluvastatin is efficacious in monotherapy. When Fluvastatin 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 Fluvastatin 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 Fluvastatin 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 Fluvastatin capsules 40 mg twice daily or as one 80 mg 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**
Fluvastatin 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 soya oil, peanut oil or any of the excipients.
- 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 lactation (see section 4.6).

### 4.4 Special warnings and precautions for use

#### Liver function
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.
- 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 (> 5 x ULN).

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy has been reported to be increased in patients receiving immunosuppressive 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.

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.

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

Lecithin:
If a patient is hypersensitive to peanut or soya, this medicine should not be used.

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 HMGCoA 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 80 mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration (Cmax) were increased 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 40 mg fluvastatin and 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 changes 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 noninsulin-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 pretreated 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 propranolol, digoxin, losartan or amlodipine. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with these agents.

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 Pregnancy and lactation

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).

Women of childbearing potential have to use effective contraception.

If a patient becomes pregnant while taking Fluvastatin, therapy should be discontinued.

Lactation
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.

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 reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions

Blood and lymphatic system disorders
Very rare: Thrombocytopenia

Immune system disorders
Very rare: Anaphylactic reaction

Psychiatric disorders
Common: Insomnia

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

Vascular disorders
Very rare: Vasculitis

Gastrointestinal disorders
Common: Dyspepsia, abdominal pain, nausea
Very rare: Pancreatitis

Hepatobiliary disorders
Very rare: Hepatitis

Skin and subcutaneous tissue disorders
Rare: Hypersensitivity reactions such as rash, urticaria
Very rare: Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema

Musculoskeletal and connective tissue disorders
Rare: Myalgia, muscle weakness, myopathy
Very rare: Rhabdomyolysis, myositis, lupus erythematosus-like reactions

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)

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 to 17 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 aminotransferase 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 Lescol 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%).

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 in the plasma cholesterol concentration.

Lescol/Lescol XL 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, Lescol 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).

Lescol XL was administered to over 800 patients in three pivotal trials of 24 weeks active treatment duration and compared to Lescol 40 mg once or twice daily. Given as a single daily dose of 80 mg, Lescol XL 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 (Lescol) and active-controlled trials (Lescol XL)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Total-C</th>
<th>TG</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% Δ</td>
<td>N</td>
<td>% Δ</td>
<td>N</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lescol 20 mg¹</td>
<td>747</td>
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<td>747</td>
<td>-12</td>
<td>747</td>
</tr>
<tr>
<td>Lescol 40 mg¹</td>
<td>748</td>
<td>-19</td>
<td>748</td>
<td>-14</td>
<td>748</td>
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<tr>
<td>Lescol 40 mg twice daily¹</td>
<td>257</td>
<td>-27</td>
<td>257</td>
<td>-18</td>
<td>257</td>
</tr>
<tr>
<td>Lescol XL 80 mg²</td>
<td>750</td>
<td>-25</td>
<td>750</td>
<td>-19</td>
<td>748</td>
</tr>
<tr>
<td><strong>Baseline TG ≥200 mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lescol 20 mg¹</td>
<td>148</td>
<td>-16</td>
<td>148</td>
<td>-17</td>
<td>148</td>
</tr>
<tr>
<td>Lescol 40 mg¹</td>
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<td>-18</td>
<td>179</td>
<td>-20</td>
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<tr>
<td>Lescol XL 80 mg²</td>
<td>239</td>
<td>-25</td>
<td>239</td>
<td>-25</td>
<td>237</td>
</tr>
</tbody>
</table>

¹ Data for Lescol from 12 placebo-controlled trials
² Data for Lescol XL 80 mg 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 the Lescol Intervention Prevention Study (LIPS), 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 Lescol and Lescol XL 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 Lescol capsules (20 mg/day to 40 mg twice daily) or Lescol XL 80 mg 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 Lescol 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 Lescol capsules 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 < 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), Lescol 20 to 80 mg 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), Lescol 20 to 80 mg 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 Fluvastatin 80 mg, 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

- Mannitol
- Talc
- Magnesium Stearate
- Gelatin
- Titanium dioxide (E171)
- Red iron oxide (E172)
- Yellow iron oxide (E172)

**Printing ink:**

- White ink on capsule cap:
- Shellac
- Titanium dioxide (E171)
- Soya lecithin
- Antifoam DC 1510
Brown ink on capsule body:
Shellac
Iron oxide red (E172)
Iron oxide black (E172)
Titanium dioxide (E171)
Propylene glycol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 Months

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package to protect from light and moisture

6.5 Nature and contents of container
1. Alu/Alu Blisters. The blister strips are packed into cardboard cartons

2. Plastic bottles, with desiccant; Polyethylene container with a snap-on cap with a tamper evident ring.

Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/12/2008

10 DATE OF REVISION OF THE TEXT
03/06/2011
Patient Information Leaflet - updated
UKPAR Fluvastatin 20 and 40mg Capsules

PACKAGE LEAFLET: INFORMATION FOR THE USER

Fluvastatin 20mg and 40mg Capsules

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Fluvastatin Capsules are and what they are used for
2. Before you take Fluvastatin Capsules
3. How to take Fluvastatin Capsules
4. Possible side effects
5. How to store Fluvastatin Capsules
6. Further information

1. WHAT FLUVASTATIN CAPSULES ARE AND WHAT THEY ARE USED FOR

Fluvastatin belongs to a group of medicines known as statins, which are lipid-lowering medicines; they lower the fat (lipids) in your blood. They are used in patients whose conditions cannot be controlled by diet and exercise alone.

- Fluvastatin is a medicine used to treat raised levels of fats in the blood in adults, in particular total cholesterol and so called “bad” or LDL cholesterol, which is associated with an increased risk of heart disease and stroke.
- in adult patients with high blood levels of cholesterol
- in adult patients with high blood levels of both cholesterol and triglycerides (another sort of blood lipid)

- Your doctor can also prescribe Fluvastatin to prevent further serious cardiac events (e.g. heart attack) in patients after they already went through a heart catheterisation, with an intervention in the heart vessel.

2. BEFORE YOU TAKE FLUVASTATIN CAPSULES

Follow all instructions given to you by your doctor carefully. They may differ from the information contained in this leaflet.

Read the following explanations before you take Fluvastin.

Do not take Fluvastatin Capsules if:

- if you are allergic (hypersensitive) to fluvastatin or any of the other ingredients of Fluvastatin listed in section 6 of this leaflet.
- if you currently have liver problems, or if you have unexplained, persistently high level of certain liver enzymes (transaminases).
- if you are pregnant or breast-feeding (see “pregnancy and breast-feeding”)

If any of these apply to you, do not take Fluvastatin and tell your doctor.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Take special care with Fluvastatin
- if you previously had a liver disease. Liver function tests will normally be done before you start Fluvastatin, when your dose is increased and at various intervals during treatment to check for side effects.
- if you have a kidney disease.
- if you have a thyroid disease (hypothyroidism).
- if you have a medical history of muscle diseases yourself or in your family.
- if you had muscle problems with another lipid-lowering medicine.
- if you regularly drink large amounts of alcohol.

Check with your doctor or pharmacist before taking Fluvastatin:
- if you have severe respiratory failure

If any of these apply to you, tell your doctor before you take Fluvastatin. Your doctor will take a blood test before prescribing Fluvastatin.

Fluvastatin and people over 70 years
If you are over 70 years your doctor may want to check if you have risk factors for muscular diseases. You may need specific blood tests.

Fluvastatin and children/adolescents:
Fluvastatin has not been investigated and is not intended for the use in children below 9 years. For dose information in children and adolescents over 9 years, see section 3.

There is no experience with the use of Fluvastatin in combination with nicotinic acid, cholestyramine or fibrates in children and adolescents.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription.
Fluvastatin can be taken on its own or with other cholesterol-lowering medicines prescribed by your doctor.

After intake of a resin, e.g. cholestyramines (primarily used to treat high cholesterol) wait at least 4 hours before taking Fluvastatin.

Tell your doctor and pharmacist if you are taking any of the following:
- Ciclosporin (a medicine used to suppress the immune system).
- Fibrates (e.g. gemfibrozil), nicotinic acid or bile acid sequestrants (medicines used to lower bad cholesterol levels).
- Fluconazole (a medicine used to treat fungal infections).
- Rifampicin (an antibiotic).
- Phenytoin (a medicine used to treat epilepsy).
- Oral anticoagulants like warfarin (medicines used to reduce blood clotting).
- Glimepiride (a medicine used to treat diabetes).
- Colchicines (used to treat gout).

Taking Fluvastatin Capsules with food and drink
Fluvastatin Capsules can be taken with or without food.
Pregnancy and breast-feeding
Do not take Fluvastatin if you are pregnant or breast-feeding as the active ingredient may lead to harm to your unborn child; and it is not known whether the active ingredient is excreted in human breast milk. If you are pregnant, consult your doctor or pharmacist before taking Fluvastatin. Use reliable contraception for the whole time that you are taking Fluvastatin.

If you become pregnant while taking this medicine, stop taking Fluvastatin and see your doctor.

Driving and using machines
There is no information on the effects of Fluvastatin on your ability to drive and use machines.

Important information about some of the ingredients of Fluvastatin Capsules
Fluvastatin Capsules contain soya oil. If you are allergic to peanut or soya, do not use this medicinal product.

3. HOW TO TAKE FLUVASTATIN CAPSULES

Follow your doctor’s instructions carefully. Do not exceed the recommended dose.

Your doctor will recommend you to follow a low-cholesterol diet. Stay on this diet while taking Fluvastatin.

How much Fluvastatin to take

- The dose range for adults is 20 to 80 mg per day and depends on the extent of cholesterol lowering which needs to be achieved. Dose adjustments may be made by your doctor at 4-week or longer intervals.
- For children (aged 9 years and older) the usual starting dose is 20 mg per day. The maximum daily dose is 80 mg. Dose adjustments may be made by your doctor at 6-week intervals.

Your doctor will tell you exactly how many capsules of Fluvastatin to take. Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

When to take Fluvastatin
If you are taking Fluvastatin, take your dose in the evening or at bedtime.
If you are taking Fluvastatin twice per day, take one capsule in the morning and one in the evening or at bedtime.
If you are taking Fluvastatin capsules you can take your dose at any time of the day.
Fluvastatin capsules can be taken with or without meals. Swallow whole with a glass of water.

If you take more Fluvastatin than you should
If you have accidentally taken too much Fluvastatin, talk to your doctor straight away. You may need medical attention.

If you forget to take Fluvastatin Capsules
Take one dose as soon as you remember. However, do not take it if there is less than 4 hours before your next dose. In this case take your next dose at the usual time.
Do not take a double dose to make up for the one that you missed.

If you stop taking Fluvastatin
To maintain the benefits of your treatment, do not stop taking Fluvastatin unless your doctor tells you to. You must continue to take Fluvastatin as directed to keep the levels of your ‘bad’ cholesterol down. Fluvastatin will not cure your condition but it does help control it. Your cholesterol levels need to be checked regularly to monitor your progress.
If you have any further questions on the use of this product, ask your doctor or pharmacist.
4. POSSIBLE SIDE EFFECTS

Like all medicines, Fluvastatin can cause side effects, although not everybody gets them.

Very common: affects more than 1 user in 10
Common: affects 1 to 10 users in 100
Uncommon: affects 1 to 10 users in 1,000
Rare: affects 1 to 10 users in 10,000
Very rare: affects less than 1 user in 10,000
Not known: frequency cannot be estimated from the available data.

Some rare or very rare effects could be serious; get medical help immediately:
- if you have unexplained muscle pain, tenderness or weakness. These might be early signs of a potentially severe muscle degradation. This can be avoided if your doctor stops your treatment with Fluvastatin as quickly as possible. These side effects have also been found with similar medicines of this class (statins).
- if you have unusual tiredness or fever, yellowing of the skin and eyes, dark coloured urine (signs of hepatitis).
- if you have signs of skin reactions such as skin rash, hives, redness, itching, swelling of the face, eyelids, and lips.
- if you have skin swelling, difficulty in breathing, dizziness (signs of severe allergic reaction).
- if you bleed or bruise more easily than normal (signs of decreased number of blood platelets).
- if you have red or purple skin lesions (signs of blood vessel inflammation).
- if you have red blotchy rash mainly on the face which may be accompanied by fatigue, fever, nausea, loss of appetite (signs of lupus erythematosus-like reaction).
- if you have severe upper stomach pain (signs of inflamed pancreas).

If you experience any of these, tell your doctor straight away.

Other side effects: tell your doctor if they worry you.

Common:
Difficulty in sleeping, headache, stomach discomfort, abdominal pain, nausea.

Very rare:
Tingling or numbness of the hands or feet disturbed or decreased sensibility.

Other possible side effects
- Sleep disturbances, including insomnia and nightmares
- Memory loss
- Sexual difficulties
- Depression
- Breathing problems including persistent cough and/or shortness of breath or fever

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE FLUVASTATIN CAPSULES

Keep out of the reach and sight of children.

Do not use Fluvastatin Capsules after the expiry date which is stated on the carton. The expiry date refers to the last day of that month. Do not store above 25°C.

Store in the original package to protect from light and moisture.
Leave your capsules in the original packaging, and only remove them when it is time for you to take your medicine.

Medicines should not be disposed of via wastewater of household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What Fluvastatin Capsules contain**

The active substance is Fluvastatin sodium.

The other ingredients are:

- Capsule contents – Mannitol, Talc, Magnesium stearate
- Capsule shell — Gelatine, Titanium dioxide (E171), Red iron oxide (E172), Yellow iron oxide (E172)
- Printing Ink:
  - White ink on capsule cap: Shellac, Titanium dioxide (E171), Soya lecithin, Antifoam DC 1510
  - Brown ink on capsule body: Shellac, Iron oxide red (E172), Iron oxide black (E172), Titanium dioxide (E171), Propylene glycol

**What Fluvastatin capsules look like and contents of the pack**

The Capsules are available in two strengths providing either 20 mg or 40 mg Fluvastatin.

The 20mg capsules contain pale yellow powder. One half of the capsule is orange and has the number “20” has been printed on it. The other half of the capsule is ivory coloured and has the letters “FST” printed on it.

The 40mg capsules contain pale yellow powder. One half of the capsule is orange and has the number “40” has been printed on it. The other half of the capsule is yellow and has the letters “FST” printed on it.

Fluvastatin capsules are available in packs of 14, 28, 30, 50, 56, 60, and 100 Capsules. *Only marketed pack sizes will be printed on the leaflet.*

**The Marketing Authorisation Holder**

Cadence Pharma Limited,
6th floor,
94 Wigmore Street,
London
W1U 3RF

**The Manufacturer**

Actavis hf,
Reykjavikurvegur 78,
15 – 220 Hafnarfjordur,
Iceland

**REMEMBER:** This medicine is only for you. Only a doctor can prescribe it for you. Never give it to anyone else. It may harm them, even if their symptoms appear to be the same as yours.

This leaflet was last approved in April 2011