IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0749/043/001
Case No: 2076636

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Teva Pharma B.V.

Computerweg 10, **3542 DR Utrecht**, **Netherlands**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Fluvastatin Teva 20 mg Capsules

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **09/04/2010** until **24/07/2013**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fluvastatin Teva 20 mg 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 with heterozygous familial hypercholesterolemia
Prior to initiating treatment with fluvastatin in children and adolescents aged 9 years and older with heterozygous familial hypercholesterolaemia, the patient should be placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

The recommended starting dose is 40 mg (1 capsule fluvastatin 40 mg) or 80 mg (1 capsule fluvastatin 40 mg twice daily). The dose of 20 mg fluvastatin (1 capsule fluvastatin 20 mg) may be adequate in mild cases. Starting doses should be individualized according to baseline LDL-C levels and the recommended goal of therapy to be accomplished.

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

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.

Children and adolescents with heterozygous familial hypercholesterolemia
In patients aged <18 years, efficacy and safety have not been studied for treatment periods longer than two years. No data are available about the physical, intellectual and sexual maturation for prolonged treatment period. The long-term efficacy of fluvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established. (see Section 5.1).

Fluvastatin has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia (for details see section 5.1 Pharmacodynamic properties). In the case of pre-pubertal children, as experience is very limited in this group, the potential risks and benefits should be carefully evaluated before the initiation of treatment.

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.

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 indidences 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 $t_{½}$ 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 H_2-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 (≥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 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.

Children and adolescents with heterozygous familial hypercholesterolemia
The safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolemia assessed in 114 patients aged 9-17 years treated in two open non-comparative clinical trials was similar to the one observed in adults. In both clinical trials no effect was observed on growth and sexual maturation. The ability of the trials to detect any effect of treatment in this area was however low.

The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares
- Memory loss
- Sexual dysfunction
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

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 transcathether 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).

Children and adolescents with heterozygous familial hypercholesterolemia
The safety and efficacy of fluvastatin in children and adolescent patients aged 9 - 16 years of age with heterozygous familial hypercholesterolemia has been evaluated in 2 open label, uncontrolled clinical trials of 2 years' duration. 114 patients (66 boys and 48 girls) were treated with fluvastatin administered as either fluvastatin capsules 20 mg - 40 mg bid or fluvastatin 80 mg extended release tablets using a dose-titration regimen based upon LDL-C response.

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

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

In the first study, fluvastatin 20 to 80 mg daily doses decreased plasma levels of total-C and LDL-C by 21% and 27%, respectively. The mean achieved LDL-C was 161 mg/dL equivalent to 4.2 mmol/L (range: 74 - 336 mg/dL equivalent 1.9 – 8.7 mol/L). In the second study, fluvastatin 20 to 80 mg daily doses decreased plasma levels of total-C and LDL-C by 22% and 28%, respectively. The mean achieved LDL-C was 159 mg/dL equivalent to 4.1 mmol/L (range: 90 - 295 mg/dL equivalent to 2.3 – 7.6 mmol/L).

The majority of patients in both studies (83% in the first study and 89% in the second study) were titrated to the maximum daily dose of 80 mg. At study endpoint, 26 to 30% of patients in both studies achieved a targeted LDL-C goal of < 130 mg/dL (3.4 mmol/L).

5.2 Pharmacokinetic properties

Absorption
Fluvastatin is absorbed rapidly and completely (98%) 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).

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

5.3 Preclinical safety data

Repeat toxicity studies with fluvastatin identified a variety of changes that are common to HMG-CoA reductase inhibitors, viz. hyperplasia and hyperkeratosis of the rodent non-glandular stomach, cataracts in dogs, myopathy in rodents, mild liver changes in most laboratory animals with gall bladder changes in 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 Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/043/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 25th July 2008

10 DATE OF REVISION OF THE TEXT

April 2010