Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

STEFLUVIN XL 80MG PROLONGED-RELEASE TABLETS

UK/H/1090/001/DC
UK licence no: PL 17277/0014

Pharmathen Pharmaceuticals SA

Medicines and Healthcare products Regulatory Agency

LAY SUMMARY

On 24th September 2008, the MHRA granted Pharmathen Pharmaceuticals SA a Marketing Authorisation (licence) for the medicinal product Stefluvin XL 80mg Prolonged Release Tablets (PL 17277/0014). This prescription only medicine (POM) belongs to a group of medicines 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.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Stefluvin XL 80mg Prolonged Release Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Stefluvin XL 80mg Prolonged Release Tablets
Type of Application	Article 10.1, Generic Application
Active Substance	Fluvastatin sodium
Form	Prolonged-Release Tablets
Strength	80mg
MA Holder	Pharmathen Pharmaceuticals SA, 6 Dervenakion Str., 153 51 Pallini, Attiki, Greece
Reference Member State	United Kingdom
Concerned Member States	Spain, Germany, Portugal
Procedure Number	UK/H/1090/001/DC
Timetable	Day 210 – 5th August 2008

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Stefluvin XL 80mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

84.2mg fluvastatin sodium corresponding to 80mg fluvastatin.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged release tablet.

Stefluvin 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

Stefluvin XL is indicated as an adjunct to diet for the reduction of elevated total cholesterol (total-C) and low-density lipoprotein cholesterol (LDL-C) 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).

Stefluvin 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 Stefluvin 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 Stefluvin 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.

Stefluvin 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 Stefluvin XL is maintained with prolonged administration.

Stefluvin XL is efficacious in monotherapy or in combination with bile acid sequestrants. When Stefluvin 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 Stefluvin 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 remains unchanged in patients with mild to severe renal

insufficiency (Creatinine Clearance < 60 mL/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
Stefluvin 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
Fluvastatin is not recommended for use in children and adolescents under the age of 18 years due to insufficient data on safety and efficacy (see section 4.4)

4.3 Contraindications

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

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

Patients with myopathy.

During pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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

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

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

Fluvastatin is not recommended for use in children and adolescents under the age of 18 years due to insufficient data on safety and efficacy (see section 4.2).

Skeletal muscle
With Stefluvin 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 pre-disposing factors for rhabdomyolysis and its complications. A creatine kinase level should be measured before starting fluvastatin treatment in the following situations:
• Renal impairment
• Hypothyroidism
• Personal or familial history of hereditary muscular disorders
• Previous history of muscular toxicity with a statin or fibrate
• Alcohol abuse
• In elderly (age> 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK-levels are significantly elevated at baseline > 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 cyclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. Minimal data exist to support the efficacy or safety of Stefluvin XL in combination with nicotinic acid, its derivatives, fibrates or cyclosporin. Stefluvin 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 (Stefluvin 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 Stefluvin 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 (Cmax) of fluvastatin by about 84% and 44% respectively. Caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

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

Antipyrine - Administration of fluvastatin 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. Stefluvin 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- Stefluvin 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 and this combination should be avoided whenever possible.

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, H_2-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

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. As small amounts of fluvastatin have been found in rat milk, Stefluvin 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. Dizziness and fatigue have been reported as side effects. 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.

System Organ Classes	**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**	**Not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders					Thrombocytopenia	
Nervous system disorders		Headache, dizziness			Paraesthesia, dysaesthesia, hypoaesthesia, peripheral neuropathy – also known to be associated with hypolipidaemic disorders	Memory loss
Gastrointestinal disorders		Dyspepsia, abdominal pain, nausea, constipation, flatulence, diarrhoea			Acute pancreatitis	
Respiratory, thoracic and mediastinal disorders						Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)
Skin and subcutaneous tissue disorders				Hypersensitivity reactions such as rash, urticaria.	Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema	
Musculoskeletal and connective tissue disorders				Myalgia, muscle weakness, myopathy, muscle tenderness	Rhabdomyolysis, myositis, lupus erythematosus-like reactions	
Vascular disorders					Vasculitis	
General disorders and administration site conditions		Fatigue				
Hepatobiliary disorders					Hepatitis	
Psychiatric disorders		Sleep disturbances, including insomnia and nightmares				Sexual dysfunction, depression

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

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

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

5.2 Pharmacokinetic properties

Fluvastatin is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. Fluvastatin is absorbed rapidly and completely (98%) following oral administration to fasted volunteers. After oral administration of fluvastatin 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%. The apparent volume of distribution ($V_z f$) 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.

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.

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 fluvastatin 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.

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 increased 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
Titanium dioxide
Macrogol 8000
Iron oxide red

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. Stefluvin XL come in packs of 10, 14, 20, 28, 30, 42, 50, 56, 98, 100, 300 tablets. The pack of 300 tablets is intended for hospital use.

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

8 MARKETING AUTHORISATION NUMBER(S)
PL 17277/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/09/2008

10 DATE OF REVISION OF THE TEXT
24/09/2008

Module 3

STEFLUVIN XL 80MG PROLONGED RELEASE TABLETS (FLUVASTATIN)

PACKAGE LEAFLET: INFORMATION FOR THE USER

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 STEFLUVIN 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.

You should have been advised to take a low fat diet. It is important to continue with this low fat diet during treatment.

This is a slow release tablet which spreads the effect of fluvastatin out over the day.

Use in children and adolescents < 18 years of age is not recommended as fluvastatin has not been tested in the age group.

2. BEFORE YOU TAKE STEFLUVIN XL

Do not take Stefluvin XL
- If you are allergic (hypersensitive) to fluvastatin or to any of the excipients of the medicine.
- If you have active liver problems or persistent raised liver blood test results.
- If you have any muscular disorders (affecting either yourself or other members of your family), previous muscular problems during treatment with other lipid-lowering medicines (e.g. other "statin" or "fibrate" medicines).
- If you are pregnant, or planning to become pregnant. If you do become pregnant whilst taking Stefluvin XL tell your doctor.
- If you are breast-feeding.

Take special care with Stefluvin XL
- If you have a history of heavy alcohol consumption.
- If you have any kidney problems.
- If you have underactive thyroid gland (hypothyroidism)
- If you have had a disease that may have affected your liver. Your doctor will usually carry out liver function tests before you start therapy and periodically thereafter as slight increases in liver enzymes have occurred in a small number of patients on Stefluvin XL therapy.
- If you have severe respiratory failure
- If you are less than 18 years of age.
- Your doctor may need to carry out a blood test before and possibly during your Stefluvin 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 Stefluvin XL and ciclosporin 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 Stefluvin 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 Stefluvin XL which increases the risk of developing muscle problems,
- Stefluvin 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. Stefluvin 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 Stefluvin XL with food and drink
- Stefluvin XL can be taken at any time of day and be swallowed whole with a glass of water.
- Concomitant use of alcohol with fluvastatin should be avoided.

Pregnancy and Breast-feeding
- Do not take Stefluvin XL if you are pregnant, planning to become pregnant, or breast feeding. If you do become pregnant whilst taking fluvastatin, tell your doctor.

Driving and using machines
- There is no information available about how Stefluvin XL might affect your ability to drive or use machinery. However, some patients who take this medicine feel dizzy or tired. If this happens do not drive or use machines or tools.

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3. HOW TO TAKE STEFLUVIN XL

You should always take your tablets exactly as advised by your doctor or pharmacist. You may have been started on a lower dose of fluvastatin. Stefluvin XL 80mg should be taken once a day. This is the highest recommended dose per day of fluvastatin.

Do not chew

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Stefluvin 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.
- 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 have signs of skin reactions such as skin rash, hives, redness, itching, swelling of the face, eyelids, and lips.
- 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 erythematous-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, joint pain.
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 you doctor or your pharmacist.

5. HOW TO STORE STEFLUVIN XL :

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

6. FURTHER INFORMATION

What Stefluvin XL contains:
The active substance is: fluvastatin. Each tablet contains 80 mg of fluvastatin as fluvastatin sodium.
The other ingredients are:
Tablet core: Carrageenan, Magnesium stearate
Film-coating: Hydroxypropyl cellulose, Hypromellose 6cP, Iron oxide yellow,
Titanium dioxide, Macrogol 8000, Iron oxide red

What Stefluvin XL looks like and contents of the pack
Stefluvin XL are dark yellow, round, biconvex tablets and are packed in
Aluminium/Aluminium blisters strips.
Each pack of Stefluvin XL contains 10 or 14 or 20 or 28 or 30 or 42 or 50 or 56 or 98 or 100 or 300 tablets.
Not all pack sizes may be marketed.

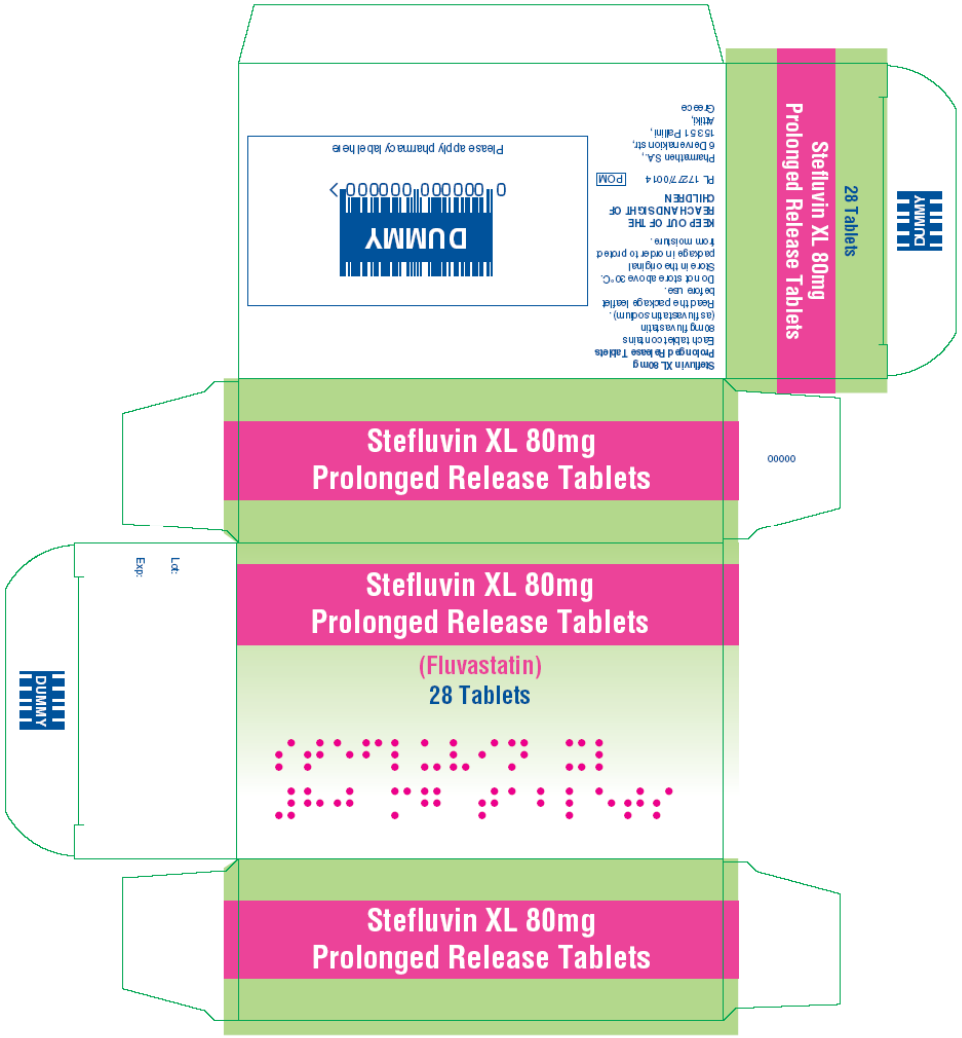
Marketing Authorisation Holder and Manufacturer

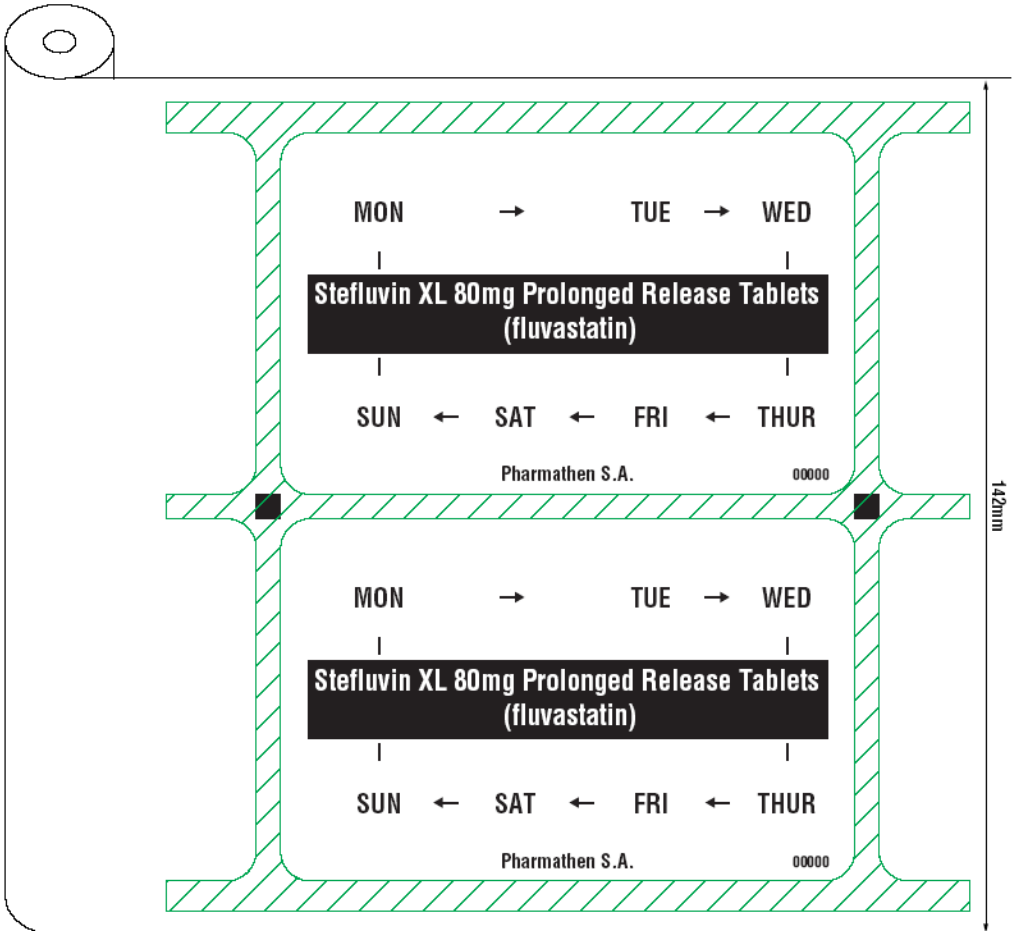
The marketing authorisation holder is:
Pharmathen S.A., 6 Dervenakion str, 153 51 Pallini, Attiki, Greece

The manufacturer is:
Pharmathen S.A., 6 Dervenakion str, 153 51 Pallini, Attiki, Greece

This leaflet was last revised in July 2008.

Module 4
Labelling

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Stefluvin XL 80mg Prolonged Release Tablets
(fluvastatin)
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Pharmathen S.A. 00000
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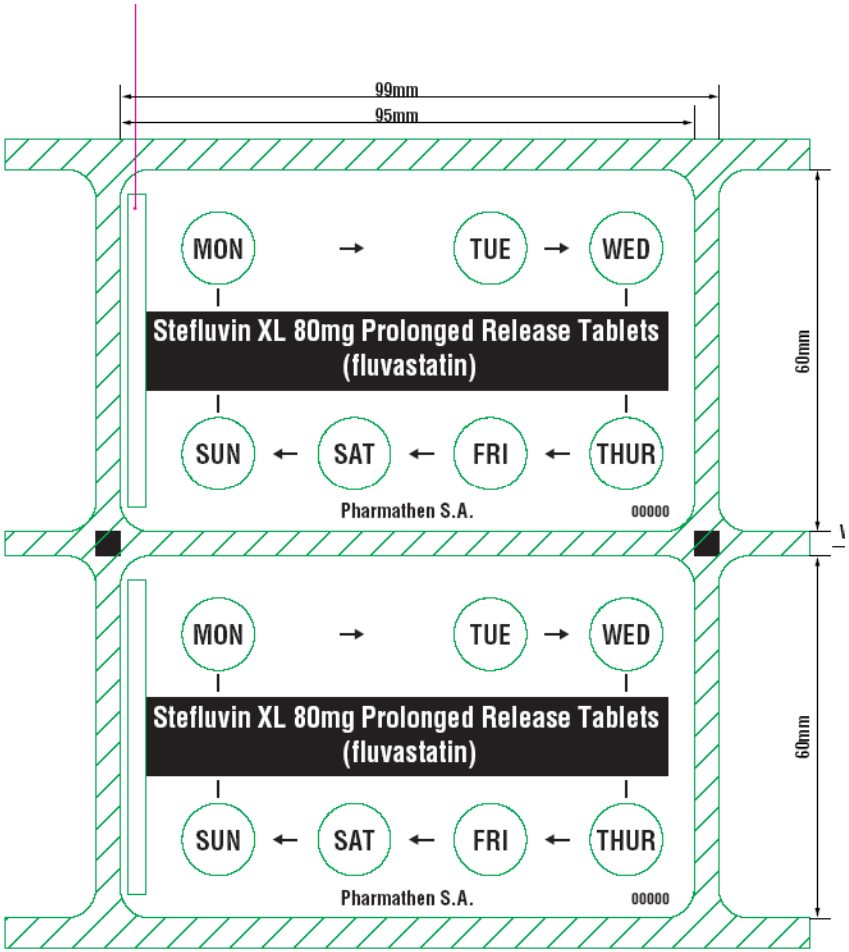
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MON → TUE → WED
Stefluvin XL 80mg Prolonged Release Tablets
(fluvastatin)
SUN ← SAT ← FRI ← THUR
Pharmathen S.A. 00000
60mm
60mm

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK, Spain, Germany and Portugal agreed to grant marketing authorisations for the medicinal product Stefluvin XL 80mg Prolonged Release Tablets on 5th August 2008. This product was assessed by the Decentralised Procedure (UK/H/1090/001/DC), with the UK as Reference Member State. A subsequent national licence was granted in the UK on 24th September 2008.

The product is a prescription-only medicine.

This is an application made under Article 10.1 of 2001/83 EC, as amended, for a generic medicinal product to Lescol XL 80mg Prolonged Release Tablets (Novartis Hellas, SA), which was granted a licence in at least one European Union state 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).

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 (5th August 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 24th September 2008.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Stefluvin XL 80mg Prolonged Release Tablets
Name(s) of the active substance(s) (INN)	Fluvastatin sodium
Pharmacotherapeutic classification (ATC code)	HMG CoA reductase inhibitors (C10A A04)
Pharmaceutical form and strength(s)	80mg prolonged release tablets
Reference numbers for the Decentralised Procedure	UK/H/1090/001/DC
Reference Member State	United Kingdom
Member States concerned	Spain, Germany and Portugal
Marketing Authorisation Number(s)	PL 17277/0014
Name and address of the authorisation holder	Pharmathen S.A., 6 Dervenakion Str, 153 51 Pallini, Attiki, Greece

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

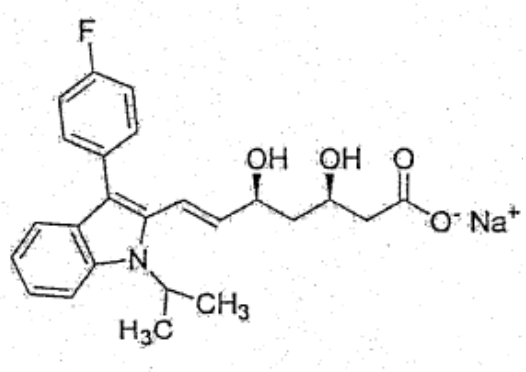
INN: Fluvastatin sodium

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



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.

The active substance is packaged in double transparent low-density polyethylene bags, which are flushed with high purity nitrogen before heat sealing. These are then packed in triple laminate aluminium bags with silica gel to protect them from moisture and light. These are also heat sealed before being packed into high-density polyethylene drums. Specifications for all packaging used have been provided and are satisfactory. 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.

P 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 Pharmacopoiea 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 pack sizes of 7, 28, 56 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.

CONCLUSION
It is recommended that a marketing authorisation is granted for this application.

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.

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 (Stefluvin 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:

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	283.015(163.487)	318.085(170.046)	72.676(38.305)	3.00	5.30 (3.59)
Reference	271.503(219.753)	313.200(253..358)	62.496(37.006)	3.00	8.17(5.23)
***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 (Stefluvin 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:

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	588.326 (265.196)	595.277 (266.377)	197.837(115.811)	5.00	3.10 (1.33)
Reference	597.527(367.400)	604.311 (369.142)	206.783(132.485)	4.50	3.86(2.32)
***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		

$AUC_{0-\infty}$ 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
$T_{1/2}$ half-life

**ln-transformed values*

Study 3:

A multiple-dose, randomised, open-label, crossover, two-period study was conducted comparing the plasma pharmacokinetics of the proposed product (Stefluvin 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:

Treatment	AUC_{0-t} ng/ml/h	C_{max} ng/ml	C_{min} h	PTF% h
Test	330.111	73.988	2.401	543.16
Reference	328.849	70.109	3.035	534.47
***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

$AUC_{0-\infty}$ 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
$T_{1/2}$ half-life

The comparative analyses of the kinetic parameters were within the bioequivalence intervals for AUC and C_{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 authorisation for this application. Bioequivalence has been successfully shown between this product 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 Stefluvin 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

Date submitted	Application type	Scope	Outcome