Public Assessment Report

Decentralised Procedure

RATIOVIN XL 80MG PROLONGED-RELEASE TABLETS
MITHESTAN XL 80MG PROLONGED-RELEASE TABLETS
EVADANIN XL 80MG PROLONGED-RELEASE TABLETS

UK/H/1181-3/001/DC
UK licence no: PL 18641/0004-6

Novopharm Limited
LAY SUMMARY

On 19th November 2008, the MHRA granted Novopharm Limited Marketing Authorisations (licences) for the medicinal products Ratiovin/Mithestan/Evadanin XL 80mg Prolonged Release Tablets (PL 18641/0004). These prescription-only medicines (POM) contain the active substance fluvastatin sodium, which belongs to a group called lipid-lowering medicines. This group of drugs works by reducing the amount of cholesterol the body makes.

Cholesterol is a type of fat, which is vital to the normal functioning of the body. If levels of cholesterol in the blood are too high, it can be deposited on the walls of the arteries. There it builds up to form plaques that can eventually block the blood vessel. It is generally accepted that reduction of high cholesterol levels in your blood reduces the risk of heart disease.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ratiovin/Mithestan/Evadanin XL 80mg Prolonged Release Tablets outweigh the risks; hence Marketing Authorisations have been granted.
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Module 6  
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## Module 1

| **Product Name** | Ratiovin XL 80mg Prolonged Release Tablets  
Mithestan XL 80mg Prolonged Release Tablets  
Evadanin XL 80mg Prolonged Release Tablets |
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<td><strong>Type of Application</strong></td>
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<td><strong>Active Substance</strong></td>
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<td><strong>Strength</strong></td>
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<td><strong>MA Holder</strong></td>
<td>Novopharm Limited, Suite 23, Park Royal House, 23 Park Royal Road, London, NW10 7JH, UK</td>
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<td><strong>Reference Member State</strong></td>
<td>United Kingdom</td>
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| **Concerned Member States** | UK/H/1181/001/DC: Austria, Czech Republic, Finland, Germany, Hungary, Italy, Luxembourg, the Netherlands, Portugal, Slovak Republic, Spain, Sweden.  
UK/H/1182/001/DC: Germany  
UK/H/1183/001/DC: Germany |
| **Procedure Number** | UK/H/1181-3/001/DC |
| **Timetable** | Day 210 – 21st September 2008 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Ratiovin XL 80mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each prolonged release tablet contains 80mg fluvastatin (as fluvastatin sodium)
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Prolonged release tablet.
Ratiovin XL tablets are dark yellow, round, biconvex tablets. 10.1 ± 0.1 mm in diameter and 4.0mm ± 0.2 mm in thickness

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Ratiovin XL is indicated as an adjunct to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo-B) and triglycerides (TG) levels when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson Types IIa and IIb).

Ratiovin XL is 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 Ratiovin XL, 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 (1 capsule Fluvastatin 40 mg) once daily although a dose of 20 mg fluvastatin (1 capsule Fluvastatin 20 mg) 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 (1 tablet Ratiovin XL) once 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 once daily.

Ratiovin XL can be administered as a single dose at any time of the day with or without food and must be swallowed whole with a glass of water. The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of Ratiovin XL is maintained with prolonged administration.

Ratiovin XL is efficacious in monotherapy or in combination with bile acid sequestrants. When Ratiovin XL is used in combination with cholestyramine or other resins, it 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 Ratiovin XL in combination with nicotinic acid or fibrates (see Section 4.5 Interactions with other medicaments and other forms of interaction).

•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 Clearance <60mL/min). No dose adjustments are therefore necessary in these patients.

However, since fluvastatin has not been studied at doses greater than 40 mg in patients with severe renal impairment, caution should be exercised when treating such patients at higher doses.

**Patients with impaired liver function**

*Ratiovin XL* is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see 4.3 Contraindications and 4.4 Special warnings and special precautions for use).

**Use in the elderly**

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

**Use in children and adolescents**

*Children and adolescents with heterozygous familial hypercholesterolemia*

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. Dietary therapy should be continued during treatment.

The recommended starting dose is 40 mg (1 capsule fluvastatin 40 mg) or 80 mg (1 tablet fluvastatin XL 80 mg once daily or one capsules fluvastatin 40 mg twice daily). The dose of 20 mg fluvastatin (1 capsule fluvastatin 20 mg) may be adequate in mild cases.

Starting doses should be individualized according to baseline LDL-C levels and the recommended goal of therapy to be accomplished.

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

Fluvastatin is not recommended for use in children under the age of 9 years.

Not all the above proposed dosage recommendations are possible with the current formulation.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Patients with active liver disease or unexplained, persistent elevations in serum transaminases (see section 4.2 and 4.8).

During pregnancy and lactation (see section 4.6). Women of childbearing potential not taking adequate contraceptive precautions (see section 4.6.)

Currently active myopathy

### 4.4 Special warnings and precautions for use

HMG-CoA reductase inhibitors, including *Ratiovin XL* 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 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 *Ratiovin XL* is administered to patients with a history of liver disease or heavy alcohol consumption.

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.

Caution should be exercised when fluvastatin is administered in patients with hypothyroidism.
Children and adolescents with heterozygous familial hypercholesterolemia

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 XL therapy in childhood to reduce morbidity and mortality in adulthood has not been established. (see Section 5.1)

Fluvastatin has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia (for details see section 5.1 Pharmacodynamic properties). In the case of 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.

Fluvastatin is not recommended for use in children under the age of 9 years.

Skeletal muscle

With Ratiovin XL, 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.

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.

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 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 (> 5xULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated (> 5xULN) at baseline, treatment should not be started.

Whilst on treatment

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

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

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.
The risk of myopathy 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 Ratiovin XL 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 colchicine and fluvastatin with ciclosporin. Ratiovin XL 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

Mean AUC and C\text{\scriptsize max} were increased by 49% and 45% respectively and t\text{\scriptsize max} prolonged when fluvastatin (Ratiovin XL) was taken with food, compared to fasting state. However, no clinically obvious differences in the lipid-lowering effects and safety are anticipated when fluvastatin is taken with or without food.

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 wherein Ratiovin XL (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{\scriptsize max}) 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 warnings and special 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 C\text{\scriptsize max} 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 (C\text{\scriptsize max}) 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 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 with propranolol has no effect on the bioavailability of fluvastatin.

Bile-acid sequestering agents - Administration of fluvastatin 4 hours after cholestyramine results in a clinically significant additive effect compared with that achieved with either drug alone. Ratiovin XL XL 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 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 with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of fluvastatin, which, however, is of no clinical relevance.

Rifampicin - Administration of fluvastatin to subjects pre-treated with rifampicin 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.

Phenytoin – In an interaction study concomitant administration of fluvastatin and phenytoin resulted in an increase of fluvastatin mean AUC and C max 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- Ratiovin XL had no effect on ciclosporin bioavailability when co-administered (see also Effects of other drugs on fluvastatin).

Phenytoin - Co-administration of fluvastatin (40 mg b.i.d. for 5 days) increased the mean C max 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), C max increased on average by 1.6 times (range: 0.9 -3.0) and the mean t 1/2 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. If the use of this combination is necessary, high doses should be avoided and the patients should be monitored appropriately.

Losartan - Losartan is an angiotensin II receptor antagonist that is metabolized by CYP2C9 and CYP3A4 to a more potent antihypertensive metabolite, E3174. The steady-state pharmacokinetics of losartan and E3174 have been assessed when administered alone and concomitantly with fluvastatin, a
specific CYP2C9 inhibitor. Interaction studies showed that fluvastatin did not significantly change the steady-state AUC0-24 or half-life of losartan or E3174. Losartan apparent oral clearance was not affected by fluvastatin. Inhibition of losartan metabolism appears to require both CYP2C9 and CYP3A4 inhibition.

Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with Losartan.

Other concomitant therapy - In clinical studies in which fluvastatin was 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.

Colchicines
Isolated cases of myopathy have been reported during post-marketing experience with concomitant administration of fluvastatin and 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 colchicine.

4.6 Pregnancy and lactation

Pregnancy
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 fetal harm when administered to pregnant women. Therefore, Fluvastatin is suspected to cause serious birth defects when administered during pregnancy. 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.

Lactation
As small amounts of fluvastatin have been found in rat milk, **Ratiovin XL** is contraindicated in nursing mothers (see section 4.3).

4.7 Effects on ability to drive and use machines
No studies of the effect of the ability to drive and use machines have been performed. Therefore caution is recommended when driving and using 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, undesirable effects are presented in order of decreasing seriousness. The most commonly reported adverse drug reactions are minor gastrointestinal symptoms, insomnia and headache.

<table>
<thead>
<tr>
<th>System Organ Classes</th>
<th>Very common ≥1/10</th>
<th>Common ≥1/100, ≤1/10</th>
<th>Uncommon ≥1/1,000, ≤1/100</th>
<th>Rare ≥1/10,000, ≤1/1,000</th>
<th>Very rare ≤1/10,000</th>
<th>Not known (cannot be estimated from the available data)</th>
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<td>Memory loss</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
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<td></td>
<td>Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)</td>
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<td>Skin and subcutaneous tissue disorders</td>
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<td>Hypersensitivity reactions such as rash, urticaria.</td>
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<td>Musculoskeletal and connective tissue disorders</td>
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<td>Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema</td>
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<td>Rhabdomyolysis, myositis, lupus erythematosus-like reactions</td>
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<td>Hepatitis</td>
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<td>Psychiatric disorders</td>
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<td>Sexual dysfunction, depression</td>
</tr>
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</table>

Children and adolescents with heterozygous familial hypercholesterolemia

The safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolemia assessed in 114 patients aged 9-17 years treated in two open 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

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 2%). 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
In a placebo-controlled study including 40 hypercholesterolaemic patients, doses up to 320 mg/day (n=7 per dose group) administered as fluvastatin 80mg XL tablets over two weeks were well tolerated. The experience with overdoses of fluvastatin 80mg XL tablets 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 inhibitors
ATC code: C10AA04

Fluvastatin is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. 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. Ratiovin XL exert 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 have 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. Ratiovin XL also produces a moderate reduction in triglycerides and a moderate increase in HDL-C. Therapeutic response is well established within 2 weeks, and maximum response is achieved within 4 weeks from treatment initiation and maintained during chronic therapy.

In the Ratiovin XL 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).

Children and adolescents with heterozygous familial hypercholesterolemia
The safety and efficacy of fluvastatin in children and adolescent patients aged 9 - 16 years of age with heterozygous familial hypercholesterolemia has been evaluated in 2 open label, uncontrolled clinical trials of 2 years' duration.

114 patients (66 boys and 48 girls) were treated with fluvastatin administered as either fluvastatin capsules 20 mg - 40 mg bid or fluvastatin XL 80 mg extended release tablets using a dose-titration regimen based upon LDL-C response.

The first study enrolled 29 pre-pubertal boys, 9-12 years of age, who had an LDL-C level > 90th percentile for age and one parent with primary hypercholesterolemia and either a family history of premature ischemic heart disease or tendon xanthomas. The mean baseline LDL-C was 226 mg/dL equivalent to 5.8 mmol/L (range: 137 - 354 mg/dL equivalent to 3.6 - 9.2 mmol/L). All patients were
started on fluvastatin capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (40 mg bid) to achieve an LDL-C goal of 96.7 to 123.7 mg/dL (2.5 mmol/L to 3.2 mmol/L).

The second study enrolled 85 male and female patients, 10 to 16 years of age, who had an LDL-C > 190 mg/dL (equivalent to 4.9 mmol/L) or LDL-C > 160 mg/dL (equivalent to 4.1 mmol/L) and one or more risk factors for coronary heart disease, or LDL-C > 160 mg/dL (equivalent to 4.1 mmol/L) and a proven LDL-receptor defect. The mean baseline LDL-C was 225 mg/dL equivalent to 5.8 mmol/L (range: 148 - 343 mg/dL equivalent to 3.8 - 8.9 mmol/L). All patients were started on fluvastatin capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (fluvastatin 80 mg XL tablet) to achieve an LDL-C goal of < 130 mg/dL (3.4 mmol/L).

In the first study, fluvastatin 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, fluvastatin 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%) following oral administration to fasted volunteers. After oral administration of Ratiovin XL and in comparison with the capsules, the absorption rate of fluvastatin is almost 60% slower while the mean residence time of fluvastatin is increased by approximately 4 hours. In a fed state, the drug is absorbed at a reduced rate. 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%.

Distribution
The apparent volume of distribution (Vf) 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.

Metabolism
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 metabolised by CYP2C9.

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

Food - Mean AUC and Cmax were increased by 49% and 45% respectively and tmax prolonged when fluvastatin (fluvastatin 80mg XL tablets) was taken with food, compared to fasting state. However, no clinically obvious differences in the lipid-lowering effects and safety are anticipated when Ratiovin XL is taken with or without food.
Plasma concentrations of fluvastatin do not vary as a function of age. Mean AUC and C_{max} were increased by 36% and 44% respectively in females compared to males. However, no clinically obvious differences in the lipid-lowering effects of fluvastatin are anticipated between males and females.

*Children and adolescents with heterozygous familial hypercholesterolemia*

No pharmacokinetic data in children are available.

5.3 Preclinical safety data

Repeat toxicity studies with fluvastatin identified a variety of changes 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 the 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 compounds.

Carcinogenicity studies in rats and mice revealed a low incidence of forestomach squamous papillomas in mice and rats and one carcinoma in rats at the highest dose (18 mg/kg per day escalated to 24 mg/kg per day after 1 year). The forestomach neoplasms reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug. In addition, an increase incidence of thyroid follicular cell neoplasms in male rats given the highest dose of fluvastatin was recorded. This is 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 incidence of hepatic adenomas or carcinomas were observed. *In vitro* and *in vivo* mutagenicity studies revealed no evidence of mutagenicity.

Reproductive toxicity studies indicated that fluvastatin had no adverse effects on fertility or reproductive performance in males or females, nor was it embryotoxic or teratogenic. Late gestational effects at high doses resulted in maternal mortality and fetal and neonatal lethality attributable to exaggerated pharmacological effects of fluvastatin during pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- **Tablet core**
  - Carrageenan
  - Magnesium stearate

- **Film-coating**
  - Hydroxypropyl cellulose
  - Hypromellose 6cP
  - Iron oxide yellow (E 172)
  - Titanium dioxide (E 171)
  - Macrogol 8000
  - Iron oxide red (E 172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Alu/Alu blister consisting of an aluminium coating foil and an aluminium covering foil. *Ratiovin XL* come in packs of 20, 28, 30, 50, 56, 60, 90, 98, 100 and 490 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.
7 MARKETING AUTHORISATION HOLDER
Novopharm Ltd, Suite 23, Park Royal House, 23 Park Royal Road, London NW10 7JH, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18641/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/11/2008

10 DATE OF REVISION OF THE TEXT
19/11/2008
1 NAME OF THE MEDICINAL PRODUCT
Mithestan XL 80mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each prolonged release tablet contains 80mg fluvastatin (as fluvastatin sodium)
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Prolonged release tablet.

Mithestan XL tablets are dark yellow, round, biconvex tablets. 10.1 ± 0.1 mm in diameter and 4.0mm ± 0.2 mm in thickness

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Mithestan XL is indicated as an adjunct to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo-B) and triglycerides (TG) levels when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson Types IIa and IIb).

Mithestan XL is 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 Mithestan XL, 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 (1 capsule Fluvastatin 40 mg) once daily although a dose of 20 mg fluvastatin (1 capsule Fluvastatin 20 mg) 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 (1 tablet Mithestan XL) once 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 once daily.

Mithestan XL can be administered as a single dose at any time of the day with or without food and must be swallowed whole with a glass of water. The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of Mithestan XL is maintained with prolonged administration.

Mithestan XL is efficacious in monotherapy or in combination with bile acid sequestrants. When Mithestan XL is used in combination with cholestyramine or other resins, it 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 Mithestan XL in combination with nicotinic acid or fibrates (see Section 4.5 Interactions with other medicaments and other forms of interaction).

•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 Clearance <60mL/min). No dose adjustments are therefore necessary in these patients.

However, since fluvastatin has not been studied at doses greater than 40 mg in patients with severe renal impairment, caution should be exercised when treating such patients at higher doses.
Patients with impaired liver function

*Mithestan XL* is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see 4.3 Contraindications and 4.4 Special warnings and special precautions for use).

Use in the elderly

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

Use in children and adolescents

*Children and adolescents with heterozygous familial hypercholesterolemia*

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. Dietary therapy should be continued during treatment.

The recommended starting dose is 40 mg (1 capsule fluvastatin 40 mg) or 80 mg (1 tablet fluvastatin XL 80 mg once daily or one capsules fluvastatin 40 mg twice daily). The dose of 20 mg fluvastatin (1 capsule fluvastatin 20 mg) may be adequate in mild cases.

Starting doses should be individualized according to baseline LDL-C levels and the recommended goal of therapy to be accomplished.

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

Fluvastatin is not recommended for use in children under the age of 9 years.

Not all the above proposed dosage recommendations are possible with the current formulation.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Patients with active liver disease or unexplained, persistent elevations in serum transaminases (see section 4.2 and 4.8).

_During pregnancy and lactation (see section 4.6)._  
Women of childbearing potential not taking adequate contraceptive precautions (see section 4.6.)

Currently active myopathy

4.4 Special warnings and precautions for use

HMG-CoA reductase inhibitors, including *Mithestan XL* are unlikely to be of benefit in patients with rare homozygous familial hypercholesterolemia.

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 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 *Mithestan XL* is administered to patients with a history of liver disease or heavy alcohol consumption.

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.

Caution should be exercised when fluvastatin is administered in patients with hypothyroidism.

*Children and adolescents with heterozygous familial hypercholesterolemia*

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 XL therapy in childhood to reduce morbidity and mortality in adulthood has not been established. (see Section 5.1)

Fluvastatin has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia (for details see section 5.1 Pharmacodynamic properties). In the case of 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.

Fluvastatin is not recommended for use in children under the age of 9 years.

Skeletal muscle
With Mithestan XL, 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.

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.

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 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 (> 5xULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated (> 5xULN) at baseline, treatment should not be started.

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

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

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

The risk of myopathy 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 Mithestan XL 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 colchicine and
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

Mean AUC and C_{max} were increased by 49% and 45% respectively and t_{max} prolonged when fluvastatin (Mithestan XL) was taken with food, compared to fasting state. However, no clinically obvious differences in the lipid-lowering effects and safety are anticipated when fluvastatin is taken with or without food.

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 wherein Mithestan XL (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 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 warnings and special 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 C_{max} 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 (C_{max}) 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 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 with propranolol has no effect on the bioavailability of fluvastatin.

Bile-acid sequestering agents - Administration of fluvastatin 4 hours after cholestyramine results in a clinically significant additive effect compared with that achieved with either drug alone. Mithestan XL 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 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 with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of fluvastatin, which, however, is of no clinical relevance.

Rifampicin - Administration of fluvastatin to subjects pre-treated with rifampicin 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.

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 - Mithestan XL had no effect on ciclosporin bioavailability when co-administered (see also Effects of other drugs on fluvastatin).

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. If the use of this combination is necessary, high doses should be avoided and the patients should be monitored appropriately.

Losartan - Losartan is an angiotensin II receptor antagonist that is metabolized by CYP2C9 and CYP3A4 to a more potent antihypertensive metabolite, E3174. The steady-state pharmacokinetics of losartan and E3174 have been assessed when administered alone and concomitantly with fluvastatin, a specific CYP2C9 inhibitor. Interaction studies showed that fluvastatin did not significantly change the steady-state AUC0-24 or half-life of losartan or E3174. Losartan apparent oral clearance was not affected by fluvastatin. Inhibition of losartan metabolism appears to require both CYP2C9 and CYP3A4 inhibition.
Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with Losartan.

*Other concomitant therapy* - In clinical studies in which fluvastatin was 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.

**Colchicines**
Isolated cases of myopathy have been reported during post-marketing experience with concomitant administration of fluvastatin and 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 colchicine.

### 4.6 Pregnancy and lactation

**Pregnancy**
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 fetal harm when administered to pregnant women. Therefore, Fluvastatin is suspected to cause serious birth defects when administered during pregnancy. 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.

**Lactation**
As small amounts of fluvastatin have been found in rat milk, *Mithestan XL* is contraindicated in nursing mothers (see section 4.3).

### 4.7 Effects on ability to drive and use machines
No studies of the effect of the ability to drive and use machines have been performed. Therefore caution is recommended when driving and using 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, undesirable effects are presented in order of decreasing seriousness. The most commonly reported adverse drug reactions are minor gastrointestinal symptoms, insomnia and headache.

<table>
<thead>
<tr>
<th>System Organ Classes</th>
<th>Very common ≥1/10</th>
<th>Common ≥1/100, ≤1/10</th>
<th>Uncommon ≥1/1,000, ≤1/100</th>
<th>Rare ≥1/10,000, ≤1/1,000</th>
<th>Very rare ≤1/10,000</th>
<th>Not known (cannot be estimated from the available data)</th>
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<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache, dizziness</td>
<td></td>
<td></td>
<td></td>
<td>Memory loss</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dyspepsia, abdominal pain, nausea, constipation, flatulence, diarrhoea,</td>
<td></td>
<td></td>
<td></td>
<td>Acute pancreatitis</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
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<td></td>
<td></td>
<td>Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)</td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Hypersensitivity reactions such as rash, urticaria.</td>
<td></td>
<td></td>
<td>Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema</td>
<td></td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>Myalgia, muscle weakness, myopathy, muscle tenderness</td>
<td></td>
<td></td>
<td>Rhabdomyolysis, myositis, lupus erythematosus-like reactions</td>
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<tr>
<td>Vascular disorders</td>
<td></td>
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<td>Vasculitis</td>
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<td>General disorders and administration site conditions</td>
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<td>Fatigue</td>
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<td>Hepatobiliary disorders</td>
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<td>Hepatitis</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Sleep disturbances, including insomnia and nightmares</td>
<td></td>
<td></td>
<td></td>
<td>Sexual dysfunction, depression</td>
<td></td>
</tr>
</tbody>
</table>

Children and adolescents with heterozygous familial hypercholesterolemia

The safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolemia assessed in 114 patients aged 9-17 years treated in two open 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

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 2%). 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
In a placebo-controlled study including 40 hypercholesterolaemic patients, doses up to 320 mg/day (n=7 per dose group) administered as fluvastatin 80mg XL tablets over two weeks were well tolerated. The experience with overdoses of fluvastatin 80mg XL tablets 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 inhibitors
ATC code: C10AA04

Fluvastatin is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. 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. Mithestan XL exert 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 have 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. Mithestan XL also produces a moderate reduction in triglycerides and a moderate increase in HDL-C. Therapeutic response is well established within 2 weeks, and maximum response is achieved within 4 weeks from treatment initiation and maintained during chronic therapy.

In the Mithestan XL 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).

Children and adolescents with heterozygous familial hypercholesterolemia
The safety and efficacy of fluvastatin in children and adolescent patients aged 9 - 16 years of age with heterozygous familial hypercholesterolemia has been evaluated in 2 open label, uncontrolled clinical trials of 2 years' duration.

114 patients (66 boys and 48 girls) were treated with fluvastatin administered as either fluvastatin capsules 20 mg - 40 mg bid or fluvastatin XL 80 mg extended release tablets using a dose-titration regimen based upon LDL-C response.

The first study enrolled 29 pre-pubertal boys, 9-12 years of age, who had an LDL-C level > 90th percentile for age and one parent with primary hypercholesterolemia and either a family history of premature ischemic heart disease or tendon xanthomas. The mean baseline LDL-C was 226 mg/dL equivalent to 5.8 mmol/L (range: 137 - 354 mg/dL equivalent to 3.6 - 9.2 mmol/L). All patients were
started on fluvastatin capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (40 mg bid) to achieve an LDL-C goal of 96.7 to 123.7 mg/dL (2.5 mmol/L to 3.2 mmol/L).

The second study enrolled 85 male and female patients, 10 to 16 years of age, who had an LDL-C > 190 mg/dL (equivalent to 4.9 mmol/L) or LDL-C > 160 mg/dL (equivalent to 4.1 mmol/L) and one or more risk factors for coronary heart disease, or LDL-C > 160 mg/dL (equivalent to 4.1 mmol/L) and a proven LDL-receptor defect. The mean baseline LDL-C was 225 mg/dL equivalent to 5.8 mmol/L (range: 148 - 343 mg/dL equivalent to 3.8 - 8.9 mmol/L). All patients were started on fluvastatin capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily (fluvastatin 80 mg XL tablet) to achieve an LDL-C goal of < 130 mg/dL (3.4 mmol/L).

In the first study, fluvastatin 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, fluvastatin 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%) following oral administration to fasted volunteers. After oral administration of Mithestan XL and in comparison with the capsules, the absorption rate of fluvastatin is almost 60% slower while the mean residence time of fluvastatin is increased by approximately 4 hours. In a fed state, the drug is absorbed at a reduced rate. 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%.

Distribution
The apparent volume of distribution (V_{zf}) 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.

Metabolism
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 metabolised by CYP2C9.

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

Food - Mean AUC and C_{max} were increased by 49% and 45% respectively and t_{max} prolonged when fluvastatin (fluvastatin 80mg XL tablets) was taken with food, compared to fasting state. However, no clinically obvious differences in the lipid-lowering effects and safety are anticipated when Mithestan XL is taken with or without food.
Plasma concentrations of fluvastatin do not vary as a function of age. Mean AUC and Cₘₐₓ were increased by 36% and 44% respectively in females compared to males. However, no clinically obvious differences in the lipid lowering effects of fluvastatin are anticipated between males and females.

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

5.3 Preclinical safety data
Repeat toxicity studies with fluvastatin identified a variety of changes 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 the 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 compounds.

Carcinogenicity studies in rats and mice revealed a low incidence of forestomach squamous papillomas in mice and rats and one carcinoma in rats at the highest dose (18 mg/kg per day escalated to 24 mg/kg per day after 1 year). The forestomach neoplasms reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug. In addition, an increase incidence of thyroid follicular cell neoplasms in male rats given the highest dose of fluvastatin was recorded. This is 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 incidence of hepatic adenomas or carcinomas were observed. In vitro and in vivo mutagenicity studies revealed no evidence of mutagenicity.

Reproductive toxicity studies indicated that fluvastatin had no adverse effects on fertility or reproductive performance in males or females, nor was it embryotoxic or teratogenic. Late gestational effects at high doses resulted in maternal mortality and fetal and neonatal lethality attributable to exaggerated pharmacological effects of fluvastatin during pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- **Tablet core**
  - Carrageenan
  - Magnesium stearate

- **Film-coating**
  - Hydroxypropyl cellulose
  - Hypromellose 6cP
  - Iron oxide yellow (E 172)
  - Titanium dioxide (E 171)
  - Macrogol 8000
  - Iron oxide red (E 172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
Alu/Alu blister consisting of an aluminium coating foil and an aluminium covering foil. Mithestan XL come in packs of 10, 20, 30, 50, 100 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.
MARKETING AUTHORISATION HOLDER
Novopharm Ltd, Suite 23, Park Royal House, 23 Park Royal Road, London NW10 7JH, United Kingdom

MARKETING AUTHORISATION NUMBER(S)
PL 18641/0005

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/11/2008

DATE OF REVISION OF THE TEXT
19/11/2008
1 **NAME OF THE MEDICINAL PRODUCT**
*Evadanin XL* 80mg prolonged release tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each prolonged release tablet contains 80mg fluvastatin (as fluvastatin sodium)
For a full list of excipients, see section 6.1

3 **PHARMACEUTICAL FORM**
Prolonged release tablet.

*Evadanin XL* tablets are dark yellow, round, biconvex tablets. 10.1 ± 0.1 mm in diameter and 4.0mm ± 0.2 mm in thickness

4 **CLINICAL PARTICULARS**
4.1 Therapeutic indications
*Evadanin XL* is indicated as an adjunct to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo-B) and triglycerides (TG) levels when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson Types IIa and IIb).

*Evadanin XL* is 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 *Evadanin XL*, 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 (1 capsule Fluvastatin 40 mg) once daily although a dose of 20 mg fluvastatin (1 capsule Fluvastatin 20 mg) 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 (1 tablet *Evadanin XL*) once 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 once daily.

*Evadanin XL* can be administered as a single dose at any time of the day with or without food and must be swallowed whole with a glass of water. The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient’s response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of *Evadanin XL* is maintained with prolonged administration.

*Evadanin XL* is efficacious in monotherapy or in combination with bile acid sequestrants. When *Evadanin XL* is used in combination with cholestyramine or other resins, it 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 *Evadanin XL* in combination with nicotinic acid or fibrates (see Section 4.5 Interactions with other medicaments and other forms of interaction).

• **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 Clearance <60mL/min). No dose adjustments are therefore necessary in these patients.

However, since fluvastatin has not been studied at doses greater than 40 mg in patients with severe renal impairment, caution should be exercised when treating such patients at higher doses.
Patients with impaired liver function

*Evadanin XL* is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see 4.3 Contraindications and 4.4 Special warnings and special precautions for use).

Use in the elderly

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

Use in children and adolescents

**Children and adolescents with heterozygous familial hypercholesterolemia**

Prior to initiating treatment with fluvastatin in children and adolescents aged 9 years and older with heterozygous familial hypercholesterolemia, the patient should be placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

The recommended starting dose is 40 mg (1 capsule fluvastatin 40 mg) or 80 mg (1 tablet fluvastatin XL 80 mg once daily or one capsules fluvastatin 40 mg twice daily). The dose of 20 mg fluvastatin (1 capsule fluvastatin 20 mg) may be adequate in mild cases.

Starting doses should be individualized according to baseline LDL-C levels and the recommended goal of therapy to be accomplished.

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

Fluvastatin is not recommended for use in children under the age of 9 years.

Not all the above proposed dosage recommendations are possible with the current formulation.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Patients with active liver disease or unexplained, persistent elevations in serum transaminases (see section 4.2 and 4.8).

*During pregnancy and lactation (see section 4.6).*

Women of childbearing potential not taking adequate contraceptive precautions (see section 4.6.)

Currently active myopathy

4.4 Special warnings and precautions for use

HMG-CoA reductase inhibitors, including *Evadanin XL* 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 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 *Evadanin XL* is administered to patients with a history of liver disease or heavy alcohol consumption.

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.

Caution should be exercised when fluvastatin is administered in patients with hypothyroidism.

**Children and adolescents with heterozygous familial hypercholesterolemia**

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 XL therapy in childhood to reduce morbidity and mortality in adulthood has not been established. (see Section 5.1)

Fluvastatin has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia (for details see section 5.1 Pharmacodynamic properties). In the case of 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.

Fluvastatin is not recommended for use in children under the age of 9 years.

**Skeletal muscle**

With *Evadanin XL*, 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.

**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.

**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 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 > 5xULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated > 5xULN) at baseline, treatment should not be started.

**Whilst on treatment**

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

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

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

The risk of myopathy 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 *Evadanin XL* 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 colchicine and
fluvastatin with ciclosporin. **Evadanin XL** 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**

Mean AUC and C_{max} were increased by 49% and 45% respectively and t_{max} prolonged when fluvastatin (**Evadanin XL**) was taken with food, compared to fasting state. However, no clinically obvious differences in the lipid-lowering effects and safety are anticipated when fluvastatin is taken with or without food.

**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 wherein **Evadanin XL** (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 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 warnings and special 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 C_{max} 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 (C_{max}) 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 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 with propranolol has no effect on the bioavailability of fluvastatin.

**Bile-acid sequestering agents** - Administration of fluvastatin 4 hours after cholestyramine results in a clinically significant additive effect compared with that achieved with either drug alone. Evadanin XL 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 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 with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of fluvastatin, which, however, is of no clinical relevance.

**Rifampicin** - Administration of fluvastatin to subjects pre-treated with rifampicin 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.

**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 fluvasatin on other drugs:**

- **Ciclosporin** - Evadanin XL had no effect on ciclosporin bioavailability when co-administered (see also Effects of other drugs on fluvastatin).

- **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. If the use of this combination is necessary, high doses should be avoided and the patients should be monitored appropriately.

**Losartan** - Losartan is an angiotensin II receptor antagonist that is metabolized by CYP2C9 and CYP3A4 to a more potent antihypertensive metabolite, E3174. The steady-state pharmacokinetics of losartan and E3174 have been assessed when administered alone and concomitantly with fluvastatin, a specific CYP2C9 inhibitor. Interaction studies showed that fluvastatin did not significantly change the steady-state AUC0-24 or half-life of losartan or E3174. Losartan apparent oral clearance was not affected by fluvastatin. Inhibition of losartan metabolism appears to require both CYP2C9 and CYP3A4 inhibition.
Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with Losartan.

Other concomitant therapy - In clinical studies in which fluvastatin was 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.

Colchicines
Isolated cases of myopathy have been reported during post-marketing experience with concomitant administration of fluvastatin and 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 colchicine.

4.6 Pregnancy and lactation

Pregnancy
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 fetal harm when administered to pregnant women. Therefore, Fluvastatin is suspected to cause serious birth defects when administered during pregnancy. 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.

Lactation
As small amounts of fluvastatin have been found in rat milk, Evadanin XL is contraindicated in nursing mothers (see section 4.3).

4.7 Effects on ability to drive and use machines
No studies of the effect of the ability to drive and use machines have been performed. Therefore caution is recommended when driving and using 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, undesirable effects are presented in order of decreasing seriousness. The most commonly reported adverse drug reactions are minor gastrointestinal symptoms, insomnia and headache.

<table>
<thead>
<tr>
<th>System Organ Classes</th>
<th>Very common ≥1/10</th>
<th>Common ≥1/100, ≤1/10</th>
<th>Uncommon ≥1/1,000, ≤1/100</th>
<th>Rare ≥1/10,000, ≤1/1,000</th>
<th>Very rare ≤1/10,000</th>
<th>Not known (cannot be estimated from the available data)</th>
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</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache, dizziness</td>
<td></td>
<td></td>
<td></td>
<td>Memory loss</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Dyspepsia, abdominal pain, nausea, constipation, flatulence, diarrhoea,</td>
<td></td>
<td></td>
<td></td>
<td>Acute pancreatitis</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td>Hypersensitivity reactions such as rash, urticaria.</td>
<td></td>
<td></td>
<td>Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td>Myalgia, muscle weakness, myopathy, muscle tenderness</td>
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<td>Rhabdomyolysis, myositis, lupus erythematous-like reactions</td>
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<td>Vascular disorders</td>
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<td>Vasculitis</td>
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<td>General disorders and administration site conditions</td>
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<td>Hepatitis</td>
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<td>Psychiatric disorders</td>
<td>Sleep disturbances, including insomnia and nightmares</td>
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**Children and adolescents with heterozygous familial hypercholesterolemia**
The safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolemia assessed in 114 patients aged 9-17 years treated in two open 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**
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 2%). 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
In a placebo-controlled study including 40 hypercholesterolaemic patients, doses up to 320 mg/day (n=7 per dose group) administered as fluvastatin 80mg XL tablets over two weeks were well tolerated. The experience with overdoses of fluvastatin 80mg XL tablets 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 inhibitors
ATC code: C10AA04

Fluvastatin is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. 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. Evadanin XL exert 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 have 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. Evadanin XL also produces a moderate reduction in triglycerides and a moderate increase in HDL-C. Therapeutic response is well established within 2 weeks, and maximum response is achieved within 4 weeks from treatment initiation and maintained during chronic therapy.

In the Evadanin XL 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).

Children and adolescents with heterozygous familial hypercholesterolemia
The safety and efficacy of fluvastatin in children and adolescent patients aged 9 - 16 years of age with heterozygous familial hypercholesterolemia has been evaluated in 2 open label, uncontrolled clinical trials of 2 years' duration.

114 patients (66 boys and 48 girls) were treated with fluvastatin administered as either fluvastatin capsules 20 mg - 40 mg bid or fluvastatin XL 80 mg extended release tablets using a dose-titration regimen based upon LDL-C response.

The first study enrolled 29 pre-pubertal boys, 9-12 years of age, who had an LDL-C level > 90th percentile for age and one parent with primary hypercholesterolemia and either a family history of premature ischemic heart disease or tendon xanthomas. The mean baseline LDL-C was 226 mg/dL equivalent to 5,8 mmol/L (range: 137 - 354 mg/dL equivalent to 3,6 - 9,2 mmol/L). All patients were
started on fluvastatin capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (40 mg bid) to achieve an LDL-C goal of 96.7 to 123.7 mg/dL (2.5 mmol/L to 3.2 mmol/L).

The second study enrolled 85 male and female patients, 10 to 16 years of age, who had an LDL-C > 190 mg/dL (equivalent to 4.9 mmol/L) or LDL-C > 160 mg/dL (equivalent to 4.1 mmol/L) and one or more risk factors for coronary heart disease, or LDL-C > 160 mg/dL (equivalent to 4.1 mmol/L) and a proven LDL-receptor defect. The mean baseline LDL-C was 225 mg/dL equivalent to 5.8 mmol/L (range: 148 - 343 mg/dL equivalent to 3.8-8.9 mmol/L). All patients were started on fluvastatin capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (fluvastatin 80 mg XL tablet) to achieve an LDL-C goal of < 130 mg/dL (3.4 mmol/L).

In the first study, fluvastatin 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, fluvastatin 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%) following oral administration to fasted volunteers. After oral administration of Evadanin XL and in comparison with the capsules, the absorption rate of fluvastatin is almost 60% slower while the mean residence time of fluvastatin is increased by approximately 4 hours. In a fed state, the drug is absorbed at a reduced rate. 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%.

Distribution
The apparent volume of distribution (Vd/f) 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.

Metabolism
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 metabolised by CYP2C9.

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

Food - Mean AUC and Cmax were increased by 49% and 45% respectively and tmax prolonged when fluvastatin (fluvastatin 80mg XL tablets) was taken with food, compared to fasting state. However, no clinically obvious differences in the lipid-lowering effects and safety are anticipated when Evadanin XL is taken with or without food.
Plasma concentrations of fluvastatin do not vary as a function of age. Mean AUC and $C_{\text{max}}$ were increased by 36% and 44% respectively in females compared to males. However, no clinically obvious differences in the lipid-lowering effects of fluvastatin are anticipated between males and females.

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

### 5.3 Preclinical safety data

Repeat toxicity studies with fluvastatin identified a variety of changes 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 the 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 compounds.

Carcinogenicity studies in rats and mice revealed a low incidence of forestomach squamous papillomas in mice and rats and one carcinoma in rats at the highest dose (18 mg/kg per day escalated to 24 mg/kg per day after 1 year). The forestomach neoplasms reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug. In addition, an increase incidence of thyroid follicular cell neoplasms in male rats given the highest dose of fluvastatin was recorded. This is 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 incidence of hepatic adenomas or carcinomas were observed. *In vitro* and *in vivo* mutagenicity studies revealed no evidence of mutagenicity.

Reproductive toxicity studies indicated that fluvastatin had no adverse effects on fertility or reproductive performance in males or females, nor was it embryotoxic or teratogenic. Late gestational effects at high doses resulted in maternal mortality and fetal and neonatal lethality attributable to exaggerated pharmacological effects of fluvastatin during pregnancy.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- **Tablet core**
  - Carrageenan
  - Magnesium stearate

- **Film-coating**
  - Hydroxypropyl cellulose
  - Hypromellose 6cP
  - Iron oxide yellow (E 172)
  - Titanium dioxide (E 171)
  - Macrogol 8000
  - Iron oxide red (E 172)

#### 6.2 Incompatibilities

Not applicable

#### 6.3 Shelf life

24 months

#### 6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

#### 6.5 Nature and contents of container

Alu/Alu blister consisting of an aluminium coating foil and an aluminium covering foil. *Evadanin XL* come in packs of 10, 20, 30, 50, 100 tablets.

Not all pack sizes may be marketed

#### 6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.
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<tbody>
<tr>
<td>Novopharm Ltd, Suite 23, Park Royal House, 23 Park Royal Road, London NW10 7JH, United Kingdom</td>
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Module 3

PAR Ratiovin/Mithestan/Evadalan XL 80mg Prolonged Release Tablets
UK/I/11181-3/001/DC

Package Leaflet: Information for the User

Ratiovin XL 80 mg prolonged release tablets

Fivasturan

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 be harmful if taken by someone else.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ratiovin XL is and what it is used for
2. How to take Ratiovin XL
3. Possible side effects
4. How to store Ratiovin XL
5. Further information

1. What Ratiovin XL is and what it is used for

The active ingredient in your tablets is fivasturan. This belongs to a group of medicines called antiandrogens. This group of drugs works by reducing the amount of certain hormone (testosterone) the body makes. Testosterone is a type of hormone that helps with the development and function of male sex organs and some male sexual characteristics.

You should be advised to take a low fat meal with this low fat diet during treatment. Other non-pharmacological treatments include exercise and weight reduction, which may also be appropriate after consultation of your doctor. From the results of other studies, your doctor has found that despite your low fat intake, your total cholesterol level is still much higher than your body. You have been prescribed Ratiovin XL, which, together with your diet, will help lower your level. You can also be prescribed with drugs from the family of the hormone (lipid-lowering agents). These drugs are not recommended to be taken in the age group.

2. How to take Ratiovin XL

Do not take Ratiovin XL
- If you are male and have been prescribed fivasturan to or any of the oestrogens of the medicine
- If you are active liver disease, liver function or possibly high liver values.
- If you are pregnant or are planning to become pregnant. If you do become pregnant whilst taking Ratiovin XL tell your doctor.
- If you are breast-feeding.
- If you are a woman of childbearing potential not using effective birth control.
- If you have already experienced generalized muscular disorders

Take special care with Ratiovin XL
- If you regularly consume large amounts of alcohol.
- If you have any kidney problems.
- If you have undergone thyroid gland (hypothyroidism).
- If you have a history of liver disease. Liver function tests will normally be done before starting Ratiovin XL. When the dose is increased and at various intervals during treatment, it is important to check for possible effects.
- If you have severe respiratory failure.
- If you have any muscular disorders affecting either yourself or another member of your family.
- If you have had previous muscular problems during treatment with other sphincter muscle relaxants (e.g. "other" or "other" medicines).
- If any of the above apply to you, your doctor may adjust your dose before and possibly during your Ratiovin XL treatment. This should be done in consultation with tests to predict your risk of muscular-related side effects. In a small number of cases, this side effect may appear as early as 30 years in order to determine your risk of muscle-related side effects.

Using other medicines
Some medicines can interfere with your treatment or blood levels of these drugs you are currently taking, so make sure to check with your doctor or pharmacist before taking any other medicines whether prescribed by a doctor or bought by you over the counter. In particular, tell your doctor if you are taking any of the following:
- Anticoagulants (an antiplatelet drug), the combination may result in an increased risk of developing muscle problems.
- Drugs to prevent blood clotting (e.g. warfarin). The combination may result in an increased risk of developing muscle problems.
- Blood-thinning drugs such as aspirin or clopidogrel (e.g. aspirin or clopidogrel). The combination may result in an increased risk of developing muscle problems.
- Fibrates, the combination may result in an increased risk of developing muscle problems.
- Antidepressants (e.g. citalopram), the combination may result in an increased risk of developing muscle problems.
- Anticonvulsants (e.g. phenobarbital), the combination may result in an increased risk of developing muscle problems.
- Antipsychotics (e.g. haloperidol), the combination may result in an increased risk of developing muscle problems.
- Glucocorticoids (e.g. prednisolone), the combination may result in an increased risk of developing muscle problems.
- Non-steroidal anti-inflammatory drugs (e.g. diclofenac or ibuprofen), the combination may result in an increased risk of developing muscle problems.
- Steroids (e.g. prednisolone), the combination may result in an increased risk of developing muscle problems.

3. How to take Ratiovin XL

Always take your tablets exactly as your doctor has told you. You should check with your doctor if you are not sure.

The normal starting dose is 40 mg of fivasturan (1 capsule of Fivasturan 40 mg) daily.

In some patients, with only small increases in cholesterol levels, 20 mg (1 tablet Fivasturan 20 mg) may be adequate to control cholesterol levels. After the cholesterol levels have been checked and are under control (according to your doctor’s instructions), the dose may be increased to 40 mg once daily. If in some patients, the dose may be increased to 80 mg (2 tablets Ratiovin XL) once daily. The maximum recommended dose is 80 mg daily.

If you have undergone heart catheter treatment (percutaneous coronary intervention procedure) in the past, your doctor may prescribe Fivasturan. In this case, the dose is 80 mg daily (1 tablet Ratiovin XL).

Ratiovin XL can be taken at any time of day and should be swallowed whole with a glass of water. Not all the above proposed dosage recommendations are possible with the current formulation.

If you take more Ratiovin XL than you should:
- If you accidentally take too much of your medicine, tell your doctor immediately or go to your nearest casualty department.

If you forget to take Ratiovin XL:
- If you forget to take a dose, just take your next scheduled dose at the correct time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Ratiovin XL:
- To maintain the benefit of your medicine, you should not stop taking Ratiovin XL. The therapeutic effect with a given dose of the drug is achieved within 4 weeks and is maintained with continuous administration.
- If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible Side Effects

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

Serious side effects:
- Serious side effects are rare (affecting less than 1 in 1000 patients) or very rare (affecting less than 1 in 10,000 patients) and lifethreatening or result in significant impairment of function which can be avoided if your doctor stops your treatment with fivasturan as quickly as possible. These side effects have been found with a similar class of drugs (statins).
- If you have unusual tiredness or fever, yellowing of the skin and eyes, darkened urine (signs of hepatitis).

Very rare (affecting less than 1 in 10,000 patients)
- If you have unexplained muscle pain, tenderness or weakness.
- If you have signs of skin reactions such as skin rash, hives, redness, itching, swelling of the face, eyelids, and lips.

Rare (affecting less than 1 in 1,000 patients and more than 1 in 10,000 patients)
- If you have unexplained muscle pain, tenderness or weakness and particularly if at the same time, you feel unwell or have fever. These might be early signs of a potentially severe muscle degeneration which can be avoided if your doctor stops your treatment with fivasturan as quickly as possible. These side effects have also been found with similar drugs of this class (statins).
- If you have unusual tiredness or fever, yellowing of the skin and eyes, darkened urine (signs of hepatitis).
- If you have red or purple skin lesions (signs of blood vessel inflammation).
- If you have red or bloody rash mainly on the face which may be accompanied by fatigue, fever, joint pain, muscle pain (signs of lupus erythematosus-like reaction).
- If you have severe upper stomach pain (signs of inflamed pancreas).

5. How to store Ratiovin XL
- Do not store above 30°C. Store in the original package in order to protect from moisture.

6. Further Information

What Ratiovin XL contains:
- The active substance is: fivasturan. Each tablet contains 80 mg of fivasturan as fivasturan sulphate.

The other ingredients are:

What Ratiovin XL looks like and contents of the pack
- Ratiovin XL are dark yellow, round, biconvex tablets and are packed in Aluminium/Aluminium blister packs.

Each pack of Ratiovin XL contains 20, 28, 30, 50, 60, 90, 100, 490, 490 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Novopharm Ltd, Suite 23, Park Royal House, 29 Park Royal Road, London NW10 7IY.

Manufacturer: Pharmacent, S.A., 60 Derivation str, 153 51, Pallini, Attiki, Greece.

This leaflet was last approved in November 2008.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Mithestan XL 80mg prolonged release tablets
Fluvastatin

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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Mithestan XL is and what it is used for
2. Before you take Mithestan XL
3. How to take Mithestan XL
4. Possible side effects
5. How to store Mithestan XL
6. Further information

1. What Mithestan XL is and what it is used for

The active ingredient in your tablets is fluvastatin. This belongs to lipid lowering medicines. This group of drugs works by reducing the amount of cholesterol your body makes. Cholesterol is a type of fat, which is vital to the normal functioning of the body. If levels of cholesterol in the blood are too high, it can be deposited on the walls of the arteries. There it builds up to form plaques that can eventually block the blood vessel. It is generally accepted that reduction of high cholesterol level in your blood reduces the risk of heart disease.

You should have been advised to take a low fat diet. It is important to continue with this low fat diet during treatment. Other non-pharmacological treatments like exercise and weight reduction may also be appropriate after recommendation of your doctor.

From the results of your blood tests, your doctor has found that despite your low fat diet, you still have too much cholesterol in your blood. You have been prescribed Mithestan XL which, together with your diet, will help lower this level. You can also be prescribed Mithestan XL if other types of fat (apolipoprotein B, triglycerides) are too high in your blood.

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

This is a slow release tablet which spreads the effect of fluvastatin out over the day.
Use in children < 9 years of age is not recommended as fluvastatin hasn’t been tested in the age group.

2. Before you take Mithestan XL

Do not take Mithestan XL
- If you are allergic (hypersensitive) to fluvastatin or to any of the excipients of the medicine.
- If you have active liver disease, liver problems or continually high liver values.
- If you are pregnant, or planning to become pregnant. If you do become pregnant whilst taking Mithestan XL tell your doctor.
- If you are breast-feeding.
- If you are a woman of childbearing potential not using effective birth control
- If you have any currently active generalised muscular disorders

Take special care with Mithestan XL
- If you regularly consume large amounts of alcohol.
- If you have any kidney problems.
- If you have underactive thyroid gland (hypothyroidism)
- If you have a history of liver disease. Liver function tests will normally be done before starting Mithestan XL, when the dose is increased and at various intervals during treatment to check for undesirable effects.
- If you have severe respiratory failure
- If you have any muscular disorders (affecting either yourself or other members of your family).
- If you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other “statin” or “fibrate” medicines)
- If any of the above apply to you, your doctor may need to carry out a blood test before and possibly during your Mithestan XL treatment. These blood tests will be used to predict your risk of muscle-related side effects. A blood test may also be required if you are older than 70 years in order to determine your risk of muscle-related side effects.

Using other medicines

Some medicines can interfere with your treatment or alter blood levels of those drugs you are currently taking, so make sure to check with your doctor or pharmacist before taking any other medication whether prescribed by a doctor or bought by you over the counter. In particular tell your doctor if you are taking any of the following:

- Ciclosporin (an immunosuppressive drug), the combination of Mithestan XL and ciclosporine may result in an increased risk of developing muscle problems.
- drugs to prevent blood clotting (coumarin derivatives such as warfarin), the combination may lead to an increase in the effects of warfarin and cause bleeding,
- other cholesterol lowering drugs such as fibric acid derivatives (e.g. gemfibrozil) or nicotinic acid, the combination may result in an increased risk of developing muscle problems.
- erythromycin (antibiotic), the combination may result in an increased risk of developing muscle problems,
- rifampicin (antituberculosis drug), the combination may result in a reduction in the effects of Mithestan XL
- phenytoin (antiepileptic medication), the combination may result in an increased 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 Mithestan XL which increases the risk of developing muscle problems,
- Mithestan XL 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 amount of glibenclamide in the bloodstream, which may in turn lead to an increased risk of hypoglycaemia (low blood sugar),
- Itraconazole and fluconazole (antifungal drugs).
- Cimetidine/ranitidine/omeprazole. These drugs may increase serum levels of fluvasatin.
- Bile-acid sequestering agents. Mithestan XL 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.
- Colchicines. Concomitant administration of fluvasatin and colchicine may increase the possibility of myopathy.

Taking Mithestan XL with food and drink
- Mithestan XL can be taken at any time of day with or without food and should be swallowed whole with a glass of water.
- Concomitant use of alcohol with fluvasatin should be avoided.

Pregnancy and Breast-feeding
- Do not take Mithestan XL if you are pregnant, planning to become pregnant, or breast feeding. Women of child-bearing age must use effective birth control. If you do become pregnant whilst taking Fluvasatin, stop taking it immediately and tell your doctor.

Driving and using machines
- As there is no information available to suggest that Mithestan XL will affect your ability to drive or to operate machinery, caution is recommended in case of carrying out these activities.

3. How to take Mithestan XL

Always take your tablets exactly as your doctor has told you. You should check with your doctor if you are not sure.
The normal starting dose is 40 mg of Fluvastatin (1 capsule of Fluvastatin 40 mg) daily.

In some patients, with only small increases in cholesterol levels, 20 mg (1 capsule Fluvastatin 20 mg) may be adequate to control cholesterol levels. After that cholesterol levels are checked periodically and the dose adjusted according to the patient’s cholesterol levels. Most patients will require a dose of 20 mg to 40 mg once daily but in some patients, the dose may be increased to 80 mg (1 tablet Mithestan XL) once daily. The maximum recommended daily dose is 80 mg.

If you have undergone heart catheter treatment (percutaneous coronary intervention procedure) in the past, your doctor may prescribe Fluvastatin. In this case, the dose is 80 mg daily (1 tablet Mithestan XL).

Mithestan XL can be taken at any time of day and should be swallowed whole with a glass of water.

Not all the above proposed dosage recommendations are possible with the current formulation.

If you take more Mithestan XL than you should:

If you accidentally take too much of your medicine, tell your doctor immediately or go to your nearest casualty department.

If you forget to take Mithestan XL:

If you forget to take a dose, just take your next scheduled dose at the correct time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Mithestan XL:

To maintain the benefits of your treatment, you should not stop taking Mithestan XL. The therapeutic effect with a given dose of the drug is achieved within 4 weeks and is maintained with continuous administration.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible Side Effects

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

Serious side effects:

Serious side effects are rare (affecting less than 1 in 1000 patients) or very rare (affecting less than 1 in 10,000 patients). The following are all serious side effects. You may need urgent medical attention if you have any of them.
Rare (affecting less than 1 in 1,000 patients and more than 1 in 10,000 patients)
- If you have unexplained muscle pain, tenderness or weakness.
- If you have signs of skin reactions such as skin rash, hives, redness, itching, swelling of the face, eyelids, and lips.

Very rare (affecting less than 1 in 10,000 patients)
- If you have unexplained muscle pain, tenderness or weakness and particularly, if at the same time, you feel unwell or have fever. These might be early signs of a potentially severe muscle degradation which can be avoided if your doctor stops your treatment with fluvastatin as quickly as possible. These side effects have also been found with similar drugs 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 bleed or bruise more easily than normal (signs of decreased number of 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, joint pain, muscle pain (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:
Common (affecting less than 1 in 10 patients):
Difficulty in sleeping including insomnia and nightmares, headache, fatigue, dizziness, stomach discomfort, abdominal pain, constipation, flatulence, diarrhoea, nausea.

Very rare (affecting less than 1 in 10,000 patients): Tingling or numbness of the hands or feet, disturbed or decreased sensations.

Not known: Breathing problems including persistent cough and/or shortness of breath or fever, memory loss, sexual difficulties.

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.

5. How to store Mithestan XL:

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6. Further Information

What Mithestan XL contains:
The active substance is: fluvastatin. Each tablet contains 80 mg of fluvastatin as fluvastatin sodium.
The other ingredients are:
Tablet core: Carageenan, Magnesium stearate
What Mithestan XL looks like and contents of the pack

Mithestan XL are dark yellow, round, biconvex tablets and are packed in Aluminium/Aluminium blisters strips.
Each pack of Mithestan XL contains 10, 20, 30, 50 or 100 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing authorisation holder: Novopharm Ltd, Suite 23, Park Royal House, 23 Park Royal Road, London NW10 7JH
Manufacturer: Pharmathen S.A., 6 Derwenaklon Str, 153 51 Pallini, Attiki, Greece

This medicinal product is authorised in the Member States of the EEA under the following names:
<br/>
<To be completed>
<br/>

This leaflet was last approved in October 2008
PACKAGE LEAFLET: INFORMATION FOR THE USER

Evadanin XL 80mg prolonged release tablets
Fluvastatin

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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Evadanin XL is and what it is used for
2. Before you take Evadanin XL
3. How to take Evadanin XL
4. Possible side effects
5. How to store Evadanin XL
6. Further information

1. What Evadanin XL is and what it is used for

The active ingredient in your tablets is fluvastatin. This belongs to lipid lowering medicines. This group of drugs works by reducing the amount of cholesterol your body makes. Cholesterol is a type of fat, which is vital to the normal functioning of the body.
If levels of cholesterol in the blood are too high, it can be deposited on the walls of the arteries. There it builds up to form plaques that can eventually block the blood vessel. It is generally accepted that reduction of high cholesterol level in your blood reduces the risk of heart disease.

You should have been advised to take a low fat diet. It is important to continue with this low fat diet during treatment. Other non-pharmacological treatments like exercise and weight reduction may also be appropriate after recommendation of your doctor.

From the results of your blood tests, your doctor has found that despite your low fat diet, you still have too much cholesterol in your blood. You have been prescribed Evadanin XL which, together with your diet, will help lower this level. You can also be prescribed with Evadanin XL if other types of fat (apolipoprotein B, triglycerides) are too high in your blood.

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

This is a slow release tablet which spreads the effect of fluvastatin out over the day.
Use in children < 9 years of age is not recommended as fluvastatin hasn't been tested in the age group.

2. Before you take Evadanin XL

Do not take Evadanin XL
- If you are allergic (hypersensitive) to fluvastatin or to any of the excipients of the medicine.
- If you have active liver disease, liver problems or continually high liver values.
- If you are pregnant, or planning to become pregnant. If you do become pregnant whilst taking Evadanin XL tell your doctor.
- If you are breast-feeding.
- If you are a woman of childbearing potential not using effective birth control
- If you have any currently active generalised muscular disorders

Take special care with Evadanin XL

- If you regularly consume large amounts of alcohol.
- If you have any kidney problems.
- If you have underactive thyroid gland (hypothyroidism)
- If you have a history of liver disease. Liver function tests will normally be done before starting Evadanin XL, when the dose is increased and at various intervals during treatment to check for undesirable effects.
- If you have severe respiratory failure
- If you have any muscular disorders (affecting either yourself or other members of your family).
- If you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other "statin" or "fibrate" medicines)
- If any of the above apply to you, your doctor may need to carry out a blood test before and possibly during your Evadanin XL treatment. These blood tests will be used to predict your risk of muscle-related side effects. A blood test may also be required if you are older than 70 years in order to determine your risk of muscle-related side effects.

Using other medicines

Some medicines can interfere with your treatment or alter blood levels of those drugs you are currently taking, so make sure to check with your doctor or pharmacist before taking any other medications whether prescribed by a doctor or bought by you over the counter. In particular tell your doctor if you are taking any of the following:

- ciclosporin (an immunosuppressive drug), the combination of Evadanin XL and ciclosporine may result in an increased risk of developing muscle problems,
- drugs to prevent blood clotting (coumarin derivatives such as warfarin), the combination may lead to an increase in the effects of warfarin and cause bleeding,
- other cholesterol lowering drugs such as fibric acid derivatives (e.g. gemfibrozil) or nicotinic acid, the combination may result in an increased risk of developing muscle problems,
- erythromycin (antibiotic), the combination may result in an increased risk of developing muscle problems,
- rifampicin (antituberculosis drug), the combination may result in a reduction in the effects of Evadanin XL
- phenytoin (antiepileptic medication), the combination may result in an increased 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 Evadanin XL which increases the risk of developing muscle problems,
- Evadanin XL 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 amount of glibenclamide in the bloodstream, which may in turn lead to an increased risk of hypoglycaemia (low blood sugar),
- Itraconazole and fluconazole (antifungal drugs).
- Cimetidine/ranitidine/omeprazole. These drugs may increase serum levels of fluvastatin.
- Bile-acid sequestering agents. Evadanin XL 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.
- Colchicines. Concomitant administration of fluvastatin and colchicine may increase the possibility of myopathy.

**Taking Evadanin XL with food and drink**
- Evadanin XL can be taken at any time of day with or without food and should be swallowed whole with a glass of water.
- Concomitant use of alcohol with fluvastatin should be avoided.

**Pregnancy and Breast-feeding**
- Do not take Evadanin XL if you are pregnant, planning to become pregnant, or breast feeding. Women of child-bearing age must use effective birth control. If you do become pregnant whilst taking Fluvastatin, stop taking it immediately and tell your doctor.

**Driving and using machines**
- As there is no information available to suggest that Evadanin XL will affect your ability to drive or to operate machinery, caution is recommended in case of carrying out these activities.

**3. How to take Evadanin XL**

Always take your tablets exactly as your doctor has told you. You should check with your doctor if you are not sure.
The normal starting dose is 40 mg of Fluvastatin (1 capsule of Fluvastatin 40 mg) daily.

In some patients, with only small increases in cholesterol levels, 20 mg (1 capsule Fluvastatin 20 mg) may be adequate to control cholesterol levels. After that cholesterol levels are checked periodically and the dose adjusted according to the patient’s cholesterol levels. Most patients will require a dose of 20 mg to 40 mg once daily but in some patients, the dose may be increased to 80 mg (1 tablet Evadanin XL) once daily. The maximum recommended daily dose is 80 mg.

If you have underdone heart catheter treatment (percutaneous coronary intervention procedure) in the past, your doctor may prescribe Fluvastatin. In this case, the dose is 80 mg daily (1 tablet Evadanin XL).

Evadanin XL can be taken at any time of day and should be swallowed whole with a glass of water.

Not all the above proposed dosage recommendations are possible with the current formulation.

If you take more Evadanin XL than you should:
If you accidentally take too much of your medicine, tell your doctor immediately or go to your nearest casualty department.

If you forget to take Evadanin XL:
If you forget to take a dose, just take your next scheduled dose at the correct time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Evadanin XL:
To maintain the benefits of your treatment, you should not stop taking Evadanin XL. The therapeutic effect with a given dose of the drug is achieved within 4 weeks and is maintained with continuous administration.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible Side Effects
Like all medicines, Evadanin XL can cause side effects, although not everybody gets them.

Serious side effects:

Serious side effects are rare (affecting less than 1 in 1000 patients) or very rare (affecting less than 1 in 10,000 patients). The following are all serious side effects. You may need urgent medical attention if you have any of them.
Rare (affecting less than 1 in 1,000 patients and more than 1 in 10,000 patients)

- If you have unexplained muscle pain, tenderness or weakness.
- If you have signs of skin reactions such as skin rash, hives, redness, itching, swelling of the face, eyelids, and lips.

Very rare (affecting less than 1 in 10,000 patients)

- If you have unexplained muscle pain, tenderness or weakness and particularly, if at the same time, you feel unwell or have fever. These might be early signs of a potentially severe muscle degradation which can be avoided if your doctor stops your treatment with fluvastatin as quickly as possible. These side effects have also been found with similar drugs 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 bleed or bruise more easily than normal (signs of decreased number of 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, joint pain, muscle pain (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:

Common (affecting less than 1 in 10 patients):
Difficulty in sleeping including insomnia and nightmares, headache, fatigue, dizziness, stomach discomfort, abdominal pain, constipation, flatulence, diarrhoea, nausea.

Very rare (affecting less than 1 in 10,000 patients): Tingling or numbness of the hands or feet, disturbed or decreased sensations.

Not known, Breathing problems including persistent cough and/or shortness of breath or fever, memory loss, sexual difficulties.

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.

5. How to store Evadanin XL:

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6. Further Information

What Evadanin XL contains:
The active substance is: fluvastatin. Each tablet contains 80 mg of fluvastatin as fluvastatin sodium.
The other ingredients are:
Tablet core: Carageenan, Magnesium stearate
Films-coating: Hydroxypropyl cellulose, Hypromellose 6cP, Iron oxide yellow, Titanium dioxide, Macrogol 8000, Iron oxide red
What Evadanin XL looks like and contents of the pack

Evadanin XL are dark yellow, round, biconvex tablets and are packed in Aluminium/Aluminium blisters strips. Each pack of Evadanin XL contains 10, 20, 30, 50 or 100 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing authorisation holder: Novopharm Ltd, Suite 23, Park Royal House, 23 Park Royal Road, London NW10 7JH

Manufacturer: Pharmathen S.A., 6 Dervenakion str, 153 51 Pallini, Attiki, Greece

This medicinal product is authorised in the Member States of the EEA under the following names:

< [To be completed] >

This leaflet was last approved in October 2008
Module 4
Labelling
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>
Carton box

1. NAME OF THE MEDICINAL PRODUCT

*Mithestan XL* 80mg prolonged release tablets
Fluvastatin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80mg fluvastatin (as fluvastatin sodium).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 Prolonged release tablets
20 Prolonged release tablets
30 Prolonged release tablets
50 Prolonged release tablets
100 Prolonged release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from moisture.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novopharm Ltd, Suite 23, Park Royal House, 23 Park Royal Road, London NW10 7RH, United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

ML 13641.0005

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

*Mithestan XL 80mg prolonged release tablets*
<table>
<thead>
<tr>
<th><strong>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</strong></th>
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<tbody>
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<td>Blister</td>
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<td><em>Mithestan</em> XL 80mg prolonged release tablets</td>
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<tr>
<td>Fluvastatin</td>
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<th>4. <strong>BATCH NUMBER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>5. <strong>OTHER</strong></th>
</tr>
</thead>
</table>
1. **NAME OF THE MEDICINAL PRODUCT**

*Evadanin* XL 80mg prolonged release tablets

Fluvastatin

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 80mg fluvastatin (as fluvastatin sodium).

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

- 10 Prolonged release tablets
- 20 Prolonged release tablets
- 30 Prolonged release tablets
- 50 Prolonged release tablets
- 100 Prolonged release tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

Exp: MM/YYYY

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 30°C. Store in the original package in order to protect from moisture.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novopharm Ltd, Suite 23, Park Royal House, 23 Park Royal Road, London NW10 7JH, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

ML: 18641/0006

13. BATCH NUMBER

Lot: 

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

_Evadanin XL_ 80mg prolonged release tablets
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blister</strong></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

*Evadanin XL 80mg prolonged release tablets*

Fluvastatin

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Novopharm Ltd

3. **EXPIRY DATE**

Exp: MM/YYYY

4. **BATCH NUMBER**

Lot:

5. **OTHER**
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the UK, Austria, Czech Republic, Finland, Germany, Hungary, Italy, Luxembourg, the Netherlands, Portugal, Slovak Republic, Spain and Sweden agreed to grant marketing authorisations for the medicinal products Ratiovin/Mithestan/Evadanin XL 80mg Prolonged Release Tablets (Day210 – 21st September 2008). This product was assessed via the Decentralised Procedure (UK/H/1181-3/001/DC), with the UK as Reference Member State. A subsequent national licence was granted in the UK on 19th November 2008.

The product is a prescription-only medicine.

This is an application made under Article 10.1 of 2001/83 EC, as amended, claiming to be generic medicinal products to Lescol XL 80mg Prolonged Release Tablets (Novartis Hellas, SA), which has been licensed in at least one European Union state for at least 10 years ago.

The product contains the active ingredient fluvastatin sodium and is indicated as an adjunct to diet for the reduction of elevated total cholesterol and low-density lipoprotein cholesterol levels, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate in patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson Types IIa and IIb). It is also indicated for the secondary prevention of coronary events in patients with coronary heart disease after percutaneous coronary intervention.

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. 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.

No new preclinical studies were conducted, which is acceptable given that the application is claiming to be a generic medicinal product to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product to a product that has been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The decentralised procedure was completed at Day 210 (21st September 2008), with the reference member state and all concerned member states agreeing that the licence was approvable. The national phase of the decentralised procedure was completed in the UK on 19th November 2008.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ratiovin/Mithestan/Evadanin XL 80mg Prolonged Release Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Fluvastatin sodium</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>HMG CoA reductase inhibitors (C10AA04)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>80mg prolonged release tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1181-3/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>UK/H/1181/001/DC: Austria, Czech Republic, Finland, Germany, Hungary, Italy, Luxembourg, the Netherlands, Portugal, Slovak Republic, Spain, Sweden. UK/H/1182/001/DC: Germany UK/H/1183/001/DC: Germany</td>
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<td>Marketing Authorisation Number(s)</td>
<td>PL 18641/0004-6</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Novopharm Ltd, Suite 23, Park Royal House, 23 Park Royal Road, London NW10 7JH, United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Fluvastatin sodium
Chemical Name: 6-Heptanoic acid, 7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-, monosodium salt, \((R^*,S^*-(E))-(\pm)\)
Sodium \((\pm)-(3R^*,5S^*,6E)-7-[3-(p-fluorophenyl)-1-isopropylindol-2-yl]-3,5-dihydroxy-6-heptanoate\)
CAS Registry No: 93957-55-2
Molecular Formula: \(C_{24}H_{25}FNNaO_4\)
Structure:

![Structure of Fluvastatin sodium](image)

Molecular Weight: 433.46
Appearance: White to pale-yellow, brownish–pale yellow or reddish–pale yellow, hygroscopic powder that is soluble in water, ethanol and methanol.

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 sodium. 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 specifications have been provided for all packaging used. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been provided to support a retest period of 24 months when stored in the proposed packaging at between 2 and 8°C. Suitable post approval commitments have been given to provide more data from these and other stability studies as and when they become available.
**Medicinal Product**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients carrageenan, magnesium stearate and Opadry Yellow (which is composed of hydroxypropyl cellulose, hypromellose 6cP, iron oxide yellow, titanium dioxide, Macrogol 8000 and iron oxide red).

All excipients used comply with respective European Pharmacopoeia monographs, with the exception of carrageenan (which is controlled to a US Pharmacopoeia monograph) and Opadry Yellow (which is controlled to a suitable in-house specification). Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin.

**Pharmaceutical Development**

The applicant has provided a suitable product development rationale and data. Comparable dissolution and impurity profiles have been provided for batches of the proposed product versus reference product.

**Manufacture**

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and has shown satisfactory results.

**Control of Drug Product**

The finished product specification proposed is acceptable and provides an assurance of the quality of the finished product. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specification.

Satisfactory data on the characterisation of impurities have been provided.

**Reference Standards or Materials**

Certificates of analysis for all reference standards used have been provided and are satisfactory.

**Container Closure System**

The finished product is packaged in aluminium/aluminium blisters in the following pack sizes:

- Ratiovin XL 80mg Prolonged Release Tablets (UK/H/1181/001/DC): 20, 28, 30, 50, 56, 60, 90, 98, 100 and 490 tablets.
- Mithestan XL 80mg Prolonged Release Tablets (UK/H/1182/001/DC): 10, 20, 30, 50 and 100 tablets.
- Evadanin XL 80mg Prolonged Release Tablets (UK/H/1183/001/DC): 10, 20, 30, 50 and 100 tablets.

**Stability of the Drug Product**

Stability data provided to support a shelf-life of 24 months, with the storage instructions “Do not store above 30°C” and “Store in the original package in order to protect from moisture”.

**Bioequivalence/Bioavailability**

Certificates of analysis have been provided for batches of test and reference product used in the bioequivalence studies.
SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL 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.

Not all pack sizes are to be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups to the regulatory authorities for assessment before marketing any pack size.

CONCLUSION
It is recommended that marketing authorisations are granted for these applications.

III.2 PRE-CLINICAL ASPECTS
Pharmacodynamic, pharmacokinetic and toxicological properties of fluvastatin are well-known. As fluvastatin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required.

The preclinical expert report has been written by an appropriately qualified person and is a suitable summary of the preclinical aspects of the dossier.

No environmental risk assessment has been provided for these applications. However, the marketing authorisation holder has provided a suitable justification for its absence, in line with the Guidelines on Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY
Pharmacodynamics
No new pharmacodynamic data have been provided and none are required for an application of this type.

Pharmacokinetics
With the exception of the bioequivalence study, no new pharmacokinetic data have been provided and none are required for an application of this type.

EFFICACY
Three bioequivalence studies have been provided for this application, which is appropriate for a modified-release form. All studies were carried out in accordance with current Good Clinical Practice (GCP).

Study 1:
A single-dose, randomised, open-label, crossover, two-period study was conducted comparing the plasma pharmacokinetics of the proposed product (Ratiovin/Mithestan/Evadanin XL 80mg Prolonged Release Tablets) versus the reference product (Lescol XL 80mg Tablets) in healthy volunteers in a fasted state. Blood samples were collected at pre-dose and up to 36 hours post dose, with at least a 7-day washout period between doses.
The results for the main pharmacokinetic parameters are presented below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} ng/ml/h</th>
<th>AUC_{0-\infty} ng/ml/h</th>
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<th>t_{max} h</th>
<th>T_{1/2} h</th>
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</thead>
<tbody>
<tr>
<td>Test</td>
<td>283.015(163.487)</td>
<td>318.085(170.046)</td>
<td>72.676(38.305)</td>
<td>3.00</td>
<td>5.30(3.59)</td>
</tr>
<tr>
<td>Reference</td>
<td>271.503(219.753)</td>
<td>313.200(253.358)</td>
<td>62.496(37.006)</td>
<td>3.00</td>
<td>8.17(5.23)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)*

|                 | 107.117 (99.38-115.45) | 105.641 (96.235-115.966) | 115.57 (107.08-124.74) |

CV (%)

|                 | 27.467 | 27.926 | 27.991 |

AUC_{0-\infty} area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration (median)
T_{1/2} half-life

*ln-transformed values

---

**Study 2:**

A single-dose, randomised, open-label, crossover, two-period study was conducted comparing the plasma pharmacokinetics of the proposed product (Ratiovin/Mithestan/Evadanin XL 80mg Prolonged Release Tablets) versus the reference product (Lescol XL 80mg Tablets) in healthy volunteers in a fed (high fat) state. Blood samples were collected at pre-dose and up to 36 hours post dose, with at least a 7-day washout period between doses.

The results for the main pharmacokinetic parameters are presented below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} ng/ml/h</th>
<th>AUC_{0-\infty} ng/ml/h</th>
<th>C_{max} ng/ml</th>
<th>t_{max} h</th>
<th>T_{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>588.326 (265.196)</td>
<td>595.277 (266.377)</td>
<td>197.8311</td>
<td>5.00</td>
<td>3.10(1.33)</td>
</tr>
<tr>
<td>Reference</td>
<td>597.527 (367.400)</td>
<td>604.311 (369.142)</td>
<td>206.783 (322.485)</td>
<td>4.50</td>
<td>3.86(2.32)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)*

|                 | 102.70 (96.99-108.75) | 102.695 (96.990-108.748) | 98.98(90.31-108.48) |

CV (%)

|                 | 22.1 | 21.8 | 36.1 |

*ln-transformed values

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**Study 3:**

A multiple-dose, randomised, open-label, crossover, two-period study was conducted comparing the plasma pharmacokinetics of the proposed product (Ratiovin/Mithestan/Evadanin XL 80mg Prolonged Release Tablets) versus the reference product (Lescol XL 80mg Tablets) in healthy volunteers in a fasted state. Blood samples were collected at pre-dose, within 5 minutes prior of the fourth and fifth administrations, and within 5 minutes of the sixth administration and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours following the final drug administration.
The results for the main pharmacokinetic parameters are presented below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) ng/ml/h</th>
<th>( C_{\text{max}} ) ng/ml</th>
<th>( C_{\text{min}} ) h</th>
<th>PTF% h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>330.111</td>
<td>73.988</td>
<td>2.401</td>
<td>543.16</td>
</tr>
<tr>
<td>Reference</td>
<td>328.849</td>
<td>70.109</td>
<td>3.035</td>
<td>534.47</td>
</tr>
</tbody>
</table>

*Ratio (90% CI) | 101.50 (93.62-110.04) | 104.60 (96.29-113.63) | 81.16 (71.15-99.55) | 103.86 (96.66-111.59) |

CV (%) | 23.48 | 44.60 | 51.4 | 23.7 |

\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to infinity
\( \text{AUC}_{\infty} \) area under the plasma concentration-time curve from time zero to infinity
\( C_{\text{max}} \) maximum plasma concentration
\( T_{\text{max}} \) time for maximum concentration
\( T_{1/2} \) half-life

The comparative analyses of the kinetic parameters were within the bioequivalence intervals for AUC and \( C_{\text{max}} \) for all studies. Thus, bioequivalence has been demonstrated between the test and reference products.

SAFETY
No new safety issues have been identified.

EXPERT REPORT
A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified physician.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
This is satisfactory and consistent with the SPC for the reference product.

PATIENT INFORMATION LEAFLET (PIL)
This is satisfactory and consistent with the SPC.

LABELLING
These are satisfactory.

CONCLUSION
There are no clinical objections to the grant of marketing authorisations for these applications. Bioequivalence has been successfully shown between these products and the reference product.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and packaging are satisfactory and consistent with those for the reference product.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Ratiovin/Mithestan/Evadanin XL 80mg Prolonged Release Tablets 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 an application of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s tablets and the originator products Lescol XL 80mg Tablets (Novartis Hellas, SA).

No new or unexpected safety concerns arise from this application.

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

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with fluvastatin sodium is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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