

Public Assessment Report
Decentralised Procedure

Fluvastatin 20mg Capsules
Fluvastatin 40mg Capsules

UK/H/977/01-02/DC
UK licence nos: PL 00289/0997-8

TEVA UK Limited

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted TEVA UK Limited Marketing Authorisations (licences) for the medicinal products Fluvastatin 20mg and 40mg Capsules. These are prescription-only medicines.

Fluvastatin works by reducing levels of fats in the blood. These types of fat include cholesterol and triglycerides. Fluvastatin is used if a low fat diet has not reduced the levels of these fats enough.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Fluvastatin 20mg and 40mg Capsules outweighs the risks, hence Marketing Authorisations have been granted.

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Module 1

Product Name	Fluvastatin 20mg and 40mg Capsules
Type of Application	Generic, Article 10.1
Active Substance	Fluvastatin sodium
Form	Capsules
Strength	20mg and 40mg
MA Holder	TEVA UK Ltd
RMS	UK
CMS	Austria, Belgium, Czech Republic, Denmark, Germany, Greece, Finland, France, Hungary, Ireland, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden and Slovakia.
Procedure Number	UK/H/977/01-02/DC
Timetable	Day 205 – 16/05/2008

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fluvastatin 20mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One 20 mg capsule contains 20 mg fluvastatin (as fluvastatin sodium).

Excipient:

99.6 mg lactose monohydrate/capsule

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

The 20 mg capsules have an ivory opaque body and pink opaque cap marked 93/7442, and are filled with an off-white to yellowish powder with small agglomerates.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluvastatin is indicated as an adjunct to diet for the reduction of elevated total cholesterol (total-C) and low-density lipoprotein cholesterol (LDL-C), when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate in adults with primary hypercholesterolaemia (heterozygous variant) and mixed dyslipidaemia (Fredrickson types IIa and IIb).

Fluvastatin is also indicated for the secondary prevention of major adverse cardiac events (cardiac death, non-fatal myocardial infarction and coronary revascularisation) after coronary transcatheter therapy).

4.2 Posology and method of administration

Prior to initiating treatment with fluvastatin, the patient should be placed on a standard cholesterol-lowering diet, which should be continued during treatment.

The recommended starting dose is 20 mg or 40 mg once daily. a dose of 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 daily (one 40 mg capsule twice daily), individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum recommended daily dose is 80 mg.

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

The capsules should be taken in the evening or at bedtime without regard to meals and should be swallowed whole with a glass of water.

The maximum lipid-lowering effect with a given dose of the substance is achieved within 4 weeks.

Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of fluvastatin is maintained with prolonged administration.

Fluvastatin is efficient in monotherapy. Data exist to support the efficacy and safety of fluvastatin in combination with nicotinic acid, cholestyramine or fibrates (see section 4.5).

When fluvastatin 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 substance to the resin.

Children and adolescents

There is no experience with the use of fluvastatin in individuals less than 18 years of age. The product should not be used in this group of patients.

Elderly

There is no evidence of reduced tolerability or altered dosage requirements in elderly patients thus, no dose adjustment is required in such patients.

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. 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.

Impaired liver function

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

4.3 Contraindications

Fluvastatin is contraindicated:

- in patients with hypersensitivity to fluvastatin or to any of the excipients.
- in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see sections 4.2, 4.4 and 4.8).
- in patients with myopathy
- during pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Liver function

As with other lipid-lowering agents, it is recommended that liver function tests be performed before the initiation of treatment, at 12 weeks following initiation of treatment or elevation in dose, and periodically thereafter in all patients. Patients whose levels increase in response to the substance should be monitored particularly closely, with immediate repetition of the measurement followed by more frequent measurements. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceed 3 times the upper limit of normal (ULN) and persist, therapy should be discontinued. In very rare cases, possibly substance-related hepatitis was observed that resolved upon discontinuation of treatment.

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

Skeletal muscle

With fluvastatin, 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 promptly report unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.

Creatine kinase measurement

There is no current evidence to require routine monitoring of plasma total 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

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 to more than 5 times the upper limit of normal (ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK levels are still significantly elevated (> 5 x ULN) at baseline, treatment should not be started.

Whilst on treatment

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

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

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

The risk of myopathy has been reported to be increased in patients receiving immunosuppressive agents (including ciclosporin), fibrates, nicotinic acid, erythromycin, together with other HMG-CoA

reductase inhibitors. However, in clinical trials in patients receiving fluvastatin in combination with nicotinic acid, fibrates or ciclosporin, myopathy has not been observed. Isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with ciclosporin and fluvastatin with colchicine. The benefits of the combined use of fluvastatin with fibrates, niacin or colchicine should be carefully weighed against the potential risks of these combinations and fluvastatin should be used with caution in patients receiving such concomitant medication (see section 4.5).

Hyperlipoproteinaemia

No data are available for the use of fluvastatin in patients with hyperlipoproteinaemia with a major increase in triglycerides.

Homozygous familial hypercholesterolaemia

No data are available for the use of fluvastatin in patients with a rare condition known as homozygous familial hypercholesterolaemia. The effect is expected to be low due to LDL-receptor deficiency in these patients. Therefore use of fluvastatin is not recommended in these patients.

Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Food interactions

There are no apparent differences in the lipid-lowering effects of fluvastatin when administered with the evening meal or 4 hours after the evening meal. Based on the lack of interaction of fluvastatin with other CYP3A4 substrates, fluvastatin is not expected to interact with grapefruit juice.

Drug interactions

Fibric acid derivatives (fibrates) and niacin (nicotinic acid)

Concomitant administration of fluvastatin with bezafibrate, gemfibrozil, ciprofibrate or niacin (nicotinic acid) has no clinically relevant effect on the bioavailability of fluvastatin or the other lipid-lowering agent. An increased risk of myopathy and/or rhabdomyolysis has been observed in patients receiving other HMG-CoA reductase inhibitors together with any of these molecules, probably because they can produce myopathy when given alone. Therefore, the benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution (see section 4.4).

Colchicines

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

Ciclosporin

Studies in renal transplant patients indicate that the bioavailability of fluvastatin (up to 40 mg/day) is not elevated to a clinically significant extent in patients on stable regimens of ciclosporin. The results from another study wherein 80 mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimens showed that fluvastatin exposure (AUC) and maximum concentration (C_{max}) were increased by 2-fold compared to historical data in healthy subjects. Although these increases in fluvastatin levels were not clinically significant, this combination should be used with caution. Starting and maintaining fluvastatin therapy should be in as dose as low as possible when combined with ciclosporin.

Fluvastatin (40 mg and 80 mg) had no effect on ciclosporin bioavailability when co-administered.

Warfarin and other coumarin derivatives

In healthy volunteers, the use of fluvastatin and warfarin (single dose) did not adversely influence warfarin plasma levels and prothrombin times compared to warfarin alone. However, isolated incidences of bleeding episodes and/or increased prothrombin times have been reported very rarely in patients on fluvastatin receiving concomitant warfarin or other coumarin derivatives. It is recommended that prothrombin times are monitored when fluvastatin treatment is initiated, discontinued, or the dosage changed in patients receiving warfarin or other coumarin derivatives.

Rifampicin (rifampin)

Administration of fluvastatin to healthy volunteers pre-treated with rifampicin (rifampin) resulted in a reduction of the bioavailability of fluvastatin by about 50%. Although at present there is no clinical evidence that fluvastatin efficacy in lowering lipid levels is altered, for patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis), appropriate adjustment of fluvastatin dosage may be warranted to ensure a satisfactory reduction in lipid levels.

Oral antidiabetic agents

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

In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean C_{max} , AUC and $t_{1/2}$ of glibenclamide approximately 50%, 69% and 121%,

respectively. Glibenclamide (5 to 20 mg daily) increased the mean C_{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin and C-peptide levels. However, patients on concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 80 mg per day.

Bile acid sequestrants

Fluvastatin should be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding of the resin.

Fluconazole

Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP2C9 inhibitor) resulted in an increase in the exposure and mean peak concentration of fluvastatin by about 84% and 44%. Although there was no clinical evidence that the safety profile of fluvastatin was altered in patients pre-treated with fluconazole for 4 days, caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Itraconazole and erythromycin

Concomitant administration of fluvastatin with the potent cytochrome P450 (CYP) 3A4 inhibitors itraconazole and erythromycin has minimal effects on the bioavailability of fluvastatin. Given the minimal involvement of this enzyme in the metabolism of fluvastatin, it is expected that other CYP3A4 inhibitors (e.g. ketoconazole, ciclosporin) are unlikely to affect the bioavailability of fluvastatin.

Histamine H₂-receptor antagonists and proton pump inhibitors

Concomitant administration of fluvastatin with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of fluvastatin, which, however, is of no clinical relevance.

Phenytoin

The overall magnitude of the changes in phenytoin pharmacokinetics during co-administration with fluvastatin is relatively small and not clinically significant. Thus, routine monitoring of phenytoin plasma levels is sufficient during co-administration with fluvastatin. The minimal effect of phenytoin on fluvastatin pharmacokinetics indicates that dosage adjustment of fluvastatin is not warranted when co-administered with phenytoin.

Cardiovascular agents

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

4.6 Pregnancy and lactation

Pregnancy

Fluvastatin is contraindicated during pregnancy (see section 4.3).

There are insufficient data on the use of fluvastatin during pregnancy. Since HMG-CoA reductase inhibitors decrease the synthesis of cholesterol and possibly of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women.

Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, fluvastatin must not be used in women who are pregnant or suspect they are pregnant and in women of child-bearing potential not taking adequate contraceptive precautions. Treatment with fluvastatin must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3).

Lactation

It is not known whether fluvastatin or its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions, women taking fluvastatin must not breast-feed their infants (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, based on its pharmacodynamic properties, fluvastatin is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

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

Blood and lymphatic system disorders

Very rare: thrombocytopenia

Psychiatric disorders

Common: insomnia

Nervous system disorders

Common: headache, dizziness, fatigue

Very rare: paraesthesia, dysaesthesia, hypoaesthesia and peripheral neuropathy also known to be associated with underlying hyperlipidaemic disorders

Vascular disorders

Very rare: vasculitis

Gastrointestinal disorders

Common: dyspepsia, abdominal pain, nausea, diarrhoea, constipation, flatulence,

Very rare: pancreatitis

Hepato-biliary disorders

Very rare: hepatitis

Skin and subcutaneous tissue disorders

Rare: hypersensitivity reactions such as rash, urticaria

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

Musculoskeletal and connective tissue disorders

Common: arthralgia

Rare: myalgia, muscle tenderness, muscle weakness and myopathy

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

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in 1 to 2% of patients. Marked elevations of CK levels to more than 5 x ULN developed in 0.3-1.0% of patients.

4.9 Overdose

Should an accidental overdose occur, administration of activated charcoal is recommended and liver function should be monitored. In the case of 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: C10A A04

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

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 (TG) and a moderate increase in HDL-C.

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

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

In this randomised, double-blind, placebo-controlled trial, fluvastatin (N = 844), given as 80 mg daily over 4 years, significantly reduced the risk of the first MACE by 22% (p=0.013) as compared to placebo (N = 833). These beneficial effects were particularly noteworthy in diabetics and patients with multivessel disease. Therapy with fluvastatin reduced the risk of cardiac death and/or myocardial infarction by 31% (p=0.065).

5.2 Pharmacokinetic properties

Absorption

Fluvastatin is absorbed rapidly and completely (98%) after oral administration to fasted volunteers. In the fed state, the substance is absorbed at a reduced rate. No significant difference in AUC was observed when fluvastatin was administered with the evening meal or 4 hours after the evening meal.

Distribution

Absolute bioavailability is variable and increases with increasing doses. The absolute bioavailability of fluvastatin following a 10 mg dose was 24% (range: 9-50%). At doses above 20 mg, fluvastatin exhibits nonlinear kinetics, at least in the fasting state, resulting in dose normalized AUC values 20-40% higher than expected for the 40 mg dose. The apparent volume of distribution for the substance is 330 L. More than 98% of the circulating substance is bound to plasma proteins, and this binding is not affected either by the concentration of fluvastatin, or by warfarin, salicylic acid, and glyburide.

Metabolism

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

The hepatic metabolic pathways of fluvastatin in humans have been completely elucidated. There are multiple, alternative cytochrome P450 (CYP450) pathways for fluvastatin biotransformation and thus fluvastatin metabolism is relatively insensitive to CYP450 inhibition, a major cause of adverse interactions involved.

Several detailed in vitro studies have addressed the inhibitory potential of fluvastatin on common CYP isoenzymes. Fluvastatin inhibited only the metabolism of compounds that are metabolized by CYP2C9. Despite the potential that therefore exists for competitive interaction between fluvastatin and compounds that are CYP2C9 substrates, such as diclofenac, phenytoin, tolbutamide, and warfarin, clinical data indicate that this interaction is unlikely.

Elimination

Following administration of 3H-fluvastatin to healthy volunteers, excretion of radioactivity is about 6% in the urine and 93% in the faeces, and fluvastatin accounts for less than 2% of the total radioactivity excreted. The plasma clearance for fluvastatin in man is calculated to be 1.8 ± 0.8 L/min. Steady-state plasma concentrations show no evidence of fluvastatin accumulation following administration of 40 mg daily. Following oral administration of 40 mg of fluvastatin, the terminal disposition half-life is 2.3 ± 0.9 hours.

Characteristics in patients

Plasma concentrations of fluvastatin do not vary as a function of either age or gender in the general population. However, enhanced treatment response was observed in women and in elderly people. Since fluvastatin is eliminated primarily via the biliary route and is subject to significant pre-systemic metabolism, the potential exists for accumulation in patients with hepatic insufficiency (see sections 4.3 and 4.4).

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 dog, monkey and hamster, thyroid weight increases in the rat and testicular degeneration in the hamster. Fluvastatin is devoid of the central nervous system (CNS) vascular and degenerative changes recorded in dogs with other members of this class of compound.

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 substance. 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****List of excipients**Core:

Lactose monohydrate
Colloidal anhydrous silica
Crospovidone
Magnesium stearate

Cap and body:

Red iron oxide (E172)
Yellow Iron Oxide (E172)
Titanium dioxide (E171)

Gelatin

Printing ink composition:

Shellac
Propylene glycol
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Blisters: Do not store above 30°C.

Bottles: This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Blisters: Aluminium – Aluminium blister packs

Bottles: White HDPE bottles with white PP child-resistant closure and silica gel as desiccant.

Pack sizes:

Blisters: 1, 14, 15, 28, 30, 50, 50x2, 56, 60, 84, 90, 98 and 100 capsules.

Hospital packs in blisters: 1, 50 and 100 capsules

Bottles: 100, 250 and 500 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road
Hampden Park
Eastbourne
East Sussex
BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0997

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/07/2008

10 DATE OF REVISION OF THE TEXT

08/07/2008

11 DOSIMETRY (IF APPLICABLE)**12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

SUMMARY OF PRODUCT CHARACTERISTICS**1 NAME OF THE MEDICINAL PRODUCT**

Fluvastatin 40mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One 40 mg capsule contains 40 mg fluvastatin (as fluvastatin sodium).

Excipient:

199.2 mg lactose monohydrate/capsule

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

The 40 mg capsules have a yellow opaque body and pink opaque cap marked 93/7443, and are filled with an off-white to yellowish powder with small agglomerates.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Fluvastatin is indicated as an adjunct to diet for the reduction of elevated total cholesterol (total-C) and low-density lipoprotein cholesterol (LDL-C), when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate in adults with primary hypercholesterolaemia (heterozygous variant) and mixed dyslipidaemia (Fredrickson types IIa and IIb).

Fluvastatin is also indicated for the secondary prevention of major adverse cardiac events (cardiac death, non-fatal myocardial infarction and coronary revascularisation) after coronary transcatheter therapy).

4.2 Posology and method of administration

Prior to initiating treatment with fluvastatin, the patient should be placed on a standard cholesterol-lowering diet, which should be continued during treatment.

The recommended starting dose is 20 mg or 40 mg once daily. a dose of 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 daily (one 40 mg capsule twice daily), individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum recommended daily dose is 80 mg.

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

The capsules should be taken in the evening or at bedtime without regard to meals and should be swallowed whole with a glass of water.

The maximum lipid-lowering effect with a given dose of the substance is achieved within 4 weeks.

Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of fluvastatin is maintained with prolonged administration.

Fluvastatin is efficient in monotherapy. Data exist to support the efficacy and safety of fluvastatin in combination with nicotinic acid, cholestyramine or fibrates (see section 4.5).

When fluvastatin 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 substance to the resin.

Children and adolescents

There is no experience with the use of fluvastatin in individuals less than 18 years of age. The product should not be used in this group of patients.

Elderly

There is no evidence of reduced tolerability or altered dosage requirements in elderly patients thus, no dose adjustment is required in such patients.

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. 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.

Impaired liver function

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

4.3 Contraindications

Fluvastatin is contraindicated:

- in patients with hypersensitivity to fluvastatin or to any of the excipients.
- in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see sections 4.2, 4.4 and 4.8).
- in patients with myopathy
- during pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Liver function

As with other lipid-lowering agents, it is recommended that liver function tests be performed before the initiation of treatment, at 12 weeks following initiation of treatment or elevation in dose, and periodically thereafter in all patients. Patients whose levels increase in response to the substance should be monitored particularly closely, with immediate repetition of the measurement followed by more frequent measurements. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceed 3 times the upper limit of normal (ULN) and persist, therapy should be discontinued. In very rare cases, possibly substance-related hepatitis was observed that resolved upon discontinuation of treatment.

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

Skeletal muscle

With fluvastatin, 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 promptly report unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.

Creatine kinase measurement

There is no current evidence to require routine monitoring of plasma total 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

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 to more than 5 times the upper limit of normal (ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK levels are still significantly elevated (> 5 x ULN) at baseline, treatment should not be started.

Whilst on treatment

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

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

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

The risk of myopathy has been reported to be increased in patients receiving immunosuppressive agents (including ciclosporin), fibrates, nicotinic acid, erythromycin, together with other HMG-CoA reductase inhibitors. However, in clinical trials in patients receiving fluvastatin in combination with nicotinic acid, fibrates or ciclosporin, myopathy has not been observed. Isolated cases of myopathy

have been reported post-marketing for concomitant administration of fluvastatin with ciclosporin and fluvastatin with colchicine. The benefits of the combined use of fluvastatin with fibrates, niacin or colchicine should be carefully weighed against the potential risks of these combinations and fluvastatin should be used with caution in patients receiving such concomitant medication (see section 4.5).

Hyperlipoproteinaemia

No data are available for the use of fluvastatin in patients with hyperlipoproteinaemia with a major increase in triglycerides.

Homozygous familial hypercholesterolaemia

No data are available for the use of fluvastatin in patients with a rare condition known as homozygous familial hypercholesterolaemia. The effect is expected to be low due to LDL-receptor deficiency in these patients. Therefore use of fluvastatin is not recommended in these patients.

Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Food interactions

There are no apparent differences in the lipid-lowering effects of fluvastatin when administered with the evening meal or 4 hours after the evening meal. Based on the lack of interaction of fluvastatin with other CYP3A4 substrates, fluvastatin is not expected to interact with grapefruit juice.

Drug interactions

Fibric acid derivatives (fibrates) and niacin (nicotinic acid)

Concomitant administration of fluvastatin with bezafibrate, gemfibrozil, ciprofibrate or niacin (nicotinic acid) has no clinically relevant effect on the bioavailability of fluvastatin or the other lipid-lowering agent. An increased risk of myopathy and/or rhabdomyolysis has been observed in patients receiving other HMG-CoA reductase inhibitors together with any of these molecules, probably because they can produce myopathy when given alone. Therefore, the benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution (see section 4.4).

Colchicines

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

Ciclosporin

Studies in renal transplant patients indicate that the bioavailability of fluvastatin (up to 40 mg/day) is not elevated to a clinically significant extent in patients on stable regimens of ciclosporin. The results from another study wherein 80 mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimens showed that fluvastatin exposure (AUC) and maximum concentration (C_{max}) were increased by 2-fold compared to historical data in healthy subjects. Although these increases in fluvastatin levels were not clinically significant, this combination should be used with caution. Starting and maintaining fluvastatin therapy should be in as dose as low as possible when combined with ciclosporin.

Fluvastatin (40 mg and 80 mg) had no effect on ciclosporin bioavailability when co-administered.

Warfarin and other coumarin derivatives

In healthy volunteers, the use of fluvastatin and warfarin (single dose) did not adversely influence warfarin plasma levels and prothrombin times compared to warfarin alone. However, isolated incidences of bleeding episodes and/or increased prothrombin times have been reported very rarely in patients on fluvastatin receiving concomitant warfarin or other coumarin derivatives. It is recommended that prothrombin times are monitored when fluvastatin treatment is initiated, discontinued, or the dosage changed in patients receiving warfarin or other coumarin derivatives.

Rifampicin (rifampin)

Administration of fluvastatin to healthy volunteers pre-treated with rifampicin (rifampin) resulted in a reduction of the bioavailability of fluvastatin by about 50%. Although at present there is no clinical evidence that fluvastatin efficacy in lowering lipid levels is altered, for patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis), appropriate adjustment of fluvastatin dosage may be warranted to ensure a satisfactory reduction in lipid levels.

Oral antidiabetic agents

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

In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean C_{max} , AUC and $t_{1/2}$ of glibenclamide approximately 50%, 69% and 121%, respectively. Glibenclamide (5 to 20 mg daily) increased the mean C_{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin and C-peptide

levels. However, patients on concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 80 mg per day.

Bile acid sequestrants

Fluvastatin should be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding of the resin.

Fluconazole

Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP2C9 inhibitor) resulted in an increase in the exposure and mean peak concentration of fluvastatin by about 84% and 44%. Although there was no clinical evidence that the safety profile of fluvastatin was altered in patients pre-treated with fluconazole for 4 days, caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Itraconazole and erythromycin

Concomitant administration of fluvastatin with the potent cytochrome P450 (CYP) 3A4 inhibitors itraconazole and erythromycin has minimal effects on the bioavailability of fluvastatin. Given the minimal involvement of this enzyme in the metabolism of fluvastatin, it is expected that other CYP3A4 inhibitors (e.g. ketoconazole, ciclosporin) are unlikely to affect the bioavailability of fluvastatin.

Histamine H₂-receptor antagonists and proton pump inhibitors

Concomitant administration of fluvastatin with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of fluvastatin, which, however, is of no clinical relevance.

Phenytoin

The overall magnitude of the changes in phenytoin pharmacokinetics during co-administration with fluvastatin is relatively small and not clinically significant. Thus, routine monitoring of phenytoin plasma levels is sufficient during co-administration with fluvastatin. The minimal effect of phenytoin on fluvastatin pharmacokinetics indicates that dosage adjustment of fluvastatin is not warranted when co-administered with phenytoin.

Cardiovascular agents

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

4.6 Pregnancy and lactation

Pregnancy

Fluvastatin is contraindicated during pregnancy (see section 4.3).

There are insufficient data on the use of fluvastatin during pregnancy. Since HMG-CoA reductase inhibitors decrease the synthesis of cholesterol and possibly of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women.

Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, fluvastatin must not be used in women who are pregnant or suspect they are pregnant and in women of child-bearing potential not taking adequate contraceptive precautions. Treatment with fluvastatin must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3).

Lactation

It is not known whether fluvastatin or its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions, women taking fluvastatin must not breast-feed their infants (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, based on its pharmacodynamic properties, fluvastatin is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness. The most commonly reported adverse reactions are minor gastrointestinal symptoms, insomnia and headache.

Blood and lymphatic system disorders

Very rare: thrombocytopenia

Psychiatric disorders

Common: insomnia

Nervous system disorders

Common: headache, dizziness, fatigue

Very rare: paraesthesia, dysaesthesia, hypoaesthesia and peripheral neuropathy also known to be associated with underlying hyperlipidaemic disorders

Vascular disorders

Very rare: vasculitis

Gastrointestinal disorders

Common: dyspepsia, abdominal pain, nausea, diarrhoea, constipation, flatulence,

Very rare: pancreatitis

Hepato-biliary disorders

Very rare: hepatitis

Skin and subcutaneous tissue disorders

Rare: hypersensitivity reactions such as rash, urticaria

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

Musculoskeletal and connective tissue disorders

Common: arthralgia

Rare: myalgia, muscle tenderness, muscle weakness and myopathy

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

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in 1 to 2% of patients. Marked elevations of CK levels to more than 5 x ULN developed in 0.3-1.0% of patients.

4.9 Overdose

Should an accidental overdose occur, administration of activated charcoal is recommended and liver function should be monitored. In the case of 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: C10A A04

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

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 (TG) and a moderate increase in HDL-C.

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

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

In this randomised, double-blind, placebo-controlled trial, fluvastatin (N = 844), given as 80 mg daily over 4 years, significantly reduced the risk of the first MACE by 22% (p=0.013) as compared to placebo (N = 833). These beneficial effects were particularly noteworthy in diabetics and patients with multivessel disease. Therapy with fluvastatin reduced the risk of cardiac death and/or myocardial infarction by 31% (p=0.065).

5.2 Pharmacokinetic properties

Absorption

Fluvastatin is absorbed rapidly and completely (98%) after oral administration to fasted volunteers. In the fed state, the substance is absorbed at a reduced rate. No significant difference in AUC was observed when fluvastatin was administered with the evening meal or 4 hours after the evening meal.

Distribution

Absolute bioavailability is variable and increases with increasing doses. The absolute bioavailability of fluvastatin following a 10 mg dose was 24% (range: 9-50%). At doses above 20 mg, fluvastatin exhibits nonlinear kinetics, at least in the fasting state, resulting in dose normalized AUC values 20-40% higher than expected for the 40 mg dose. The apparent volume of distribution for the substance is 330 L. More than 98% of the circulating substance is bound to plasma proteins, and this binding is not affected either by the concentration of fluvastatin, or by warfarin, salicylic acid, and glyburide.

Metabolism

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

The hepatic metabolic pathways of fluvastatin in humans have been completely elucidated. There are multiple, alternative cytochrome P450 (CYP450) pathways for fluvastatin biotransformation and thus fluvastatin metabolism is relatively insensitive to CYP450 inhibition, a major cause of adverse interactions involved.

Several detailed in vitro studies have addressed the inhibitory potential of fluvastatin on common CYP isoenzymes. Fluvastatin inhibited only the metabolism of compounds that are metabolized by CYP2C9. Despite the potential that therefore exists for competitive interaction between fluvastatin and compounds that are CYP2C9 substrates, such as diclofenac, phenytoin, tolbutamide, and warfarin, clinical data indicate that this interaction is unlikely.

Elimination

Following administration of 3H-fluvastatin to healthy volunteers, excretion of radioactivity is about 6% in the urine and 93% in the faeces, and fluvastatin accounts for less than 2% of the total radioactivity excreted. The plasma clearance for fluvastatin in man is calculated to be 1.8 ± 0.8 L/min. Steady-state plasma concentrations show no evidence of fluvastatin accumulation following administration of 40 mg daily. Following oral administration of 40 mg of fluvastatin, the terminal disposition half-life is 2.3 ± 0.9 hours.

Characteristics in patients

Plasma concentrations of fluvastatin do not vary as a function of either age or gender in the general population. However, enhanced treatment response was observed in women and in elderly people. Since fluvastatin is eliminated primarily via the biliary route and is subject to significant pre-systemic metabolism, the potential exists for accumulation in patients with hepatic insufficiency (see sections 4.3 and 4.4).

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 dog, monkey and hamster, thyroid weight increases in the rat and testicular degeneration in the hamster. Fluvastatin is devoid of the central nervous system (CNS) vascular and degenerative changes recorded in dogs with other members of this class of compound.

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 substance. 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**Core:

Lactose monohydrate
Colloidal anhydrous silica
Crospovidone
Magnesium stearate

Cap and body:

Red iron oxide (E172)
Yellow Iron Oxide (E172)
Titanium dioxide (E171)

Gelatin

Printing ink composition:

Shellac
Propylene glycol
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Blisters: Do not store above 30°C.

Bottles: This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Blisters: Aluminium – Aluminium blister packs

Bottles: White HDPE bottles with white PP child-resistant closure and silica gel as desiccant.

Pack sizes:

Blisters: 1, 14, 15, 28, 30, 50, 50x2, 56, 60, 84, 90, 98 and 100 capsules.

Hospital packs in blisters: 1, 50 and 100 capsules

Bottles: 100, 250 and 500 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road
Hampden Park
Eastbourne
East Sussex
BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0998

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/07/2008

10 DATE OF REVISION OF THE TEXT

08/07/2008

11 DOSIMETRY (IF APPLICABLE)**12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

Module 3

PATIENT INFORMATION LEAFLET

FLUVASTATIN 20 mg and 40 mg CAPSULES

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 fluvastatin is and what it is used for
2. Before you take fluvastatin
3. How to take Fluvastatin Capsules
4. Possible side effects
5. How to store Fluvastatin Capsules
6. Further information

1 WHAT FLUVASTATIN IS AND WHAT IT IS USED FOR

- Fluvastatin is one of a group of medicines called statins, which are cholesterol-regulating agents
- Your doctor has prescribed Fluvastatin to reduce your cholesterol and recommended changes in your lifestyle and diet. High levels of cholesterol in the blood are linked to an increased risk of heart disease and stroke
- Fluvastatin has also been shown to prevent heart attacks in patients who have recently had catheter treatment for narrowed coronary arteries.

2 BEFORE YOU TAKE FLUVASTATIN

Before taking this medicine, you should have started a standard cholesterol-lowering diet. Continue with this diet while taking fluvastatin. Follow carefully all instructions given to you by your doctor. They may be different from the information contained in this leaflet. Read the following explanations before you take fluvastatin.

Do NOT take Fluvastatin Capsules:

- If you are allergic (hypersensitive) to fluvastatin or to any of the other ingredients of this medicine: see the list at the end of this leaflet (section 6)
- If you have an active liver disease, or yellowing of the skin or whites of the eyes caused by liver problems or unexplained, continually high liver values (transaminases)
- If you have a muscle disorder called myopathy (repeated or unexplained muscle aches or pains)
- If you are pregnant or breast-feeding.

If you think you may be allergic, ask your doctor for advice.

Take special care with Fluvastatin Capsules

You should check with your doctor BEFORE taking this medicine:

- If you have a history of liver disease. Liver function tests will normally be done before starting fluvastatin, when the dose is increased and at various intervals during treatment to check for undesirable effects
- If you suffer from kidney disease
- If you suffer from thyroid disease
- If you or your family have a medical history of muscle disease
- If you are older than 70 years, your doctor may want to clarify whether you are at risk from muscular diseases
- If you have experienced muscular problems with lipid-lowering medicine before

- If you regularly consume large amounts of alcohol.
- If any of the above apply to you, tell your doctor before taking fluvastatin.

Under any of these circumstances, your doctor will take a blood sample for analysis before prescribing fluvastatin.

Taking other medicines

Tell your doctor or pharmacist if you are taking any of the following:

- Ciclosporin (a medicine used to suppress the immune system), fluconazole (medicine used to treat fungal infections), or colchicine (a medicine used to treat gout): the combination may result in an increased risk of developing muscle problems
- Fibrates (e.g. gemfibrozil) or nicotinic acid (medicines used to lower cholesterol levels): the combination may result in an increased risk of developing muscle problems
- Resins used to lower your cholesterol (e.g. cholestyramine): the combination may reduce the effects of fluvastatin (see also section 3)
- Rifampicin (an antibiotic): the combination may reduce the effects of fluvastatin
- Phenytoin (a medicine used to treat epilepsy): the combination may result in an increased amount of phenytoin in the blood which may cause side effects
- Medicines used to reduce blood clotting, like warfarin: the combination may increase the effects of warfarin and cause bleeding
- Glibenclamide (a medicine used to treat diabetes): if your doctor thinks the combination is necessary you should be aware that it may increase the amount of glibenclamide in the bloodstream, which may in turn lead to an increased risk of low blood sugar (hypoglycaemia).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Do not take fluvastatin if you are pregnant, if you think you may be pregnant, or if you are trying to become pregnant. Women of child-bearing age must use effective birth control.

Do not take fluvastatin if you are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Fluvastatin may cause dizziness which could affect driving or operating machinery.

Important information about some of the ingredients of Fluvastatin Capsules

This medicinal product contains a small amount of lactose: if you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3 HOW TO TAKE FLUVASTATIN CAPSULES

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will recommend you follow a low-cholesterol diet. Stay on this diet while taking this medicine.

How much to take

The usual dose is 20 to 40 mg once a day, taken in the evening. After starting treatment, your doctor will periodically check your cholesterol levels and may adjust your dose.

The maximum dose is 80 mg daily. If you are taking the maximum dose you should take 40 mg in the morning and 40 mg in the evening.

If you have undergone a catheter treatment for narrow coronary arteries in the past, your doctor may prescribe 80 mg daily.

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

How to take Fluvastatin Capsules

- The capsules should be swallowed whole with a glass of water
- They may be taken with or without food
- Wait at least 4 hours before taking fluvastatin after you have taken a resin-type medicine like cholestyramine. This type of medicine also helps to lower your cholesterol but may interfere with the way fluvastatin is taken up in the body.

This medicine is not recommended in patients below 18 years of age as there is no experience in these patients.

If you take more Fluvastatin Capsules than you should

If you have accidentally taken too many capsules, contact your doctor or nearest hospital for advice.

If you forget to take Fluvastatin Capsules

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

If you stop taking Fluvastatin Capsules

Remember that this medicine will not cure your condition but it will help to control it. Therefore, you must continue to take fluvastatin as directed to keep the levels of your 'bad' cholesterol down. Your cholesterol levels should be checked regularly to monitor your progress. To maintain the benefits of your treatment, you should not stop taking fluvastatin.

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

4 POSSIBLE SIDE EFFECTS

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

Serious side effects

Serious side effects are rare (affecting fewer than 1 in 1,000 patients) or very rare (affecting fewer 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 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 medicines of this class (statins)
- If you have unusual tiredness or fever, yellowing of the skin and eyes, dark-coloured urine (signs of hepatitis)
- If you have signs of skin reactions such as skin rash, hives, redness, itching, swelling of the face, eyelids, and lips
- If you 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 a 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 (sign of an inflamed pancreas).

If you experience any of these, **tell your doctor straight away.**

Other side effects

Common (affecting fewer than one in 10 patients):

Difficulty in sleeping, headache, fatigue, dizziness, stomach discomfort, abdominal pain, constipation, flatulence, diarrhoea, nausea, joint pain.

Very rare (affecting fewer than one in 10,000 patients):

Tingling or numbness of the hands or feet, disturbed or decreased sensations.

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

5 HOW TO STORE FLUVASTATIN CAPSULES

Keep out of the reach and sight of children.

Blisters:

Do not use this medicine after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of the month. Do not store above 30°C.

Bottles:

Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of the month.

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

6 FURTHER INFORMATION

What Fluvastatin Capsules contain

The active ingredient is fluvastatin.

One 20 mg capsule contains 20 mg fluvastatin (as fluvastatin sodium).

One 40 mg capsule contains 40 mg fluvastatin (as fluvastatin sodium).

The other ingredients are lactose monohydrate, colloidal anhydrous silica, crospovidone, magnesium stearate, red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172), titanium dioxide (E171), gelatin, shellac and propylene glycol.

What Fluvastatin Capsules look like and contents of the pack

Fluvastatin 20 mg Capsules have an ivory opaque body and pink opaque cap marked 93/7442.

Fluvastatin 40 mg Capsules have a yellow opaque body and pink opaque cap marked 93/7443.

Fluvastatin 20 and 40 mg Capsules
Blisters: 1, 14, 15, 28, 30, 50, 50 x 2, 56, 60, 84, 90, 98 and 100 capsules.
Hospital packs in blisters: 1, 50 and 100 capsules.
Bottles: 100, 250 and 500 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation holder is TEVA UK Limited, Eastbourne, BN22 9AG and the company responsible for manufacture is TEVA Pharmaceutical Works Private Limited Company, Pallagi út 13, 4042 Debrecen, Hungary.

This leaflet was last revised in MAY 2008

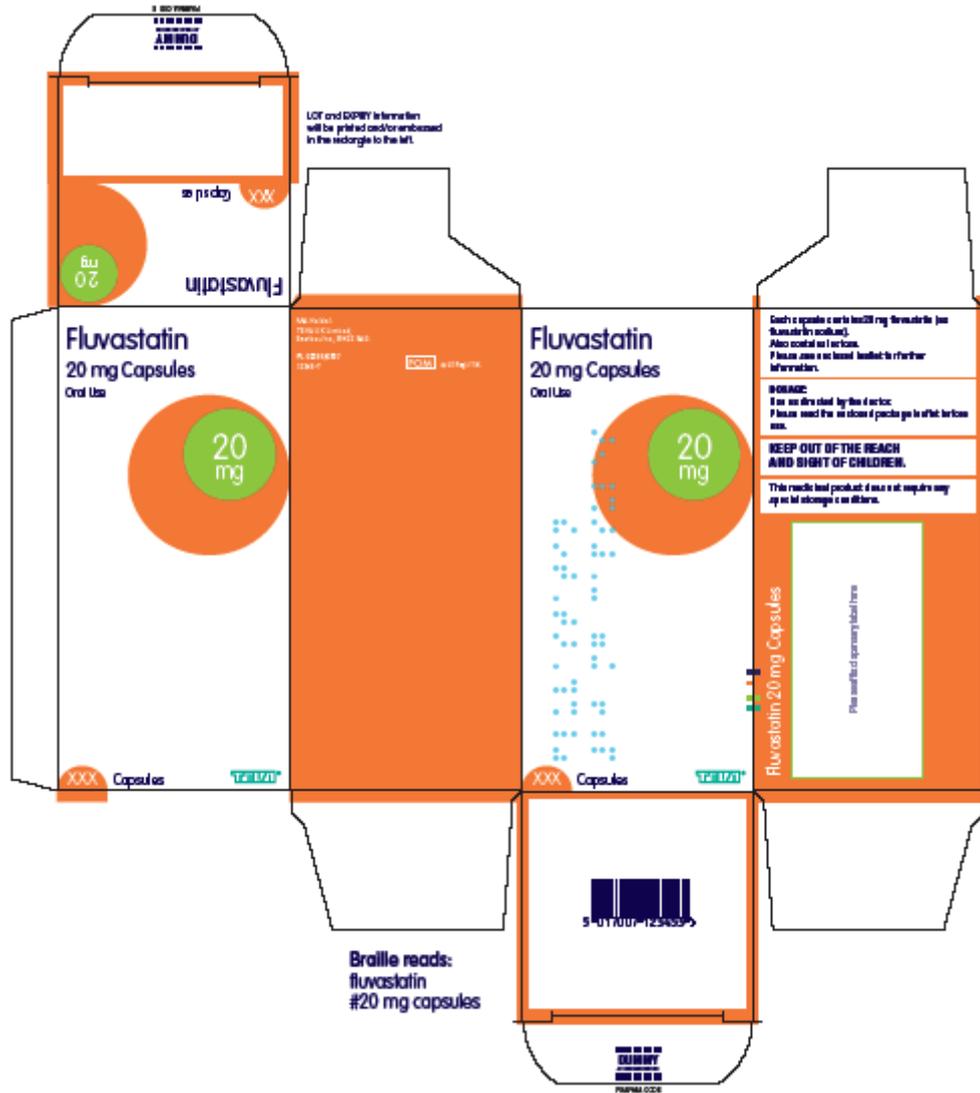
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Module 4 Labelling

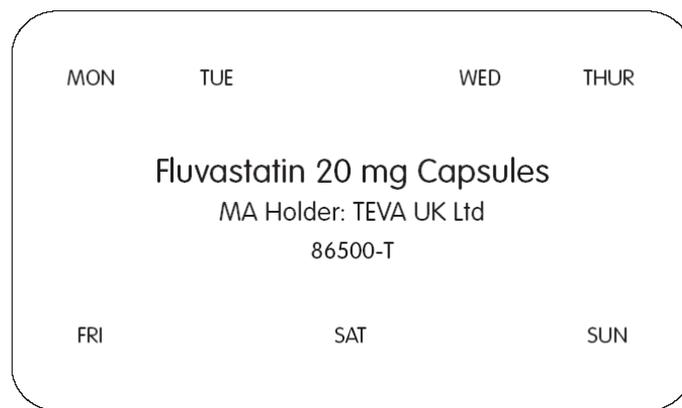
Carton (Bottle)- 20mg Capsules



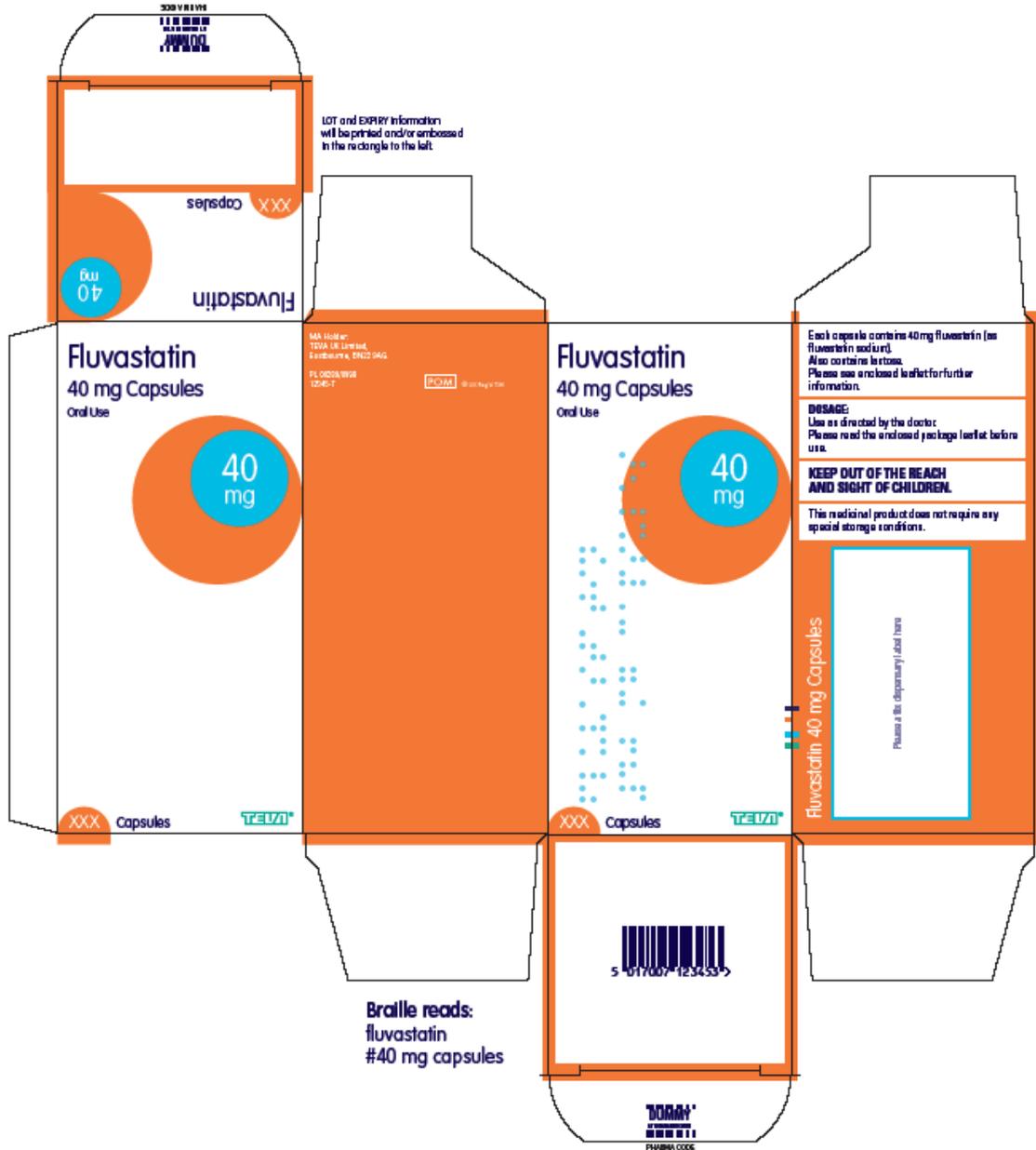
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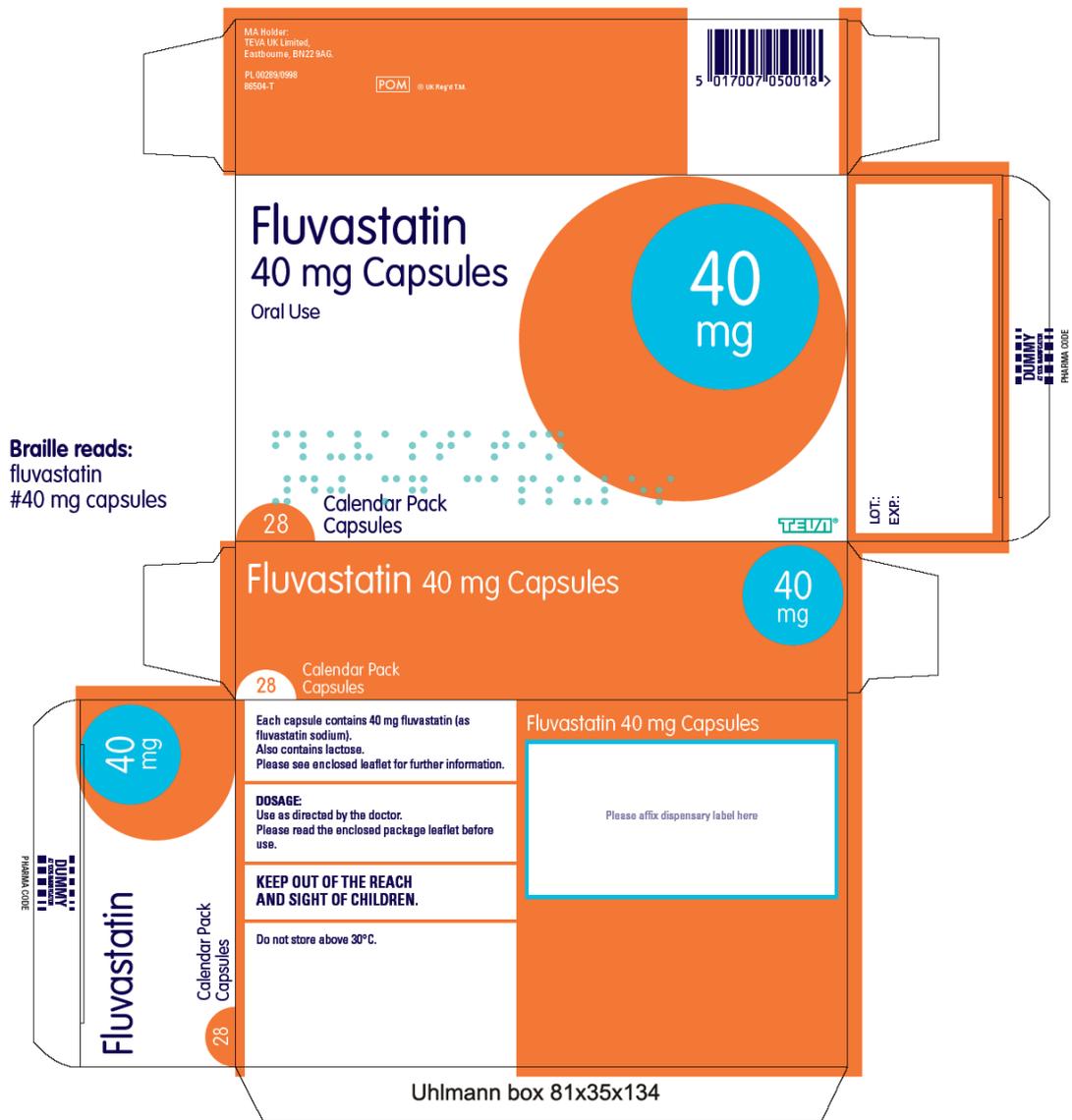
Blister foil



Carton (Bottle)- 40mg Capsules



Carton (Blister pack)- 40mg Capsules



Blister foil



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Fluvastatin 20mg and 40mg Capsules, in the treatment of primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson types IIa and IIb), as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. Secondary prevention of major coronary events (coronary revascularisation, cardiac death, non-fatal myocardial infarction) after percutaneous coronary intervention, is approvable.

This application is made under Article 10.1 of 2001/83 EC, as amended, Fluvastatin 20mg and 40mg Capsules, has been shown to be a generic product of Lescol 20mg and 40mg Capsules which was first granted to Novartis, on 23rd August 1993, over 10 years ago.

Hyperlipidemia, primary or secondary is a major risk factor for development of atherosclerosis and cardiovascular disease. HMG-CoA reductase inhibitors such as statins have shown significant impact on hyperlipidemia both in terms of severity of the lipidemia and risk reduction from events relating to cardiovascular disease. The use of Fluvastatin has been well established in hyperlipidaemic individuals with a favourable Benefit: Risk ratio. The brand leader, Lescol (Novartis Pharmaceuticals) is authorised in a number of countries, both in the EU and worldwide.

Fluvastatin, a fully synthetic cholesterol-lowering agent, is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Fluvastatin exerts its main effect in the liver. Unlike the other HMG-CoA reductase inhibitors which are fungal derivatives, fluvastatin is the first synthetic agent of its class. Chemically, Fluvastatin sodium is $[R^*,S^*-(E)]-(\pm)-7-[3-(4\text{-fluorophenyl})-1-(1\text{-methylethyl})-1H\text{-indol-2-yl}]-3,5\text{-dihydroxy-6-heptenoic acid}$, monosodium salt. The empirical formula of fluvastatin sodium is $C_{24}H_{25}FNO_4 \cdot Na$, its molecular weight is 433.46.

Pharmacodynamics;

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

No new preclinical or clinical studies were conducted and none are required for applications of this type. These applications are for generic products and refer to Lescol 20mg and 40mg Capsules authorised to Novartis, which have been licensed within the EEA for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, batch release and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as

certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS has been reassured that the submitted studies have been carried out in accordance with GCP, and agreed ethical principles.

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

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Fluvastatin 20mg & 40mg Capsules
Name(s) of the active substance(s) (INN)	Fluvastatin sodium
Pharmacotherapeutic classification (ATC code)	HMG CoA reductase inhibitors / C10 AA04
Pharmaceutical form and strength(s)	Capsules, 20mg and 40mg
Reference numbers for the Mutual Recognition Procedure	UK/H/977/01-02/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, The Netherlands, Norway, Portugal, Sweden and Slovak Republic
Marketing Authorisation Number(s)	PL 00289/0997
Name and address of the authorisation holder	TEVA UK Ltd, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG

III SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

S. Active substance

General Information

S.1.1 Nomenclature

INN: Fluvastatin Sodium

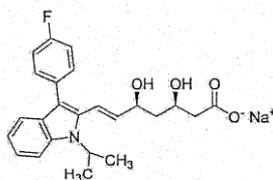
Chemical name(s):

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

CAS registry no.: 93957-55-2

S.1.2 Structure

Structural formula



Molecular formula $C_{24}H_{25}FNNaO_4$

Molecular weight
(monosodium) 433.46

S.1.3 General Properties Physico-chemical characterisation

The drug substance is a white to pale-yellow, brownish-pale yellow or reddish-pale yellow, hygroscopic powder.

The drug substance is not described in the Ph Eur but a monograph exists in the USP.

Manufacture

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

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active fluvastatin sodium is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data have been provided and comply with the proposed specification.

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

Appropriate stability data have been generated supporting a shelf-life of 24 months with no specific storage conditions.

P Medicinal Product

Other ingredients consist of pharmaceutical excipients lactose monohydrate, colloidal anhydrous silica, crospovidone and magnesium stearate. All the ingredients within the body of the capsule comply with their relevant Ph Eur monographs.

The capsule shell contains: red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin. Both titanium dioxide (E171) and gelatin comply with their relevant Ph Eur monographs. Red iron oxide (E172), yellow iron oxide (E172) comply with in-house specifications.

The printing ink contains: shellac, propylene glycol and black iron oxide (E172). Both shellac and propylene glycol comply with their relevant Ph Eur monographs and black iron oxide (E172) complies with in-house specifications. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their respective monograph/specifications.

The only excipients used that contain material of animal or human origin are lactose monohydrate and gelatin. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption. A satisfactory TSE certificate of suitability has been provided for the supplier of gelatin.

The development of the product has been described, the choice of excipients is justified and their functions explained.

Dissolution and impurity profiles

Dissolution and impurity profiles of drug product were found to be similar to those for the reference product.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Validations of the analytical methods have been presented. Preliminary validation studies have been carried out on four pilot-scale batches with the commitment to provide the results for the first three consecutive full-scale batches; this is satisfactory. The batch analysis results show that the finished products meet the specifications proposed. Certificates of analysis have been provided for any working standards used.

Container Closure System

Either the product is packaged in blister packs composed of aluminium or bottles composed of white high density polyethylene (HDPE) with white polypropylene (PP) child-resistant closures with silica gel as desiccant. Specifications and certificates of analysis for the packaging types used have been provided. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 100, 250 and 500 capsules for the HDPE bottles; sizes of 1, 14, 15, 28, 30, 50, 50x2, 56, 60, 84, 90, 98 and 100 capsules for the blister packs and sizes of 1, 50 and 100 capsules in blister packs for hospitals.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are "Do not store above 30°C" for the blister packs and no specific storage conditions required for the HDPE bottles.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications. The proposed products have met the requirements of a generic medicinal product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

PRE-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of fluvastatin sodium are well known. As fluvastatin sodium is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by a suitably qualified person, dated 29 November 2006. The report refers to only 2 publications, Fluvastatin in DRUGDEX® system and the Physicians' Desk Reference entry for Lescol XL Tablets (2006), although several more references are included in the text of the overview. The text is lifted in part from these publications but covers the mechanism of action, (clinical) pharmacokinetics and interactions, and toxicology.

The drug substance and drug product specifications are discussed in the non-clinical overview. In the drug substance, named impurities are stated to be limited in accordance with the USP monograph for fluvastatin sodium. The other named and 'any other' impurities are appropriately limited in accordance with the qualification and identification thresholds in ICH guidance for impurities in new drug substances. The residual solvents are appropriately controlled in the specification

For the drug product, named impurities are appropriately controlled in the product specification

The applicant has also conducted a comparison of the impurity profiles of the drug substance, drug product and EU reference products and shown qualitatively similar profiles. Overall, the non-clinical overview is adequate.

A suitable justification was provided for the absence of an Environmental Risk Assessment.

Conclusions

There are no objections to approval of Fluvastatin 20mg & 40mg Capsules from a non-clinical point of view.

CLINICAL ASPECTS

Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

A suitably qualified person has written the clinical overview and the report is dated November 2006.

The clinical overview on the clinical pharmacology, efficacy and safety is adequate. The overview also discusses the issues of biowaiver and the biopharmaceutics including the bioequivalence studies.

Assessor's comment

The overview is adequate and provides sufficient information regarding the clinical pharmacology biopharmaceutics, the efficacy and safety of fluvastatin.

Clinical study reports

To support the application, the applicant has submitted no new clinical trials; none are required for this type of applications that are based on claims of essential similarity. One single bioequivalence study (2005-1016) has been submitted as per requirements and biowaiver claimed for one other strength.

Assessor's comment

The single bioequivalence study submitted is in line with the current requirements.

Biowaiver

The applications relate to 20 and 40 mg strengths. The Bioequivalence studies have been conducted with the 40mg strength. Biowaiver has been claimed for the lower strength based on the standard criteria as detailed in the CPMP guidance note (CPMP/EWP/QWP/1401/98). The applicant and expert claim that the required criteria are fulfilled.

Assessor's comment:

The biowaiver claim is accepted as the applicant has indeed fulfilled the criteria for biowaiver as specified in the guidance note. The manufacturer is the same, the composition of the two strengths is the same in terms of active/excipient ratios, the kinetics (drug input) of fluvastatin is linear within the dose range and the dissolution profiles demonstrated have been similar.

Pharmacokinetic studies (Code)

Methods

Study design

Study number 2005-1016

A single dose, single centre, randomised, open label, crossover, two-period, bioequivalence study of two formulations of Fluvastatin under fasting conditions.

Test and reference products

TEST [Treatment –A]; 40mg capsules

REF [Treatment –B]; Lescol 40 mg capsules

The compositions of the test and reference products are qualitatively similar. Detailed information on the test formulation is found in module 3.

Overall 80 healthy male and female volunteers (75 M, 5 F) aged 18-55 years were included. All had to fulfil specific inclusion/ exclusion criteria. The mean age was 36 ± 10 years (range of 20-54). Of these 65 were caucasian, 8 blacks and 7 were asian.

Study period;

Period -1;	16 th Jan, 2006
Period 2;	23 rd Jan, 2006
Washout	7 days
Analytical Period;	Feb 2006

Assessor's comment:

The 2x2 crossover study under fasting conditions using the 40mg (higher strength) is acceptable. The Reference product is from the UK market (EU community authorised) and is thus appropriate. As discussed previously, the biowaiver criteria have been satisfactory addressed and the choice of the strength is acceptable with results extrapolatable to the lower strength. The healthy population included is appropriate. Healthy volunteer studies are acceptable for demonstration of bioequivalence and the results considered applicable to the general population or patients. The inclusion of females and racial groups are acceptable, although the distribution is frequently unequal as in this study. This however is unlikely to affect the results in the crossover, intra-individual comparison of pharmacokinetic parameters. The wash out period of 7 days should be sufficient to avoid any carry over effect, as the β -elimination half-life is reported to be less than 3 hours. The study was conducted in accordance with GCP, local regulatory requirements and the Declaration of Helsinki.

Analytical methods

The plasma samples were assayed for fluvastatin using a validated assay method. In each period, 23 blood samples were obtained at 22 time points [pre-dose, 0.167, 0.33, 0.5, 0.67, 0.83, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours following drug administration].

Assessor's comment

The sample collection period covers the elimination half-life of fluvastatin adequately. Blood sampling points are appropriate to allow an accurate measurement of T_{max} . The sampling interval was sufficiently close in the first three hours to cover the period of anticipated C_{max} / t_{max} . The method of collection the assay used and analysis appear to be appropriate.

Pharmacokinetic Variables

The standard pharmacokinetic parameters were obtained using a non-compartmental approach. These included; AUC_t (0- last measurable time point), AUC_{inf} , C_{max} , $Kel(\lambda)$ and $t_{1/2}$. AUC_{inf} , Kel , and $t_{1/2}$ were not estimated from concentration-time profiles where the terminal linear elimination phase was not clearly defined.

Statistical methods

The statistical analysis was applied to the quality assured final data set from all subjects. The ANOVA method was applied to log transformed AUC_t , AUC_{inf} and C_{max} and to untransformed Kel and $t_{1/2}$ parameters. The significance of the sequence, period, and treatment effects were tested. In addition, the subject within sequence random effects was also tested. Using the same models, the least square means the differences between

treatments LSM and the standard errors were estimated for log transformed parameters. Based on these the bioequivalence criteria were defined as below.

Bioequivalence criteria:

90% geometric intervals of the ratio (A/B) of least square means from the ln-transformed values for AUC_{0-t} for fluvastatin should be within 80-125% and C_{max} was to be within 70-143% for fluvastatin.

The decision to use wider intervals for C_{max} was based on the efficacy and safety calculations. The reasons are presented in the protocol and are founded on the compendium of pharmaceuticals & Specialities (2004), a publication by Dujovne CA *et al* regarding similar efficacy /safety of fluvastatin administered at bedtime or 4 hours after an evening meal.

The applicant has presented data demonstrating that the dose at which non-linearity takes effect is beyond 40mg. A number of publications do support this including the NDA file that the applicant discusses. It is considered that the applicant has addressed the issue of linearity. The results demonstrate that the two enantiomers are within the acceptability limits of 80-125%.

Sample size

Sample size of 76 was estimated from calculations using an in-house study indicating an intra-subject variability of ~42%. Further assumptions were used (50% variability and a treatment difference of <10%) a necessary sample for 95% probability to retain 90% CI within 70-143 was estimated to be 76 subjects. Four further subjects were added and thus 80 subjects were recruited.

Assessors comment

The PK variables are appropriate for a bioequivalence study. The statistical methods deployed follow the standard principles and are acceptable.

Results

Table 1. Pharmacokinetic parameters

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUC _t (ng*h/mL)	400.38 435.55 (46)	358.22 395.21 (48)	111.77	106.07 - 117.78	20
AUC _{inf} (ng*h/mL)	404.92 440.15 (45)	362.79 399.72 (48)	111.61	105.96 - 117.56	20
C _{max} (ng/mL)	295.99 337.69 (57)	290.91 343.36 (61)	101.75	90.64 - 114.21	46
T _{max} ^a (h)	1.10 (55)	0.78 (31)	-	-	-
K _{el} ^a (1/h)	0.3499 (42)	0.3461 (39)	-	-	-
T _{half} ^a (h)	2.30 (39)	2.31 (37)	-	-	-

Safety results:

There were a few adverse events reported for both formulations; 26 overall in 18 subjects. Of these, 17 were with the test and 9 with the REF formulation. All events were mild to moderate and only one needed further action/ intervention. Thirteen were considered possibly related to the study medication. The predominant ADR was headache. A summary table is included below.

There were 26 adverse events involving 18 subjects in the study.

Treatment Group	Severity			Relation to the Drug				Intervention	
	Mild	Mod	Severe	Unrelated	Unlikely	Possible	Probable	Required Drug Therapy	Required Non-Drug Therapy
A	17	0	0	7	0	10	0	0	1
B	9	0	0	6	0	3	0	0	0
Total	26	0	0	13	0	13	0	0	1

Assessor's comment:

The study report provides a summary table that is represented above. Both the arithmetic mean and geometric mean are presented. 90% CI for both C_{max} and AUC were within the conventional acceptance criteria of 80-125%.

Pharmacokinetic conclusion

Based on the submitted bioequivalence study, Fluvastatin Teva capsules are considered bioequivalent with Lescol 40mg and corresponding tablets in other nationally authorised brand leader products (Novartis Pharmaceuticals).

The results of study 2005-1016 with 40mg formulation can be extrapolated to other strengths 20 mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Pharmacodynamic studies

Not applicable.

Additional data

No additional clinical data submitted and none are required.

Post marketing experience

No post-marketing data is available. The medicinal product has not been marketed in other any country.

According to Volume 9 - Pharmacovigilance 1.4.2.5.2, less frequent submissions of PSURs than customary for new medicinal products can be appropriate. Lescol 20 & 40mg (UK brand leader) was granted marketing authorisations in 1993 and also marketed since then in UK.

Benefit-Risk assessment

The application contains an adequate review of published clinical data and bioequivalence has been shown. Approval is recommended from the clinical point of view.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**QUALITY**

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

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence data has been demonstrated between the applicant's Fluvastatin 40mg Capsules and Lescol 40mg Capsules (Novartis). No new or unexpected safety concerns arise from these applications. The SPC, PIL and labelling are satisfactory and consistent with that for the innovator products.

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