PRODUCT MONOGRAPH

[Pr] TEVA-FLUVASTATIN

Fluvastatin Sodium Capsules
20 and 40 mg capsules

Teva Canada Standard

Lipid Metabolism Regulator

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9

Revision Date:
November 7, 2016

Control No: 199645

Table of Contents

[Pr] TEVA-FLUVASTATIN

(fluvastatin as fluvastatin sodium)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	Capsules / 20 mg and 40 mg	Lactose monohydrate, colloidal anhydrous silica, crospovidone, lactose monohydrate, magnesium stearate. **Capsule shell and printing ink:** antifoam DC 1510, black iron oxide, dehydrated alcohol, gelatin, industrial methylated spirit 74 OP BP, n-butyl alcohol, red iron oxide, SDA 3A alcohol, shellac, soya lecithin, titanium dioxide, yellow iron oxide.

INDICATIONS AND CLINICAL USE

Therapy with lipid-altering agents should be considered a component of multiple risk factor intervention in those individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. TEVA-FLUVASTATIN (fluvastatin sodium) should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other non-pharmacological measures alone has been inadequate.

Hypercholesterolemia and Mixed Hyperlipidemia

Adults
TEVA-FLUVASTATIN (fluvastatin sodium) is indicated as an adjunct to diet (at least equivalent to the Adult Treatment Panel III (ATP III TLC diet)) in the treatment of elevated total cholesterol (Total-C), LDL-C and triglycerides (TG) and Apo B levels in patients with primary hypercholesterolemia and mixed hyperlipidemia (Fredrickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures has not been adequate.

Therapy with lipid-altering agents should be considered only after secondary causes for hyperlipidemia such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other medication, or alcoholism, have been excluded. Prior to initiation of fluvastatin sodium, a lipid profile should be performed to measure Total-C, HDL-C and TG. For patients with TG < 4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

LDL-C (mmol/L) = Total-C - HDL-C - 0.37 TG

For TG levels > 4.52 mmol/L, (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases, as with other HMG-CoA reductase inhibitors, TEVA-FLUVASTATIN is not indicated.

Since the goal of treatment is to lower LDL-C, LDL-C levels should be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the Total-C be used to monitor therapy.

TEVA-FLUVASTATIN has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e. hyperlipoproteinemia Types I, III, IV, or V).

Secondary Prevention of Cardiovascular Events
In patients with coronary heart diseases who had undergone a percutaneous intervention (PCI) procedures, TEVA-FLUVASTATIN has been shown to delay the occurrence of major adverse cardiac events (MACE), defined as the first occurrence of cardiac death, nonfatal myocardial infarction or re-intervention procedures (see **CLINICAL TRIALS**).

CONTRAINDICATIONS

TEVA-FLUVASTATIN (fluvastatin sodium) is contraindicated under the following conditions:

- TEVA-FLUVASTATIN (fluvastatin sodium) is contraindicated in patients with known hypersensitivity to any component of this medication (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- TEVA-FLUVASTATIN is contraindicated in patients with active liver disease or unexplained, persistent clinically relevant elevations in serum transaminases (see WARNINGS AND PRECAUTIONS - Hepatic).
- As with other drugs of this class, TEVA-FLUVASTATIN is contraindicated during pregnancy and in nursing mothers (see WARNINGS AND PRECAUTIONS – Special Populations – Pregnant Women / Nursing Women). Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). TEVA-FLUVASTATIN should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the possible harm. If the patient becomes pregnant while taking TEVA-FLUVASTATIN, the drug should be discontinued immediately and the patient apprised of the potential harm to the fetus. Atherosclerosis being a chronic process, discontinuation of lipid metabolism regulating drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia (see WARNINGS AND PRECAUTIONS – Special Populations - Pregnant Women / Nursing Women).

WARNINGS AND PRECAUTIONS

General

Before instituting therapy with TEVA-FLUVASTATIN (fluvastatin sodium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight and obese patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). The patient should be advised to inform subsequent physicians of the prior use of TEVA-FLUVASTATIN or any other lipid metabolism regulator.

Endocrine and Metabolism

Increases in fasting glucose and HbA1c levels have been reported with inhibitors of HMG-CoA reductase as a class. For some patients, at high risk of diabetes mellitus, hyperglycemia was sufficient to shift them to the diabetes status. The benefit of treatment continues to outweigh the small increased risk. Periodic monitoring of these patients is recommended.

Muscle Effects

Effects on skeletal muscle such as rare cases of myalgia, myopathy and, very rarely, rhabdomyolysis have been reported in patients treated with fluvastatin sodium.

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with TEVA-FULVASTATIN and with other HMG-CoA reductase inhibitors.

Myopathy, defined as muscle pain or muscle weakness in conjunction with increases in creatine phosphokinase (CK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or a marked elevation of CK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if associated with malaise or fever. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. TEVA-FLUVASTATIN therapy should be discontinued if markedly elevated CK levels are measured or myopathy is diagnosed or suspected.

CK measurement:

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

Pre-disposing Factors for Myopathy/Rhabdomyolysis:

TEVA-FLUVASTATIN, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- Personal or family history of hereditary muscular disorders
- Previous history of muscle toxicity with another HMG-CoA reductase inhibitor
- Concomitant use of a fibrate or niacin
- Hypothyroidism
- Alcohol Abuse
- Excessive physical exercise
- Age >70 years
- Renal impairment
- Hepatic impairment
- Diabetes with hepatic fatty change
- Severe metabolic, endocrine or electrolyte disorders
- Surgery and trauma
- Frailty
- Situations where an increase in plasma levels of active ingredient may occur
- Sepsis
- Hypotension
- Uncontrolled epilepsy

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (> 5 x Upper Levels 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.

TEVA-FLUVASTATIN therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of myopathy or predisposing to the development of rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic endocrine and electrolyte disorders, or uncontrolled seizures).

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

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

An increased risk of myopathy has been reported with HMG-CoA reductase inhibitors which are predominantly CYP3A4 substrates when administered concomitantly with other drugs metabolized by the CYP3A4 isoenzymes such as immunosuppressive drugs, including cyclosporine, colchicines, fibrates, macrolide antibiotics, azole antifungal agents, selective serotonine reuptake inhibitors, or niacin at lipid lowering doses.

Since fluvastatin is predominantly metabolized by the CYP2C9 isoenzyme and not metabolized to a significant extent by other cytochrome subclasses, including CYP3A4, it is not expected to increase the risks of myopathy when co-administered with other drugs metabolized by the P450 isoenzyme system. The benefits and risks of using HMG-CoA reductase inhibitors concomitantly

with immunosuppressive drugs, erythromycin, or other drugs metabolized by the P450 enzyme system, fibrates or lipid-lowering doses of niacin should nevertheless be carefully considered (see WARNINGS AND PRECAUTIONS - Pharmacokinetic Interactions, and DRUG INTERACTIONS - Cytochrome P450).

Experience to date with the use of fluvastatin together with cyclosporine consists of 3 pharmacokinetics studies (fluvastatin doses of 20 mg, 40 mg), 17 clinical trials of small-medium size and short-, medium-term duration (fluvastatin doses of 20 mg, 40 mg, 40 mg BID) in renal and heart transplant recipients, and one large prospective placebo-controlled trial in 2,102 renal transplant recipients followed up for 5 to 6 years (fluvastatin doses of 40 mg and 40 mg BID). Published data indicate that the trough concentration of cyclosporine A was not changed (see DETAILED PHARMACOLOGY - Pharmacokinetics, DRUG INTERACTIONS – Drug-Drug Interactions – Immunosuppressive Drugs, and REFERENCES). No correlation between systemic fluvastatin levels and musculoskeletal adverse events or biochemical markers of musculoskeletal damage or renal function impairment have been observed in clinical trials conducted to date. In post-marketing experience, isolated cases of myopathy have been reported when fluvastatin was co-administered with cyclosporine**.**

Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with fluvastatin sodium together with niacin at lipid lowering doses.

The use of fibrates alone or in combination with HMG-CoA reductase inhibitors has been occasionally associated with myopathy. In short-term studies involving a small number of patients, myopathy was not reported during administration of bezafibrate and fluvastatin sodium at doses of 40 mg/day and 60 mg/day. To date, the 80 mg/day dose has not been evaluated with bezafibrate.

Interruption of therapy with TEVA-FLUVASTATIN should be considered in any patient with an acute serious condition suggestive of myopathy or having a risk factor predisposing to the development of renal failure or rhabdomyolysis, such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine or electrolyte disorders and uncontrolled seizures.

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the same cytochrome P-450 isoenzyme system particularly the CYP3A4. The various HMG-CoA reductase inhibitors differ with respect to the P450 isoenzyme involved in their metabolism. Fluvastatin sodium is predominantly metabolized by the CYP2C9 subclass of the P450 cytochromes and therefore is not expected to interact with drugs known to be CYP3A4 substrates, such as immunosuppressants, macrolide antibiotics, selective serotonine reuptake inhibitors, azole antifungal agents, or grapefruit juice. It may interact, however, with CYP2C9 substrates, e.g. nonsteroidal anti-inflammatory drugs or oral anticoagulants. These potential interactions may be less clinically relevant due to the overlap between the different CYP2C isoenzymes (see WARNINGS AND PRECAUTIONS - Muscle Effects and DRUG INTERACTIONS).

For more information, please refer to REFERENCES - Drug Interactions.

Carcinogenesis and Mutagenesis
See TOXICOLOGY

Cardiovascular
Effect on CoQ_{10} levels (ubiquinone)
A significant decrease in plasma CoQ_{10} levels in patients treated with fluvastatin sodium and other statins has been observed in short-term clinical trials. The clinical significance of a potential long-term statin-induced deficiency of CoQ_{10} has not yet been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure.

Endocrine and Metabolism
Homozygous Familial Hypercholesterolemia
Fluvastatin sodium has not been evaluated in patients with rare homozygous familial hypercholesterolemia. Most HMG-CoA reductase inhibitors are less or not effective in this subgroup of hypercholesterolemic patients. For heterozygous familial hypercholeslerolemia (see CLINICAL TRIALS).

Effect on lipoprotein (A) [Lp(a)]
In some patients the beneficial effect of lowered total cholesterol and LDL cholesterol levels may be partly blunted by a concomitant increase in the Lp(a) levels. Until further experience is obtained from controlled clinical trials, it is suggested, where feasible, that Lp(a) measurements be carried out in patients placed on therapy with TEVA-FLUVASTATIN.

Endocrine function
HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such could theoretically blunt adrenal and/or gonadal steroid production.

Fluvastatin sodium exhibited no effect upon non-stimulated cortisol levels, FSH (males only) or thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treated groups, but no commensurate elevation in LH occurred. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in an adequate number of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with fluvastatin sodium who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones.

Hepatic
TEVA-FLUVASTATIN, as well as other HMG-CoA reductase inhibitors should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

Active liver disease or unexplained transaminase elevations are contraindications to the use of

TEVA-FLUVASTATIN; if such condition develops during therapy, the drug should be discontinued.

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents.

Overall, 25 of 2373 patients (1.1%) treated with fluvastatin sodium in worldwide controlled clinical trials developed marked persistent elevations (to more than 3 times the upper limit of normal) in transaminase levels requiring discontinuation of treatment in 14 (0.6%) patients. The incidence of such elevations varied from 0.9% at 20 mg/day to 1.9 % at 80 mg/day.

In all clinical trials (controlled and uncontrolled) with fluvastatin sodium, ranging from 28 to 71.2 weeks of exposure, 33 of 2969 (1.1%) patients had persistent transaminase elevations requiring discontinuation of treatment in 19 (0.6%) patients. In the majority of patients, these abnormal biochemical findings were asymptomatic.

In a retrospective pooled analysis of all placebo-controlled studies of at least 6 weeks and up to 130 weeks with fluvastatin sodium, all patients with transaminase elevations >3 times the upper limit of normal were evaluated. A total of 1814 patients received daily either 20 mg, 40 mg or 80 mg (40 mg b.i.d.) fluvastatin sodium.

All patients with persistent (two consecutive occasions) transaminase elevations >3 times the upper limit of normal had abnormal transaminase elevations at either baseline (before initiation of therapy) and/or by 8 weeks after the start of therapy or dose increase.

Post marketing cases of fatal and non-fatal hepatic failures have been reported with fluvastatin sodium regardless of the dose used. Although a causal relationship with fluvastatin treatment has not been determined, patients should be advised to report any potential symptoms or signs of hepatic failure (e.g. nausea, vomiting, loss of appetite, jaundice, impaired brain function, easy bruising or bleeding), and treatment discontinuation should be considered.

It is recommended that liver function tests be performed at baseline and 8 weeks after initiation of treatment as well as after an increase in the dose. Particular attention should be paid to patients who develop abnormal serum transaminase levels or signs and symptoms of liver disease. In these patients, measurements should be repeated promptly to confirm the finding and then performed more frequently until the abnormality(ies) returns to normal.

If the transaminase levels show evidence of progression, particularly if they rise to three times the upper limit of normal and are persistent, the drug should be discontinued.

Immune

Rare cases of hypersensitivity reactions, such as rash, urticaria, eczema and other skin reactions (e.g. dermatitis, bullous exanthema), thrombocytopenia, angioedema, face edema, vasculitis and lupus erythematous syndrome have been reported during post-marketing experience with fluvastatin sodium capsules. If hypersensitivity is suspected, TEVA-FLUVASTATIN should be discontinued. Patients should be advised to report to their doctors promptly any signs of

hypersensitivity such as rash, angioedema, urticaria, photosensitivity, polyarthralgia, fever and malaise.

Immune mediated necrotizing myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by:

- proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment;
- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents.

Ophthalmologic

Current data from long-term clinical trials do not indicate an adverse effect of fluvastatin sodium on the human lens.

Renal

Because fluvastatin sodium does not undergo significant renal excretion modification of dosage should not be necessary in patients with mild to moderate renal impairment (creatinine clearance > 30 mL/min).

As there is no experience with fluvastatin sodium in patients with severe renal insufficiency (creatinine > 260 μmol/L, i.e. creatinine clearance < 30 mL/min), its use cannot be recommended in this patient population.

Special Populations

Pregnant Women:

TEVA-FLUVASTATIN is contraindicated during pregnancy (see CONTRAINDICATIONS). Data on the use of fluvastatin sodium in pregnant women is limited. A few reports have been received of congenital anomalies in infants whose mothers were treated during a critical period of pregnancy with other HMG-CoA reductase inhibitors. During the clinical program, a total of 5 women who were receiving fluvastatin sodium became pregnant and were discontinued from the studies. Of these 5 women, 3 gave birth to healthy babies, one experienced an ectopic pregnancy which was attributed to a severely scarred fallopian tube and one spontaneously aborted.

Atherosclerosis is a chronic process and discontinuation of lipid metabolism regulators during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women.

TEVA-FLUVASTATIN should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus (see CONTRAINDICATIONS).

Nursing Women
It is not known whether fluvastatin sodium is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fluvastatin sodium, women receiving TEVA-FLUVASTATIN should not breast-feed (see CONTRAINDICATIONS).

Pediatrics
Limited experience with the use of other HMG-CoA reductase inhibitors is available in children. Safety and effectiveness of fluvastatin sodium in children have not been established.

Geriatrics
The effect of age on the pharmacokinetics of immediate release fluvastatin sodium capsules was evaluated. Results indicate that for the general patient population plasma concentrations of fluvastatin sodium do not vary either as a function of age or gender (see ACTIONS AND CLINICAL PHARMACOLOGY: Pharmacokinetics). Elderly patients may be more susceptible to myopathy (see WARNINGS AND PRECAUTIONS – Muscle Effects – Pre-disposing Factors for Myopathy/Rhabdomyolysis).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

In all clinical studies (controlled and uncontrolled) with fluvastatin sodium capsules, 1% (32/2969) of fluvastatin sodium patients were discontinued due to adverse experiences attributed to study drug (mean exposure of approximately 16 months ranging in duration from one to more than 36 months). This result, in controlled studies, in an exposure adjusted incidence of 0.8% per patient year in fluvastatin patients compared to an incidence of 1.1% in placebo patients. Adverse events were usually mild and transient.

Clinical adverse reactions of positive or uncertain relationship to study medication occurring at a frequency $\geq$ 1% in controlled clinical trials with fluvastatin sodium capsules are shown in the table below.

Table 1: Adverse Events of Positive or Uncertain Relationship to Study Medication Occurring in ≥ 1% in Controlled Clinical Trials with fluvastatin sodium.

ADVERSE EVENT	fluvastatin sodium [1]			PLACEBO [1]
	20 mg OD (N=1425) %	40 mg OD (N=1136) %	40 mg BID (N=369) %	(N=960) %
GASTROINTESTINAL				
Dyspepsia	4.7	4.8	7.3	2.3
Constipation	2.8	1.8	2.4	2.5
Abdominal Pain	2.7	2.1	3.8	2.0
Flatulence	2.5	1.9	1.6	2.2
Diarrhea	2.5	1.5	1.6	2.1
Nausea	2.0	1.6	0.8	1.4
Eructation	1.4	0.6	0.5	1.1
MUSCOLOSKELETAL				
Myalgia	1.7	1.8	2.7	2.3
Arthralgia	1.4	1.4	1.4	1.5
Back pain	1.0	0.8	1.1	1.6
CENTRAL NERVOUS SYSTEM				
Dizziness	0.9	1.1	0.5	1.8
Abnormal vision	1.0	0.9	1.1	1.4
PSYCHIATRIC				
Insomnia	1.9	1.3	0.3	0.9
RESPIRATORY				
Upper respiratory infection	1.1	0.9	2.4	1.9
INTEGUMENTARY				
Rash	1.5	0.8	1.9	1.6
MISCELLANEOUS				
Headache	3.8	2.7	1.9	3.0
Fatigue	1.8	1.5	0.5	1.8
Chest pain	0.3	0.9	1.4	0.5

1. Controlled trials with Fluvastatin sodium capsules (20 and 40 mg daily and 40 mg twice daily)

Other Adverse Events occurring more than 1% in controlled clinical trials include: heartburn, tooth disorder, pharyngitis, sinusitis, coughing, and accidental trauma.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Other clinical adverse reactions of positive or uncertain relationship to study medication occurring in 0.5% to 1.0% of patients receiving 20-80mg fluvastatin sodium capsules monotherapy in controlled clinical trials (N=2326) are listed below:

Gastrointestinal: Vomiting, gastritis.
Musculoskeletal: Arthritis.
Central Nervous System: conjunctivitis, paresthesia.
Respiratory: Rhinitis.
Integumentary: Pruritus.
Miscellaneous: Leg pain, influenza-like symptoms, allergy.

Post-Market Adverse Drug Reactions:

The following adverse events have also been reported during post-marketing experience with fluvastatin sodium, regardless of causality assessment.

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Endocrine disorders

Increases in fasting glucose and HbA1c levels have been reported with fluvastatin sodium.

Hypersensitivity Reaction

Rare cases of hypersensitivity reactions, such as rash, urticaria, eczema, and other skin reactions (e.g. dermatitis, bullous exanthema), thrombocytopenia, angioedema, face edema, vasculitis, and lupus erythematous-like syndrome have been reported during post-marketing experience.

An apparent hypersensitivity syndrome has also been reported rarely with other HMG-CoA reductase inhibitors and has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocytes sedimentation rate (ESR) increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiform, including Stevens-Johnson syndrome.

Very rare cases of anaphylactic reaction have been reported with fluvastatin sodium.

Skeletal: Rarely: muscle tenderness, muscle weakness and myopathy. Very rarely: myositis, rhabdomyolysis (see WARNINGS AND PRECAUTIONS – Muscle Effects).

Musculoskeletal and connective tissue disorders: Immune-mediated necrotizing myopathy (see WARNINGS AND PRECAUTIONS).

Central and Peripheral Nervous System: Very rarely: dysesthesia and hypoesthesia, also know to be associated with the underlying hyperlipidemic disorder.

Liver: Very rarely: hepatitis, fatal and non-fatal liver failure.

Gastrointestinal: Very rarely: pancreatitis.

Investigations: Common: Blood CK increased, blood transaminases increased.

Reproductive system and breast disorders: Erectile dysfunction.

The following effects have been reported with drugs of this class:

Skeletal: Myopathy, rhabdomyolysis (see WARNINGS AND PRECAUTIONS – Muscle Effects), muscle cramping/pain.

Neurological: Paresthesia, peripheral neuropathy, psychiatric disturbances/anxiety, mood related disorders including depression, sleep disturbances including insomnia and nightmares.

Gastrointestinal: Hepatitis, cholestatic jaundice, anorexia, vomiting. Very rarely: acute pancreatitis.

Skin: Alopecia.

Pulmonary: Very rare cases of interstitial lung disease, especially with long term therapy. If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Miscellaneous: Asthenia, sweating, hot flushes, gynecomastia.

DRUG INTERACTIONS

Overview

Pharmacokinetic and pharmacodynamic studies conducted with drugs in healthy subjects may not detect the possibility of potential drug interactions in some patients due to differences in underlying disease(s), age or renal function (see WARNINGS AND PRECAUTIONS – Renal, Special Populations – Geriatrics; and DRUG INTERACTIONS - Patients with Severe Hypercholesterolemia).

Concomitant Therapy with other Lipid Metabolism Regulators

Information on combination drug therapy from controlled studies is limited. Based on post-marketing surveillance, gemfibrozil, fenofibrate, other fibrates and lipid lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone (see WARNINGS AND PRECAUTIONS - Muscle Effects). Therefore, combined drug therapy should be approached with caution.

Drug-Drug Interactions

A drug interactive effect (pharmacokinetic and/or clinical) has been shown for the following drugs in combination with fluvastatin sodium:

Cholestyramine:
The cholesterol-lowering effects of fluvastatin sodium and the bile acid sequestrant, cholestyramine, are additive.

Administration of immediate release fluvastatin sodium concomitantly 2 to 4 hours after cholestyramine, results in fluvastatin decreases of more than 50% for the fluvastatin AUC and

50-80% for the fluvastatin C_{max}. However, administration of immediate release fluvastatin sodium 4 hours after cholestyramine resulted in a clinically significant additive effect in reducing Total-C and LDL-C compared with that achieved with either component drug.

Gemfibrozil/Fenofibrate/Niacin:
Myopathy, including rhabdomyolysis, has occurred in patients who were receiving co-administration of HMG-CoA reductase inhibitors with fibric acid derivatives and niacin (in lipid lowering doses), particularly in subjects with pre-existing renal insufficiency (see WARNINGS AND PRECAUTIONS - Muscle Effects). Fluvastatin sodium capsules have been safely administered concomitantly with nicotinic acid, gemfibrozil and bezafibrate in clinical studies.

In short-term studies involving a small number of patients, myopathy was not reported during administration of bezafibrate and fluvastatin sodium at doses of 40 mg/day and 60 mg/day. To date, the 80 mg/day dose has not been evaluated with bezafibrate. An additional interaction study between 20mg o.d. fluvastatin and 200mg t.d.s. bezafibrate showed that mean AUC and C_{max} values of fluvastatin were increased on average by about 50-60%. No effect was seen on bezafibrate pharmacokinetics. This combination should be used with caution**,** however, due to the increased risk of developing myopathy and/or rhabdomyolysis when HMG-CoA reductase inhibitors including fluvastatin have been combined with fibrates. Any patient complaining of myalgia should be carefully evaluated.

Cimetidine/Ranitidine/Omeprazole:
Concomitant administration of fluvastatin sodium capsules with cimetidine, ranitidine and omeprazole results in a significant increase in the fluvastatin C_{max} (43%, 70% and 50%, respectively) and AUC (24 to 33%), with an 18 to 23% decrease in apparent oral plasma clearance (Cl/F).

Digoxin:
In a crossover study involving 18 patients chronically receiving digoxin, concomitant administration of a single 40 mg dose of fluvastatin sodium capsule had no effect on digoxin AUC and small but clinically insignificant increases in the digoxin C_{max} and urinary clearance were noted.

Rifampicin:
Administration of fluvastatin sodium capsules to subjects pre-treated with rifampicin results in significant reduction in C_{max} (59%) and AUC (51%) of fluvastatin, with a large increase (95%) in plasma clearance.

Antipyrine:
Administration of fluvastatin sodium does not influence the metabolism and excretion of antipyrine, either by induction or inhibition.

Cardiovascular agents:
Concomitant administration of propranolol has no effect on the bioavailability of fluvastatin sodium. No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with losartan or amlodipine, although mild to moderate adverse events were reported upon concomitant administration of fluvastatin and amlodipine (see

ADVERSE REACTIONS).

Warfarin and other coumarin derivatives:
In vitro protein binding studies demonstrated no interaction at therapeutic concentrations. In a drug interaction study, the concomitant use of fluvastatin sodium capsules and warfarin did not alter the 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.

Cytochrome P450
Fluvastatin is predominantly metabolized by the hepatic microsomal CYP2C9 subclass of the P450 cytochromes. It is not metabolized to a significant extent by other cytochrome subclasses, including CYP3A4. The clearance of drugs which are also CYP2C9 substrates may decrease when co-administered with fluvastatin. However, for those CYP2C9-metabolized drugs which have been studied directly, including diclofenac, tolbutamide, and warfarin, the effect on clearance is small and no clinically significant drug interactions of fluvastatin with other CYP2C9 substrates have been demonstrated. Caution should nevertheless be exercised with concomitant use of drugs metabolized by the CYP2C9 subclass of the P450 cytochromes such as phenytoin, oral anticoagulants (e.g. warfarin), oral hypoglycemic agents (e.g. tolbutamide, chlorpropamide) and nonsteroidal anti-inflammatory drugs (e.g. diclofenac) (see WARNINGS AND PRECAUTIONS - Muscle Effects).

Since fluvastatin sodium is predominantly metabolized by the CYP2C9 subclass of the P450 cytochromes and not metabolized to a significant extent by other cytochrome subclasses, including CYP3A4, it is not expected to increase the risks of drug interactions when combined with drugs or common agents such as grapefruit juice that inhibit this enzyme (immunosuppressants, azole-type antifungal agents, macrolide antibiotics or antidepressants) (see WARNINGS AND PRECAUTIONS – Pharmacokinetics Interactions - Muscle Effects, and REFERENCES).

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, cyclosporin) are unlikely to affect the bioavailability of fluvastatin (see WARNINGS AND PRECAUTIONS – Muscle Effects).

Fluconazole
Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP2C9 inhibitor) resulted in a significant increase in the exposure, elimination half life and peak concentration of fluvastatin by about 84%, 80% and 44%, respectively. 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.

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 glycemic control.

In glyburide-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 glyburide approximately 50%, 69% and 121%, respectively. Glyburide (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 glyburide (glibenclamide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 80 mg per day.

Phenytoin
The overall magnitude of the changes in phenytoin pharmacokinetics during co-administration with fluvastatin are 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.

Colchicines
Myotoxicity, including muscle pain and weakness and rhabdomyolysis, has been reported anecdotally with concomitant administration of fluvastatin and colchicine during acute exacerbation of gouty arthritis.

Patients with severe hypercholesterolemia
Higher dosages (80 mg/day) required for some patients with severe hypercholesterolemia are associated with increased plasma levels of fluvastatin. Caution should be exercised in such patients who are also significantly renally impaired, elderly, or are also concomitantly being administered digoxin, or CYP 450 inhibitors (see WARNINGS AND PRECAUTIONS - Pharmacokinetic Interactions, and Muscle Effects; and DRUG INTERACTIONS).

Although specific interaction studies were not performed with all drugs listed below, in clinical studies, fluvastatin sodium was used concomitantly with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium-channel blockers, oral sulphonylureas, antacids, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence to date of clinically significant interactions.

Immunosuppressive Drugs:
In a pharmacokinetic study conducted in 19 stable renal transplant patients receiving cyclosporine A concomitantly with fluvastatin 20 mg/day, the AUC for fluvastatin was increased by 1.9 times. Similarly, in a pharmacokinetic study conducted in 19 stable renal transplant patients on stable cyclosporine A regimen who received fluvastatin extended release 80 mg/day for 1 week, both the AUC and C_{max} for fluvastatin were increased by two fold as compared with data from historical controls treated with the same fluvastatin regimen. The trough concentration of cyclosporine A was not changed. In heart transplant patients treated with fluvastatin 40 mg/day and cyclosporine A for four weeks, AUC for fluvastatin was increased 3.5 times and 3.1 times in

patients than in the age-matched healthy controls on study days 1 and 28, respectively (see DETAILED PHARMACOLOGY - Pharmacokinetics, and REFERENCES). In post-marketing experience, isolated cases of myopathy have been reported when fluvastatin was co-administered with cyclosporine (see WARNINGS AND PRECAUTIONS: Muscle Effects).

Drug-Food Interactions

There were no apparent differences in the lipid-lowering effects of fluvastatin when administered with the evening meal or four (4) hours after the evening meal (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics – Absorption). Based on the lack of interaction of fluvastatin with other CYP3A4 substrates, fluvastatin is not expected to interact with grapefruit juice.

Drug-Laboratory Interactions

The HMG-CoA reductase inhibitors may cause elevation of transaminase levels (see WARNINGS AND PRECAUTIONS). Marked elevations of CK levels to more than 5 x ULN developed in a very small number (0.3-1.0%) of patients on fluvastatin sodium. In the differential diagnosis of chest pain in a patient on TEVA-FLUVASTATIN cardiac and noncardiac fractions of these enzymes should be determined.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the Adult Treatment Panel III (ATP III TLC diet)] before receiving TEVA-FLUVASTATIN, and should continue on this diet during treatment with TEVA-FLUVASTATIN. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with TEVA-FLUVASTATIN, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of TEVA-FLUVASTATIN capsule, if cholesterol levels fall below the desired range.

Recommended Dose and Dosage Adjustment

Adults

Hypercholesterolemia and Mixed Hyperlipidemia

For patients requiring LDL-C reduction of less than 25%, a starting dose of 20 mg TEVA-FLUVASTATIN capsule taken once daily is recommended.

For patients requiring LDL-C reduction of at least 25%, the recommended starting dose is 40 mg daily of TEVA-FLUVASTATIN capsule taken once daily. If necessary, the dosage of TEVA-FLUVASTATIN may then be increased to 80 mg of TEVA-FLUVASTATIN taken in divided doses of 40 mg twice daily.

TEVA-FLUVASTATIN capsules may be taken consistently with or without food, in the evening or at bedtime. TEVA-FLUVASTATIN capsules must be swallowed whole with a glass of water.

Since maximal reduction in LDL-C is seen within 4 weeks of administration of a given dose of TEVA-FLUVASTATIN capsule, periodic lipid level determination should be performed with dosage adjusted to a maximum of 80 mg of fluvastatin daily, according to patient response.

Severe Hypercholesterolemia
In patients with severe hypercholesterolemia, higher dosages (up to 80 mg/day) may be required (see WARNINGS AND PRECAUTIONS - Pharmacokinetic Interactions and Muscle Effects - DRUG INTERACTIONS). The maximum recommended daily dosage is 80 mg/day.

Secondary Prevention of Cardiovascular Events (See Hypercholesterolemia and Mixed Hypercholesterolemia)
During the Fluvastatin Sodium Intervention Prevention Study, patients were initiated on fluvastatin treatment at 40 mg twice a day with no titration from a lower dose level. This daily dose was proven to be as well tolerated as placebo.

Therefore, in patients with coronary heart disease who have undergone a percutaneous intervention procedure, the appropriate dose of TEVA-FLUVASTATIN is 40 mg twice a day.

Concomitant Therapy
See DRUG INTERACTIONS

Dosage in Patients with Renal Impairment
See WARNINGS AND PRECAUTIONS - Renal

Dosage in Patients with Hepatic Impairment
See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS - Hepatic

Use in the Elderly
See WARNINGS AND PRECAUTIONS – Geriatrics

Use in Children
See WARNINGS AND PRECAUTIONS – Pediatrics

The dosage of TEVA-FLUVASTATIN should be individualized according to baseline LDL-C, total-C/HDL-C ratio and/or TG levels to achieve the desired lipid values at the lowest possible dose. Lipid levels should be monitored periodically and, if necessary, the dose of TEVA-FLUVASTATIN adjusted accordingly.

OVERDOSAGE

For management of a suspected drug overdose, contact your Regional Poison Control Centre immediately.

The maximum single oral dose of fluvastatin sodium received by healthy volunteers was 80 mg. No clinically significant adverse experiences were seen at this dose.

The maximum dose administered with an extended release formulation was 640 mg for two weeks. This dose was not well tolerated and produced a variety of GI complaints and an increase in transaminase values (i.e., ALT and AST).

There has been a single report of two children, one 2 year old and the other 3 years of age, either of whom may have possibly ingested fluvastatin sodium. The maximum amount of fluvastatin sodium ingested was 80 mg (4 x 20 mg capsules). Vomiting was induced by ipecac in both children and no capsules were noted in their emesis. Neither child experienced any adverse symptoms and both recovered from the incident without problems.

Specific treatment is not available for TEVA-FLUVASTATIN overdose. Should an overdose occur, the patient should be treated symptomatically and supporting measures should be undertaken as required. Liver function tests and serum CK levels should be monitored. The dialysability of fluvastatin sodium and its metabolites in man is not known at present.

ACTION AND CLINICAL PHARMACOLOGY

TEVA-FLUVASTATIN (fluvastatin sodium) is a fully synthetic HMG-CoA reductase inhibitor and is hydrophilic. Fluvastatin sodium is a racemate of two erythro enantiomers of which one exerts the pharmacological activity.

Mechanism of Action

Fluvastatin sodium is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (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 the 3R,5S enantiomer exerts the pharmacological activity. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The ultimate result of these mechanisms is a reduction of the plasma total cholesterol (Total-C) and low density lipoprotein cholesterol (LDL-C) concentrations.

Epidemiologic and clinical studies have associated the risk of coronary artery disease (CAD) with elevated levels of Total-C, LDL-C and decreased levels of HDL-C. These abnormalities of lipoprotein metabolism are considered as major contributors to the development of the disease. Other factors, e.g. interactions between lipids/lipoproteins and endothelium, platelets and macrophages, have also been incriminated in the development of human atherosclerosis and of its complications. Effective treatment of hypercholesterolemia/dyslipidemia in long-term clinical

trials has consistently been associated with a reduced risk of CAD.

Pharmacodynamics

A variety of clinical studies has demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (a membrane transport complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. In multicentre clinical trials, those pharmacologic and/or non-pharmacologic interventions that simultaneously lowered LDL-C and increased HDL-C reduced the rate of cardiovascular events (both fatal and non-fatal myocardial infarctions) in high risk males or in males and females with established coronary artery disease.

Fluvastatin sodium reduces total-C, LDL-C, apo-B, and TG, and marginally increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is well established within 2 weeks, and maximum response is achieved within 4 weeks from treatment initiation and maintained during chronic therapy.

Pharmacokinetics

Table 2: Summary of Fluvastatin Sodium Pharmacokinetic Parameters in Single-Dose and Steady-State Studies

	C_{max} (ng/mL) mean ± SD (range)	$t_{½}$ (h) mean ± SD (range)	$AUC_{0-\infty}$ (ng • h/mL) mean ± SD (range)	Clearance (L/h) mean ± SD (range)	T_{max} (h) mean ± SD (range)
Capsules					
20 mg single dose (n = 17)	166 ± 106 (48.9-517)	2.5 ± 1.7 (0.5-6.6)	207 ± 65 (111-288)	107 ± 38.1 (69.5-181)	0.9 ± 0.4 (0.5-2.0)
20 mg twice daily (n = 17)	200 ± 86 (71.8-366)	2.8 ± 1.7 (0.9-6.0)	275 ± 111 (91.6-467)	87.8 ± 45 (42.8-218)	1.2 ± 0.9 (0.5-4.0)
40 mg single dose (n = 16)	273 ± 189 (72.8-812)	2.7 ± 1.3 (0.8-5.9)	456 ± 259 (207-1221)	108 ± 44.7 (32.8-193)	1.2 ± 0.7 (0.75-3.0)
40 mg twice daily (n = 16)	432 ± 236 (119-990)	2.7 ± 1.3 (0.7-5.0)	697 ± 275 (359-1559)	64.2 ± 21.1 (25.7-111)	1.2 ± 0.6 (0.5-2.5)

Absorption:

TEVA-FLUVASTATIN (fluvastatin sodium) is absorbed rapidly and completely following oral administration of the capsule, with peak concentrations reached in less than 1 hour. Following administration of a 10 mg dose, the absolute bioavailability is 24% (range 9%-50%). Administration with food reduces the rate but not the extent of absorption. At steady-state, administration of fluvastatin with the evening meal results in a two-fold decrease in C_{max} and more than two-fold increase in T_{max} as compared to administration 4 hours after the evening meal. No significant differences in extent of absorption or in the lipid-lowering effects were observed between the two administrations. After single or multiple doses above 20 mg,

fluvastatin exhibits saturable first-pass metabolism resulting in higher-than-expected plasma fluvastatin concentrations.

Fluvastatin has two optical enantiomers, an active 3R,5S and an inactive 3S,5R form. In vivo studies showed that stereo-selective hepatic binding of the active form occurs during the first pass resulting in a difference in the peak levels of the two enantiomers, with the active to inactive peak concentration ratio being about 0.7. The approximate ratio of the active to inactive approaches unity after the peak is seen and thereafter the two enantiomers decline with the same half-life. After an intravenous administration, bypassing the first-pass metabolism, the ratios of the enantiomers in plasma were similar throughout the concentration-time profiles.

Distribution:
Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution (VDss) is estimated at 0.35 L/kg. The parent drug is targeted to the liver and no active metabolites are present systemically. At therapeutic concentrations, the protein binding of fluvastatin is not affected by warfarin, salicylic acid and glyburide.

Metabolism:
Fluvastatin is metabolized in the liver, primarily via hydroxylation of the indole ring at the 5 and 6-positions. N-dealkylation and beta-oxidation of the side-chain also occurs. The hydroxy metabolites have some pharmacologic activity, but do not circulate in the blood. Both enantiomers of fluvastatin are metabolized in a similar manner.

In vitro studies demonstrated that fluvastatin undergoes oxidative metabolism, predominantly via 2C9 isozyme systems (75%). Other isozymes that contribute to fluvastatin metabolism are 2C8 (~5%) and 3A4 (~20%) (see **DRUG INTERACTIONS**).

Excretion:
Fluvastatin is primarily (about 90%) eliminated in the feces as metabolites, with less than 2% present as unchanged drug. Urinary recovery is about 5%. After a radiolabeled dose of fluvastatin, the clearance was 0.8 L/h/kg. Following multiple oral doses of radiolabeled compound, there was no accumulation of fluvastatin; however, there was a 2.3 fold accumulation of total radioactivity.

Steady-state plasma concentrations show no evidence of accumulation of fluvastatin following immediate release capsule administration of up to 80 mg daily, as evidenced by a beta-elimination half-life of less than 3 hours. However, under conditions of maximum rate of absorption (i.e., fasting) systemic exposure to fluvastatin is increased 33% to 53% compared to a single 20 mg or 40 mg dose of the immediate release capsule.

STORAGE AND STABILITY
Store between 15 and 30°C in a tight container. Protect from light and humidity.

SPECIAL HANDLING INSTRUCTIONS

Not applicable

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Active Ingredient: fluvastatin sodium

Inactive Ingredients: colloidal anhydrous silica, crospovidone, lactose monohydrate, magnesium stearate. **Capsule shell and printing ink:** antifoam DC 1510, black iron oxide, dehydrated alcohol, gelatin, industrial methylated spirit 74 OP BP, n-butyl alcohol, red iron oxide, SDA 3A alcohol, shellac, soya lecithin, titanium dioxide, yellow iron oxide.

Dosage Forms and Packaging:

TEVA-FLUVASTATIN Capsules 20 mg – Hard gelatin capsules with light yellow opaque body and pink opaque cap, filled with an off-white to yellowish powder with small agglomerates.
Body and cap imprint: 93
7442
Available in bottles of 100.

TEVA-FLUVASTATIN Capsules 40 mg - Hard gelatin capsules with yellow opaque body and pink opaque cap, filled with an off-white to yellowish powder with small agglomerates.
Body and cap imprint: 93
7443
Available in bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

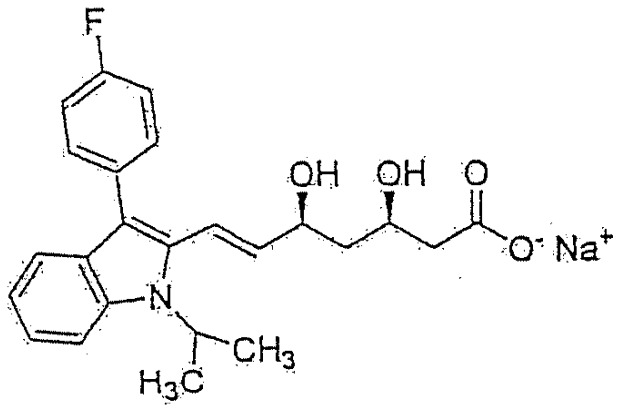
Common name: Fluvastatin Sodium

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

Molecular formula: $C_{24}H_{25}FNO_4 \bullet Na$

Molecular mass: 433.46

Structural formula:



Physicochemical properties: Fluvastatin Sodium is a white to pale-yellow, brownish-pale yellow or reddish-pale yellow hygroscopic powder soluble in water, ethanol and methanol. The pKa value is approximately 5.5.

CLINICAL TRIALS

COMPARATIVE BIOAVAILABILITY STUDY

A single-dose, randomized, crossover comparative bioavailability study of two formulations of Fluvastatin Sodium capsules, TEVA-FLUVASTATIN 40 mg capsules and Lescol® 40 mg capsules was carried out in 36 healthy male subjects, under fasting conditions. A summary of the results is presented below.

Table 5: Bioavailability study

Fluvastatin Sodium (1 x 40 mg) From measured data Geometric Least Square Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Least Square Means	90% Confidence Interval
AUC_T (ng*h/mL)	345.60 366.86 (35)	352.99 367.75 (31)	97.91	91.23 - 105.08
AUC_I (ng*h/mL)	349.92 371.34 (35)	357.76 372.55 (30)	97.81	91.22 - 104.88
C_{max} (ng/mL)	254.58 290.66 (51)	295.55 321.34 (41)	86.14	73.34 - 101.17
T_{max}§ (h)	1.08 (60)	0.98 (50)		
$T_{½}$§ (h)	2.46 (38)	2.52 (37)		

* Fluvastatin 40 mg Capsules manufactured by Teva Pharmaceutical Industries Ltd. for Teva Canada Limited.
† Lescol® 40 mg Capsules manufactured by Novartis Pharmaceuticals Canada Inc., and purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only.

Hypercholesterolemia

Fluvastatin sodium is highly effective in reducing Total-C and LDL-C in patients with hypercholesterolemia. A marked response is seen within one week, and the maximum therapeutic response usually occurs within four weeks. The response is maintained during extended periods of therapy.

In a multicenter, double-blind, placebo-controlled, dose-response study in patients with familial and non-familial hypercholesterolemia, fluvastatin sodium capsules, given as a single dose at bedtime or on a twice daily basis for 12 weeks, resulted in similar lipid lowering effect. However, in patients with heterozygous familial hypercholesterolemia (FH), optimal reduction in total and LDL cholesterol necessitates combination drug therapy in the majority of patients. For homozygous FH, see WARNINGS AND PRECAUTIONS, Homozygous Familial Hypercholesterolemia).

In a large multicenter, double-blind, placebo-controlled study, the administration of Fluvastatin sodium capsules at doses of 40 mg b.i.d. (N=266 patients) resulted in mean LDL-C reduction of 35% after 8 weeks of exposure and a mean LDL-C reduction of 32% at endpoint (28 weeks of

exposure). Similarly, in another double blind study, the administration of fluvastatin sodium at a dose of 80 mg/day resulted in statistically significant ($p < 0.001$) percent reductions in TC (-21 to -30.1), LDL-C (-30 to -37.2) and LDL/HDL ratio (-33 to -37.7).

The concomitant administration of fluvastatin sodium and cholestyramine results in a clinically significant additive effect in reducing Total-C, LDL-C compared with that achieved with either component drug. The results of a randomized, double-blind, parallel-group, placebo-controlled study which investigated the concomitant administration of fluvastatin capsules 20 mg and open-label cholestyramine 4 g/day resulted in LDL-C reductions up to -30.6% .

Primary Mixed Hyperlipidemia
In a retrospective pooled analysis of all placebo controlled studies, patients with primary hypercholesterolemia treated with fluvastatin sodium capsules in daily doses ranging from 20 mg to 80 mg (40 mg b.i.d.) demonstrated consistent and significant median decreases (percent change) in total-C (16.6 to 27.0%), LDL-C (22.2 to 35.9%), TG (11.9 to 17.8%) and Apo B (18.3 to 28.4%) and modest median increases (percent change) in HDL-C (3.3 to 5.6%).

In patients with primary combined (mixed) hyperlipidemia (Type IIb) defined as baseline TG levels ≥ 200 mg/dL, treatment with fluvastatin sodium capsules in daily doses ranging from 20 mg to 80 mg (40 mg b.i.d.) demonstrated consistent and significant median decreases (percent change) in total-C (16.4 to 26.8%), LDL-C (21.6 to 34.6%), TG (17.3 to 23.2%) and Apo B (18.3 to 28.1%) and modest median increases (percent change) in HDL-C (5.8 to 9.0%).

Secondary Prevention of Cardiovascular Events

Fluvastatin Sodium Intervention Prevention Study:
The Fluvastatin Sodium Intervention Prevention Study assessed the effect of fluvastatin sodium 80 mg daily in 1,677 patients with coronary heart disease who had undergone their first percutaneous coronary intervention (PCI) procedure in the preceding 6 months. Patients in this multicenter, randomized, double-blind, placebo-controlled study were treated with dietary/lifestyle counseling and either fluvastatin sodium, 40 mg (n=844) or placebo (n=833) given twice daily for a median of 3.9 years.

Patients were eligible for enrollment in the study if they had a total cholesterol level between 135 and 270 mg/dL (3.5 – 7.0 nmol/L), with fasting triglycerides levels of less than 400 mg/dL (4.5 mmol/L) before the index procedure. The upper total cholesterol limit for eligibility was 212 mg/dL (5.5 mmol/L) for patients whose baseline lipids were measured from blood drawn 24 hours to 4 weeks following MI and 232 mg/dL (6.0 mmol/L) for patients with type 1 or 2 diabetes mellitus. Exclusion criteria included sustained systolic blood pressure of more than 180 mm Hg and diastolic blood pressure of more than 100 mm Hg despite medical therapy, left ventricular ejection fraction of less than 30%, a history of previous PCI or CABG, severe valvular disease, idiopathic cardiomyopathy or congenital heart disease, severe renal dysfunction (defined as serum creatinine level > 1.8 mg/dL [160 μmol/L]), obesity (defined as a body mass index > 35 kg/m^2), and the presence of malignant or other disease with a life expectancy of less than 4 years.

The primary endpoint of the Fluvastatin Sodium Intervention Prevention Study was time from

randomization to the first occurrence of a major adverse cardiac endpoint, defined as either cardiac death, nonfatal myocardial infarction or re-intervention procedure. Secondary endpoints included cardiac death, combined cardiac death/nonfatal myocardial infarction, all death, combined all death/nonfatal myocardial infarction, noncardiac death and major adverse cardiac endpoints excluding repeat procedures of the index lesion, within the first 6 months of follow-up.

The mean time between randomization and index procedure was 2.7 days in both groups. Fluvastatin sodium significantly reduced the risk of major adverse cardiac events by 22% (p = 0.013, 181 events in the fluvastatin sodium group versus 222 in the placebo group). The risk reduction in major cardiac events observed with fluvastatin sodium was irrespective of baseline LDL-C levels or previous history of myocardial infarction. Greater risk reductions were observed in patients with diabetes (47%, p = 0.041), patients >65 years of age (38%, p = 0.006) and patients with multivessel coronary disease (34%, p = 0.011).

Secondary endpoints, cardiac death, noncardiac death, all death, combined cardiac death/MI and combined all death/MI, failed to reach statistical significance. Over the course of the study, treatment with fluvastatin sodium led to median reductions in total cholesterol, LDL-C, triglycerides of 18%, 26% and 14%, and an increase in HDL-C of 10%.

Outcome data for the Fluvastatin Sodium Intervention Prevention Study are shown in Figure 1.

Figure 1: MACE-Free Survival Time

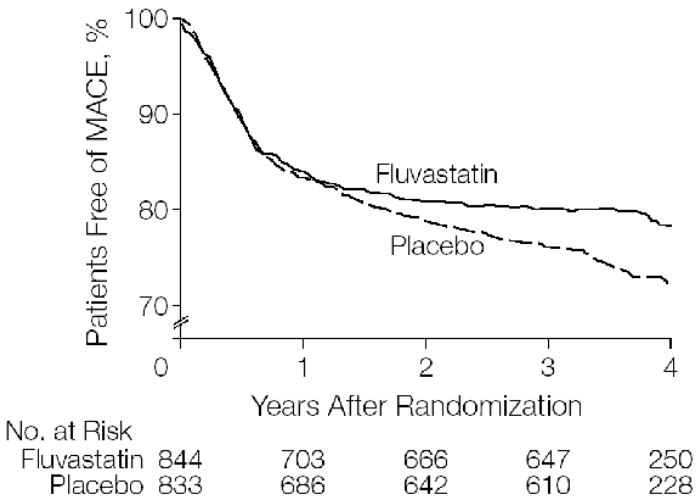


Table 3 presents the incidence and risk of primary and secondary outcome end points in the intent-to-treat population.

Table 3: Incidence and Risk of Primary and Secondary Outcome End Points in the Intent-to-Treat Population*

	Incidence, No. (%)			Fluvastatin vs Placebo	
	Fluvastatin (n=844)	**Placebo (n=833)**	**P Value †**	**RR (95% CI)**	**P Value ‡**
MACE (primary Outcome)	181 (21.4)	222 (26.7)	0.006	0.78 (0.64-0.95)	0.01
Secondary outcomes Cardiac death	13 (1.5)	24 (2.9)	0.06	0.53 (0.27-1.05)	0.07

Table 3: Incidence and Risk of Primary and Secondary Outcome End Points in the Intent-to-Treat Population*

	Incidence, No. (%)			Fluvastatin vs Placebo	
	Fluvastatin (n=844)	**Placebo (n=833)**	**P Value †**	**RR (95% CI)**	**P Value ‡**
Noncardiac death	23 (2.7)	25 (3.0)	0.65	0.84 (0.48-1.49)	0.56
All-cause death	36 (4.3)	49 (5.9)	0.11	0.69 (0.45-1.07)	0.10
Cardiac death/MI	42 (5.0)	60 (7.2)	0.05	0.69 (0.46-1.02)	0.07
All-cause death/MI	65 (7.7)	84 (10.1)	0.07	0.75 (0.54-1.03)	0.08
MACE other than restenosis §	135 (16.0)	187 (22.5)	<0.001	0.67 (0.54-0.84)	<0.001

* RR indicates relative risk; CI, confidence interval; and MACE, major adverse cardiac event (composite end point of cardiac death, non fatal myocardia1 infarction [MI], or intervention procedure).
† By Cochrane - Mantel - Haenszel test
‡ Based on Cox proportional hazards model
§ MACE excluding reinterventions (surgical or percutaneous coronary reintervention) occurring in the first of follow-up for lesions treated at the index procedure.

Atherosclerosis

Fluvastatin sodium was also found to reduce the rate of progression of atherosclerosis in patients with coronary artery disease and mild to moderate elevations of cholesterol as part of a treatment strategy to lower total and LDL cholesterol to target levels. In a placebo controlled trial including such patients, fluvastatin sodium monotherapy reduced the rate of progression of atherosclerosis as evaluated by quantitative coronary angiography (QCA).

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of fluvastatin sodium therapy on coronary atherosclerosis was assessed by quantitative coronary angiography (QCA) in patients with coronary artery disease and mild to moderate hypercholesterolemia (baseline LDL-C range 3 - 5 mmol/L). In this randomized, double-blind, placebo controlled trial, 429 patients were treated with conventional measures (step I AHA diet) and either fluvastatin sodium capsule 40 mg/day or placebo. In order to provide treatment to patients with LDL-C $\geq$ 4.1 mmol/L at baseline receiving placebo, adjunctive therapy with cholestyramine was added after week 12 to all patients in the study with baseline LDL-C values $\geq$ 4.1 mmol/L. These baseline levels were present in 25% of the study population.

The primary endpoint, assessed by QCA, was within-patient per-lesion change in minimum lumen diameter (MLD) of qualifying lesions. QCA were evaluated at baseline and 2.5 years.

Fluvastatin sodium significantly slowed the progression of coronary atherosclerosis. Primary endpoint analysis showed significantly less progression in the all fluvastatin sodium (± cholesterolamine) versus all placebo patients (change in MLD -0.028 mm *versus* -0.100 mm, $p<0.01$) and for fluvastatin alone versus placebo alone (change in MLD - 0.024 *versus* - 0.094 mm, $p< 0.02$).

Beneficial trends with treatment were consistently seen in clinical event rates (new occurrence or worsening of angina, coronary revascularization procedures [PTCA] or CABG surgery, myocardial infarction [MI] and total mortality) within the 2.5 years treatment, but were not statistically significant. This trial was however not designed to demonstrate a reduction in the risk of coronary morbidity and mortality.

DETAILED PHARMACOLOGY

Human Pharmacology

Fluvastatin sodium capsules have been studied in 19 controlled trials worldwide involving patients with Type IIa and IIb hyperlipoproteinemia. Fluvastatin sodium alone was administered to 2326 patients in daily dose regimens of 20 mg, 40 mg and 80 mg (40 mg b.i.d.) for periods ranging from 6 weeks up to 36 weeks. At doses of 20 mg/day to 80 mg/day (40 mg b.i.d.), fluvastatin sodium resulted in highly significant decreases in LDL-C from 22.2% to 35%. Significant reductions of apolipoprotein B, statistically significant reductions of triglycerides (TG) and increased HDL-C were also noted. Fluvastatin had no effect on fibrinogen. The LDL lowering effect of fluvastatin sodium is mediated through the inhibition of cholesterol biosynthesis and the increased catabolism of LDL-C induction of the LDL receptor.

Pharmacokinetics

Fluvastatin sodium is not a pro-drug. It is absorbed rapidly and completely (98%) following oral administration to fasted volunteers. The drug is also completely absorbed, even when administered up to 4 hours post-prandial, but at a reduced rate (C_{max} is reduced by 40-70%). Fluvastatin is targeted to, and sequestered by the liver; therefore, absolute bioavailability based on systemic blood concentrations is about 25%. At doses above 20 mg given in the fasted state, absolute bioavailability can be dose dependent. Dose-normalized values at 40 mg were 20-40% higher than at 20 mg in the fasted state.

The volume of distribution (VD_{ss} for the drug is calculated to be approximately 30 litres (0.35 L/kg). More than 98% of the circulating drug is bound to plasma albumin, and this binding is unaffected by drug concentration. The parent drug is targeted to the liver and no active metabolites are present systemically. At therapeutic concentrations, the protein binding of fluvastatin is not affected by warfarin, salicylic acid and glyburide.

Fluvastatin is predominantly metabolized by the hepatic microsomal CYP2C9 subclass of the P450 cytochromes. It is not metabolized to a significant extent by other cytochrome subclasses, including CYP3A4. Interactions between fluvastatin and drugs metabolized by the CYP2C9 or CYP3A4 subclasses of the P450 cytochromes may occur in some patients.

Following administration of ^{3}H-fluvastatin sodium to healthy volunteers, excretion of radioactivity was about 5%, in the urine and 90% in the feces, and fluvastatin accounted for less than 2% of the total radioactivity excreted. The plasma clearance for fluvastatin in man is calculated to be approximately 40 litres per hour. Steady-state plasma concentrations show no evidence of fluvastatin accumulation following administration of up to 80 mg daily for 25 days. However, under conditions of maximum rate of absorption (i.e. fasting), systemic exposure to fluvastatin is increased 33% to 53% compared to a single 20 or 40 mg dose. This increase in systemic exposure may result from saturation of uptake and sequestration of fluvastatin by the liver when fluvastatin is administered under fasting conditions. After single (or multiple) 20 mg and 40 mg (40 and 80 mg/day) oral doses of fluvastatin sodium, no differences in the fluvastatin elimination half-life are observed. The beta elimination half-life for fluvastatin is 1.2 hours (range of 0.53 to 3.1 hours).

The extent of absorption of fluvastatin sodium 20 mg capsules is equivalent to that of a solution of fluvastatin sodium except that the time to peak under fasted conditions is about 0.7 hours following administration of the capsule compared to about 0.4 hours for the solution. Following ingestion of a single 20 mg fluvastatin sodium capsule under fasted conditions, measurable plasma concentrations of fluvastatin appear systemically within 10 minutes after dosing and reach a peak of 147 ± 86 ng/mL at 0.66 ± 0.3 hours. Fluvastatin sodium, like the other HMG-CoA reductase inhibitors, has variable bioavailability. The coefficient of variation (based on the inter-subject variability) was 47 to 57% for AUC, and 58 to 69% for C_{max}.

Results from an overnight pharmacokinetic evaluation following steady-state (15 weeks) administration of fluvastatin sodium with the evening meal or 4 hours after the evening meal, showed no significant difference in AUC and no apparent difference in the lipid-lowering effects between the two treatment groups. The administration of fluvastatin sodium with the evening meal resulted in a two-fold decrease in C_{max} and more than a two-fold increase in T_{max} as compared to patients receiving the drug 4 hours after the evening meal.

The effects of gender and age on the pharmacokinetics of fluvastatin sodium were evaluated in four patient subgroups; young and elderly, males and females. All patients were administered 20 mg fluvastatin sodium daily, at least two hours after the evening meal, for twenty-one days. Overnight pharmacokinetic evaluations indicate that for the general patient population, plasma concentrations of fluvastatin do not significantly vary either as a function of age or gender.

In a single-dose study the kinetics of fluvastatin sodium in subjects with cirrhosis (n=11) and in healthy age-and sex-matched subjects (n = 11) were compared. The mean AUC and C_{max} parameters were about 2.5 times higher in the subjects with hepatic insufficiency. There was a 28% decrease in plasma clearance and a 31% smaller volume of distribution. No apparent difference was observed in the plasma elimination half-lives for the two groups.

In a study conducted in 14 healthy volunteers, co-administration of diclofenac 25 mg/day and fluvastatin sodium 40 mg/day for 8 days resulted in a significant increase in the fluvastatin $AUC_{(0-9)}$ and C_{max} on day 8 when compared to baseline (54% and 77%, respectively). Diclofenac C_{max} and AUC were increased (60% and 25%, respectively) and oral clearance decreased by 16% on day 8 when compared to baseline.

Dyslipidemia is frequent in organ transplant recipients primarily as a result of immunosuppressive drug treatment. Experience to date with the use of fluvastatin together with cyclosporine consists of 3 pharmacokinetics studies (fluvastatin doses of 20 mg, 40 mg), 17 clinical trials of small-medium size and short-, medium-term duration (fluvastatin doses of 20 mg, 40 mg, 40 mg BID) in renal and heart transplant recipients, and one large prospective placebo-controlled trial in 2,102 renal transplant recipients followed up for 5 to 6 years (fluvastatin doses of 40 mg and 40 mg BID). In a pharmacokinetic study conducted in 19 stable renal transplant patients with hypercholesterolemia receiving cyclosporine A concomitantly with fluvastatin capsules 20 mg/day, the AUC for fluvastatin was increased by 1.9 times compared to that of control subjects from another study who had received the same dose of fluvastatin. The C_{max} was increased by 30% but the T_{max} remained unchanged. Similarly, in a pharmacokinetic study conducted in 19 stable renal transplant patients on stable cyclosporine A regimen who

received fluvastatin extended release 80 mg/day for 1 week, both the AUC and C_{max} for fluvastatin were increased by two fold as compared with data from historical controls treated with the same fluvastatin regimen. Published data show that plasma trough concentrations of cyclosporine A are not significantly changed during co-administration with fluvastatin 20 mg/day. In patients receiving cyclosporine A in combination with fluvastatin, liver enzymes and CK levels should be carefully monitored and the dose of fluvastatin adjusted, if necessary. In heart transplant patients treated with fluvastatin 40 mg/day and cyclosporine A for four weeks, AUC for fluvastatin was increased 3.5 times and 3.1 times in patients than in the age-matched healthy controls on study days 1 and 28, respectively. No correlation between systemic fluvastatin levels and musculoskeletal adverse events or biochemical markers of musculoskeletal damage or renal function impairment have been observed in clinical trials conducted to date.

Biotransformation pathways for fluvastatin include: a) hydroxylation of the indole ring at the 5- and 6-positions, b) N-dealkylation; and c) beta-oxidation. The major circulating blood components are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate systemically. Both enantiomers of fluvastatin are metabolized in a similar manner resulting in only minor differences in systemic exposure.

ANIMAL PHARMACOLOGY

In vitro

Fluvastatin sodium is a synthetic, hydrophilic, competitive inhibitor of HMG-CoA reductase. The IC50 values for the inhibition of sterol synthesis by fluvastatin sodium are 0.007 μM in rat liver microsomes, 0.03 μM rat hepatoma Fu5AH cells, and 0.05 μM in human hepatoma HepG2 cells. The IC50 for the induction of LDL receptors in the HepG2 cells is 0.05 μM.

In vivo

The administration of fluvastatin sodium resulted in large reductions in serum cholesterol concentrations in rats, hamsters, dogs and Rhesus monkeys demonstrating its significant lipid-lowering effect.

In the rats and dogs, the reduction in serum cholesterol resulted primarily from a decrease in the VLDL + LDL fraction with ED50's of 0.09 mg/kg and 2 mg/kg, respectively. In the Rhesus monkey, the ED25 for the reduction in total serum cholesterol was estimated at 24 mg/kg.

In the hamster model, which best represents human LDL metabolism, fluvastatin sodium resulted in an increased catabolic removal of LDL as the result of the up-regulation of the LDL receptors. At 6 mg/kg in the hamster, fluvastatin sodium reduced both the VLDL-C and LDL-C while slightly increasing the HDL-C.

At oral doses at least 100 times the ED50 for inhibition of sterol synthesis in rats, fluvastatin sodium had no effect on overt behaviour, fasting serum glucose levels, estrogen-like activity in a vaginal response test, anti-inflammatory activity, or cardiovascular activity (with the exception of a mild, reversible reduction in blood pressure) in the rat. At a dose 10 times the ED50 for the reduction of VLDL+LDL-C in dogs, fluvastatin sodium had no effect on blood pressure, heart

rate or autonomic responses to norepinephrine, isoproterenol and acetylcholine in anesthetized dogs.

Pharmacokinetics
The pharmacokinetics and disposition of fluvastatin sodium was studied in the mouse, rat, dog and monkey. In all species, absorption of fluvastatin sodium was rapid and essentially complete. Peak plasma concentrations were generally achieved within 0.5 to 3 hours post dose.

Distribution of fluvastatin sodium and its metabolites were studied in mice and rats. In both species, the highest concentrations were observed in the liver followed by substantially lower levels in the kidney, heart and adrenals.

The permeability of fluvastatin versus lovastatin across the blood-brain barrier was measured using three techniques: the brain uptake index technique, brain perfusion studies in the rat, and an in vitro model consisting of a primary culture of confluent monolayers of bovine brain microvessel endothelial cells. In all three models, lovastatin showed a considerably greater permeability coefficient (0.011 cm/min) than fluvastatin sodium (0.00072 cm/min).

Extensive presystemic hepatic extraction followed by direct excretion via the bile occurred with fluvastatin sodium. Biotransformation pathways for fluvastatin include: a) hydroxylation of the indole ring at the 5- and 6-positions; b) N-dealkylation; and c) beta-oxidation. Renal excretion accounted for less than 8% of the dose in all species except the rabbit (ca.30%).

MICROBIOLOGY
Not applicable

TOXICOLOGY

Acute Toxicity

Table 6: Single Dose Toxicity Studies with Fluvastatin sodium

Species	Sex	Route	LD50 (mg/kg)
MOUSE	Female	Oral	2739
	Male	Oral	2175
	Female	Intraperitoneal	140
	Male	Intraperitoneal	118
RAT	Female	Oral	707
	Male	Oral	707
	Female	Intraperitoneal	120
	Male	Intraperitoneal	165
RABBIT	Female & male	Oral	506
	Female & male	Intraperitoneal	50
HAMSTER	Female	Oral	886
	male	Oral	1225

Signs of toxicity were decreased locomotor activity, ataxia, loss of righting reflex, dehydration, hypothermia, ptosis, shallow breathing, piloerection, soft feces/diarrhea, and/or splayed gait.

Subacute and Chronic Toxicity

The spectrum of effects produced by fluvastatin sodium in mice, rats, hamsters, dogs and monkeys shown in the following table is not unexpected in view of the magnitude of the dosage levels employed.

Table 7: Multiple Dose Toxicity Studies with Fluvastatin sodium

TARGET ORGANS OBSERVED IN ANIMAL STUDIES					
Organ	**Mouse**	**Rat**	**Hamster**	**Dog**	**Monkey**
CNS	-	-	-	-	-
Liver	-	+	E	E	E
Stomach (non-glandular)	+	+	-	NA	NA
Gallbladder	-	NA	CC	+	+
Heart/skeletal muscle*	-	+	+	-	-
Eye	-	-	-	+	-
Thyroid	-	+	-	-	-
Testes	-	-	+	-	-
+ = organ affected in some way by drug treatment			E = increased liver enzymes		
- = no effect was observed in this organ in these species			CC = cholesterol calculi		
NA = not applicable			* decedents only		

The following table summarizes the significant adverse changes noticed during the long-term toxicology studies with fluvastatin sodium.

Table 8: Significant Adverse Events During Long-term Toxicology Studies with Fluvastatin Sodium

SIGNIFICANT ADVERSE CHANGES		
	Minimal Toxic Dose (mg/kg/day)	**No Effect Dose (mg/kg/day)**
MICE		
Non-glandular gastric mucosal hyperplasia/hyperkeratosis	5	0.3
RATS		
Non-glandular gastric mucosal hyperplasia/hyperkeratosis	0.25	0.03
Hepatocellular necrosis/cytomegaly	10	1
Cardiac muscle* degeneration (pregnant females in Segment III study only)	6	2
Skeletal muscle* degeneration	50	nd
Thyroid follicular tumors (males only)	18	9
Increased thyroid weight (no histopathology)	9	6
HAMSTERS		
Non-glandular* ulcerative gastritis (males only)	40	nd
Gallbladder cholesterol calculi	5	nd
Hepatic periportal lipidosis	5	nd
↑ ALAT/ASAT	20	5
Cardiac muscle* degeneration	40	nd
Skeletal muscle* degeneration	40	nd
Testicular degeneration	40	20
DOGS		
Gallbladder hyperplasis	8	1
Cataract	16	8
Focal hemorrhage in* heart, diaphragm, intestines, mesentery, mediastinum	24	16
↑ ALAT/ASAT	24	16
MONKEYS		
Gallbladder epithelial hyperplasia	12	0.6
↑ ALAT/ASAT	108	60

nd = not determined
* = Seen only in decedents

The fluvastatin-induced hyperplasia/hyperkeratosis was confined to the forestomach epithelial mucosa in mice and rats. This phenomenon did not occur in other species without a non-glandular forestomach (i.e. dog, monkey) nor was there evidence of a hyperplastic lesion of the esophagus.

Cataract development is a species-specific effect in the dog. The no effect dose level was defined as 8 mg/kg/day in the dog, which is approximately 88 times the mean AUC in man following a 40 mg dose.

Evidence of hepatotoxicity in the rat was characterized by elevated serum enzyme activities generally associated with the histopathological diagnosis of hepatocellular change. These changes are classic evidence of the direct hepatotoxic effects of a xenobiotic substance which typically for the rat model were dose- and time-dependent and reversible upon withdrawal of drug treatment.

At 8 and 36 mg/kg/day for 26 weeks, gallbladder changes characterized by inflammation and hyperplasia of the mucosa were noted in the dog. However, after two years at 8 mg/kg/day no pathology was apparent and at 16 mg/kg/day only mild hypertrophy of the gallbladder mucosa was noted. In hamsters, dose levels of 5 to 40 mg/kg/day induced the formation of gallbladder cholesterol calculi with a low frequency of bile duct capillary proliferation. In non-human primates, minimal to trace epithelial hyperplasia of the gallbladder epithelium was seen following administration of fluvastatin sodium at doses of 12 mg/kg/day and above for 26 weeks. A large proportion of the drug is excreted in the bile of which approximately 30% is unchanged drug. This may account for the changes encountered in animal studies, whereas man does not appear to excrete the parent drug.

Focal hemorrhages were noted in the gallbladder, heart, diaphragm, pancreas, intestines, mesentery and mediastinum. This lesion was probably related to injury of the vascular bed and was considered to be a manifestation of general systemic toxicity in debilitated animals rather than a primary effect of fluvastatin exposure. Hemorrhages have not occurred in the brain or nervous tissue of dogs treated with fluvastatin sodium.

The increased incidence of follicular cell neoplasm in the male rats is consistent with species-specific findings from other HMG-CoA reductase inhibitors.

No CNS lesions have been observed in any species (mouse, rat, or dog) chronically treated for 2 years with fluvastatin sodium. However, CNS vascular lesions, characterized by perivascular hemorrhages and edema and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other drugs of this class.

Carcinogenicity/Mutagenicity
A 2-year study was performed in rats at dose levels of 6, 9, and 18-24 (escalated after 1 year) mg/kg/day to establish a clear maximum tolerated dose (determined to be 9 mg/kg/day). These treatment levels represented plasma drug levels of approximately 9, 13, and 26-35 times the mean human plasma drug concentration after a 40 mg oral dose. An increased incidence of forestomach

squamous papillomas and one carcinoma of the forestomach at the 24 mg/kg/day dose level were considered to reflect the prolonged hyperplasia induced by direct contact exposure to fluvastatin sodium rather than to a systemic (genotoxic) effect of the drug. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded for males treated with 18-24 mg/kg/day. The increased incidence of thyroid follicular cell neoplasm in male rats with fluvastatin sodium appears to be consistent with species specific findings from other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg/day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg/day and in females at 15 mg/kg/day. These treatment levels represented plasma drug levels of approximately 0.2, 10, and 30 times the mean human plasma drug concentration after a 40 mg oral dose. As with the rat carcinogenicity results, it was concluded that the increased incidence of forestomach squamous papillomas reflected the prolonged hyperplasia induced by direct contact exposure to fluvastatin sodium rather than to a specific (genotoxic) effect of the drug.

The carcinogenicity study in mice was repeated at oral dose levels of 50, 150 and 350 mg/kg/day. Reduced body weight gain was recorded at all dose levels, and excessive mortality at the high dose confirmed that the maximum tolerated dose is less than 150 mg/kg/day in the mouse. There was no evidence of increased neoplasia at these doses.

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

Teratology and Reproductive Studies
In a study in rats at dose levels for females at 0.6, 2 and 6 mg/kg/day and for males at 2, 10 and 20 mg/kg/day fluvastatin sodium had no adverse effects on the fertility or reproductive performance at any of the dose levels studied. A study in which female rats were dosed during the third trimester at 12 and 24 mg/kg/day resulted in maternal mortality at or near term and postpartum. In addition, fetal and neonatal lethality were apparent. No effects on the dam or fetus occurred at the low dose level of 2 mg/kg/day. A second study at levels of 2, 6, 12 and 24 mg/kg/day confirmed the findings in the first study.

REFERENCES

Preclinical

1. Hockwin O, Evans M, Roberts SA, Stoll RE. Post-mortem biochemistry of beagle dog lenses after treatment with fluvastatin for 2 years at different dose levels. Lens and Eye Tox Res 1990; 7(3&4): 563-575.

2. Kathawala FG. HMG-CoA reductase inhibitors: an exciting development in the treatment of hyperlipoproteinemia. Medicinal Res Rev 1991; 11(2): 121-146.

3. Tse FLS, Smith HT, Ballard FH, et al. Disposition of fluvastatin, an inhibitor of HMG-CoA reductase, in mouse, rat, dog, and monkey. Biopharm and Drug Disp 1990; 11:519-531.

Clinical

1. Bell LP, Hunninghake DB, Pharmacology and clinical use of HMG-CoA reductase inhibitors. J of Cardiol 1989; 15(10): 25-31.

2. Folkers K, Langsjoen P, *et al*. Lovastatin decreases coenzyme Q levels in humans. Proc. Nat. Acad. Sci. 1990; 87 (22): 8931-893.

3. Frick HM, Elo O, Haapa K, et al. Helsinki Heart Study: Primary Prevention Trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of Treatment, Changes in Risk Factors, and Incidence of Coronary Heart Disease. N Engl J Med 1987; 317(20): 1237-45.

4. Garnett WR, Venitz J, Wilkens R, *et al*. Double-blind evaluation to determine the influence of fluvastatin administration on the pharmacokinetics of oral digoxin in a patient population chronically receiving digoxin. AAPS 1991; 8(10): S63.

5. Herd JA, Ballantyne CM, *et al*. Effects of Fluvastatin on Coronary Atherosclerosis in Patients with Mild to Moderate Cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). Am J Cardiol. 1997; 80: 278-286.

6. Lipid Research Clinics Program. The lipid research clinics coronary primary prevention trial results. JAMA 1984; 251(3): 365-374.

7. Yuan J, Tsai MY, Heglands J, et al. Effects of fluvastatin, an HMG-CoA reductase inhibitor, on the distribution and composition of low density lipoprotein subspecies in humans. Atherosclerosis 1991; 87: 147-157.

8. Uauy R, Vega GL, Grundy SM, Bilheimer DM. Lovastatin therapy in receptor-negative homozygous familial hypercholesterolemia: Lack of effect on low-density lipoprotein concentrations or turnover. J. Pediatr. 1988; 113: 387-392.

9. Stein EA. Treatment of familial hypercholesterolemia with drugs in children. Arteriosclerosis Suppl. I. 1989; 9: I-145 - I-151.

10. Ghirlanda G, Oradei A, Manto A, Lippa S, Liccioli L et al. Evidence of plasma CoQ10 lowering effect by HMG CoA reductase inhibitor: Double-blind placebo control study. J. Clin. Pharmacol. 1993; 33: 226-229.

11. Scanu AM. Lipoprotein(a) as a cardiovascular risk factor. Trends Cardiovasc. Med. 1991; 1: 294-299.

12. Ghidini A *et al*. Congenital abnormalities (VATER) in baby born to mother using lovastatin. Lancet 1992; 339: 1417-17.

13. Illingsworth DR. How effective is drug therapy in heterozygous familial hypercholesterolemia? Am. J. Cardiol. 1993; 72: 54D-58D.

Drug interactions

14. Åberg J et al. Effects of erythromycin on plasma fluvastatin levels: A pharmacokinetic study. Atherosclerosis. 1997; 134: 118A.

15. Bertz RJ and Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. Clin Pharmacokinet. 1997; 32: 210-258.

16. Christians U. et al. Metabolism and Drug Interactions of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors in Transplant Patients: Are the Statins Mechanistically Similar? Pharmacol Ther. 1998; 80 (1): 1-34.

17. Fischer V. et al. The 3-Hydroxy-Methylglutaryl Coenzyme A Reductase Inhibitor Fluvastatin: Effect on Human Cytochrome P-450 and Implications for Metabolic Drug Interactions. 1999; 27 (3): 410-416.

18. Herman RJ. Drug Interactions and the Statins. CMAJ 1999; 161 (10): 1281-6.

19. Li PKT et al. The Interaction of fluvastatin and cyclosporine A in renal transplant patients. Int. J. Clin. Pharm. Ther. 1995; 33(4): 246-248.

20. Shapiro LE, Sheir NH. Drug-Drug Interactions: How scared should we be? CMAJ 1999; 161 (10): 1266-7.

21. Transon C, Leeman T, et al. *In vivo* inhibition profile of cytochrome P450TB (CYP2C9) by (±) - fluvastatin. Clin Pharmacol Ther 1995; 58: 412-417.

22. Transon C. et al. In vitro comparative inhibition profiles of major human drug metabolizing cytochrome P450 isozymes (CYP2C9, CYP2D6 and CYP3A4) by HMG-CoA reductase inhibitors. Eur J Clin Pharmacol 1996; 50: 209-215.

23. Holdaas H, Hartmann A, Stenstrom J, Dahl KJ, Borge M, Pfister P. Effect of fluvastatin for safely lowering atherogenic lipids in renal transplant patients receiving cyclosporin. Am J Cardiol 1995; 76: 102A-l06A.

24. Li PKT, Mak TWL, Chan TH, Wang A, Lam CWK, Lai KN. Effect of fluvastatin on lipoprotein profiles in treating renal transplant recipients with dyslipoproteinemia. Transplantation 1995; 60: 652-656.

25. Ghods AJ, Milanian I, Arghani H, Ghadiri G. The efficacy and safety of fluvastatin in hypercholesterolemia in renal transplant recipients. Transplant Proc 1995; 27(5): 2579-80.

26. Austen JL, Shrifin FA, Bartucci MR, Knauss TC, Schulak JA, Hricik DE. Effects of fluvastatin on hyperlipidemia after renal transplantation. Ann Pharmaco Ther 1996; 30: 1386-1389.

27. Goldberg RB, Roth D. Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporin. Transplantation. 1996; 62: 1559-1564.

28. Holdaas H, Hartmann A, Stenstrom J, Nordal K, Berg K, Fauchald P. Fluvastatin lowers lipids safely in patients treated with cyclosporine Neoral. Nephrol Dial Transplant 1996; 11: A296.

29. Hadjigavriel M, Kyriakides G. Fluvastatin in renal transplantation. Transplant Proc 1997; 29: 3050.

30. Lal SM, Gupta N, Georgiev O, Ross G. Lipid-lowering effects of fluvastatin in renal transplant patients. A clinical observation. Int J Artif Organs 1997; 20: 18-21.

31. Locsey L, Asztalos L, Kincses Z, Balazs G. Fluvastatin (Lescol®) treatment of hyperlipidaemia in patients with renal transplants. Int Urol Nephrol 1997; 29: 95-106.

32. Földes K, Maklary E, Vargha P, Janssen J., Jaray J., Perner F, Gero L. Effect of diet and fluvastatin treatment on the serum lipid profile of kidney transplant, diabetic recipients: a 1 year follow up. Transpl Int 1998; 11(Suppl 1): S65-S68.

33. Melchor JL, Gracida C. Treatment of hypercholesterolemia with fluvastatin in kidney. Transplant Proc 1998; 30: 2054.

34. Schrama YC, Hene RJ, de Jonge N, Joles JA, van Rijn HJM, Bar DR, et al. Efficacy and muscle safety of fluvastatin in cyclosporine-treated cardiac and renal transplant recipients. Transplantation 1998; 66: 1175-1181.

35. Martinez-Castelao A, Grinyo JM, Fiol C, et al. Fluvastatin and low-density lipoprotein oxidation in hypercholesterolemic renal transplant patients. Kidney Int 1999; 56: S231-S234.

36. Akiyama T, Ishii T, Imanishi M, et al. Efficacy and safety of treatment with low-dose

fluvastatin in hypercholesterolemic renal transplant recipients. Transplant Proc 2001; 33: 2115-18,

37. Park J, Siekmeier R, Lattke P et al., Pharmacokinetics and pharmacodynamics of fluvastatin in heart transplant recipients taking cyclosporine A. J. Cardiovasc Pharmacol Ther., 2001, 6: 351-361

38. Türk S, Yildiz A, Tükek T, et al. The effect of fluvastatin on hyperlipidemia in renal transplant recipients: a prospective, placebo-controlled study. Int Urol Nephrol 2001; 32: 713-16.

39. Holdaas H, Jardine AG, Wheeler DC, et al. Effect of fluvastatin on acute renal allograft rejection: a randomized multicenter trial. Kidney Int 2001; 60: 1990-97.

40. Malyszko J, Malyszko JS, Brzosko S, et al. Effects of fluvastatin on homocysteine and serum lipids in kidney allograft recipients. Ann Tranplant 2002; 7: 52-54.

41. Kosch M, Barenbrock M, Suwelack B, et al. Effect of a 3-year therapy with the 3-hydroxy-3-methylglutaryl coenzyme A reductase-inhibitor fluvastatin on endothelial function and distensibility of large arteries in hypercholesterolemic renal transplant recipient. Am J Kidney Dis 2003; 41: 1088-96.

42. O'Rourke B, Barbir M, Mitchell AG, Yacoub MH, Banner NR. Efficacy and safety of fluvastatin therapy for hypercholesterolemia after heart transplantation. Results of a randomized double blind placebo controlled study. Int J Cardiol 2004; 94: 235-40.

43. Holdaas H, Fellström B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomized, placebo-controlled trial. Lancet 2003; 361: 2024-31.

44. Product Monograph for Lescol®, Lescol® XL, Novartis Pharmaceuticals Canada Inc., Dorval, Quebec, Canada. Date of Revision: August 26, 2016.

45. Single-Dose, Randomized, Crossover Comparative Bioavailability Study of Two Formulations of Fluvastatin 40 mg Capsules in Healthy Subjects, under Fed Conditions. Data on file at Teva Canada Limited.

46. Single-Dose, Randomized, Crossover Comparative Bioavailability Study of Two Formulations of Fluvastatin 40 mg Capsules in Healthy Subjects, under Fasting Conditions. Data on file at Teva Canada Limited.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

[Pr]TEVA-FLUVASTATIN
Fluvastatin sodium Capsules

This leaflet is part III of a three-part "Product Monograph" published when TEVA-FLUVASTATIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-FLUVASTATIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TEVA-FLUVASTATIN is to be used along with a medically recommended and carefully supervised diet for the long-term treatment of high cholesterol and fatty acids and is not a substitute for such a diet. In addition, depending on your condition, your physician may recommend an appropriate regimen of exercise, weight control and other measures.

TEVA-FLUVASTATIN may be prescribed by your physician if you suffer from coronary heart disease, and have undergone a percutaneous coronary intervention (PCI) (a medical procedure on your heart (or its vessels) that was performed through an incision on your leg or arm), to reduce your risk of developing any major heart problems, such as loss of heart muscle, nonfatal heart attack, or the need to perform other medical procedures on the heart or its vessels.

What it does:
TEVA-FLUVASTATIN lower the level of cholesterol, particularly low density lipoprotein (LDL) cholesterol, in the blood. TEVA-FLUVASTATIN reduce cholesterol production by the liver and induce some changes of cholesterol transport and the way it is distributed in the blood and tissues.

When it should not be used:
Do not take TEVA-FLUVASTATIN:

- if you are hypersensitive (allergic) to fluvastatin or any of the other ingredients of TEVA-FLUVASTATIN.
- if you have an active liver disease, or unexplained, persistent elevations in liver function values (transaminases)
- if you are pregnant or breast-feeding

If any of these apply to you, **tell your doctor without taking TEVA-FLUVASTATIN.**

What the medicinal ingredient is:
fluvastatin sodium.

What the nonmedicinal ingredients are:
Inactive Ingredients: colloidal anhydrous silica, crospovidone, lactose monohydrate, magnesium stearate. **Capsule shell and printing ink:** antifoam, black iron oxide, dehydrated alcohol, gelatin, industrial methylated spirit, n-butyl alcohol, red iron oxide, alcohol, shellac, soya lecithin, titanium dioxide, yellow iron oxide.

What dosage forms it comes in:
TEVA-FLUVASTATIN capsules 20 mg and 40 mg

WARNINGS AND PRECAUTIONS

Pregnancy
TEVA-FLUVASTATIN should not be used during pregnancy. Cholesterol is essential for the development of a baby. Cholesterol-lowering drugs can harm the baby. If you become pregnant while using TEVA-FLUVASTATIN, stop using the medication immediately and contact your doctor.

BEFORE you use TEVA-FLUVASTATIN capsule, talk to your doctor or pharmacist if you:

- have thyroid problems
- regularly drink *three or more* alcoholic drinks daily
- are taking any other cholesterol lowering medication such as fibrates (gemfibrozil, fenofibrate, bezafibrate), niacin or ezetimibe
- are taking any other medications, including prescription, nonprescription and natural health products as drug interactions are possible, in particular corticosteroids, cyclosporine (NEORAL®), fibrates (e.g. gemfibrozil [LOPID®]), oral anticoagulants (e.g. warfarin [COUMADIN®]), phenytoin, oral hypoglycemics, non steroidal anti-inflammatory drugs, erythromycin, lipid lowering doses of niacin (nicotinic acid), nefazodone (SERZONE®) and colchicines
- have a personal or family history of muscular disorders
- had any past muscle problems (pain, tenderness), after using an HMG-CoA reductase inhibitor ("statin") such as atorvastatin (LIPITOR®), fluvastatin (LESCOL®/LESCOL® XL), lovastatin (MEVACOR®), pravastatin (PRAVACOLl®), rosuvastatin (CRESTOR®) or simvastatin (ZOCOR®) or have developed an allergy or intolerance to any of them
- have unexplained muscle pain, tenderness or weakness, as these might be early signs of potentially severe muscle degradation.
- have kidney disease
- have liver problems: liver function tests will normally be done before starting TEVA-FLUVASTATIN, at dose increase and at various intervals during treatment to check for undesirable effects
- have severe metabolic, endocrine or electrolyte disorders such as decompensated diabetes and low blood potassium

Slightly increased blood sugar can occur when you take TEVA-FLUVASTATIN Discuss with the doctor your risk of developing diabetes.

- have undergone surgery or other tissue injury
- do excessive physical exercise
- have a serious infection
- have very low blood pressure (signs may include dizziness, lightheadedness)
- have congestive heart failure
- suffer from seizures
- are older than 70 years your doctor may want to clarify whether you have risk factors for muscular diseases. This may require specific blood tests

Your doctor will monitor your progress with TEVA-FLUVASTATIN and may occasionally perform some tests to ensure your health and safety.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with TEVA-FLUVASTATIN include:

- corticosteroids
- cholestyramine
- gemfibrozil/fenofibrate/bezafibrate/niacin
- cimetidine/ranitidine/omeprazole
- digoxin
- rifampicin
- warfarin and other coumarin derivatives
- phenytoin
- fluconazole
- oral hypoglycemic agents (e.g. tolbutamide, chlorpropamide, glyburide)
- non-steroidal anti-inflammatory drugs (NSAIDs)
- nefazodone
- alcohol
- spironolactone
- amlodipine
- cyclosporine

Notify your physician about any illness which may develop during your treatment with TEVA-FLUVASTATIN and about any new prescription or nonprescription medication you may take. If you require medical help for other reasons, inform the attending physician that you are taking TEVA-FLUVASTATIN.

PROPER USE OF THIS MEDICATION

Use only as specifically directed. Do not alter the dosage unless ordered to do so by your physician. Check with your physician before discontinuing medication since this may result in an increase of your fat substances in the blood.

Usual dose:

- If your doctor recommends you take only 1 dose of TEVA-FLUVASTATIN per day, take it in the evening or at bedtime. If your doctor recommends taking divided doses (2 times per day), take one in the morning and one in the evening. TEVA-FLUVASTATIN can be taken with or without food, but continue to take it the same way (either with *OR* without food) each time. Swallow TEVA-FLUVASTATIN whole with a glass of water.
- Do not change the dose unless directed by a doctor.
- Your physician will monitor your clinical condition and your blood tests at regular intervals. It is important to have these check-ups done on schedule. Please keep your appointments accurately.
- Notify your physician if you are going to have major surgery or have sustained a severe injury.

Overdose:
If you take more TEVA-FLUVASTATIN than you should, tell your doctor immediately or go to your nearest hospital.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take TEVA-FLUVASTATIN, take one dose as soon as you remember.

Do not take a double dose to make up for the one that you missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, patients treated with TEVA-FLUVASTATIN may experience side effects, although not everybody gets them.

Other side effects may occasionally occur which usually do not require stopping treatment. They may come and go during treatment without any particular danger, but you should mention them to your physician, without undue delay, if they become persistent or bothersome. Such adverse experiences include:

- abdominal pain/indigestion,
- constipation,
- diarrhea,
- nausea,
- headache,
- abnormal blood test values for muscle and liver,
- influenza,
- infections,
- poor memory, confusion and memory loss
- insomnia and
- dizziness

Possible side effects reported with some statins: liver failure (symptoms like nausea, vomiting, loss of appetite, yellow eyes or skin, confusion, euphoria or depression, mental slowing, slurred speech, sleep disturbances, tremors, easy bruising or bleeding), breathing problems

including persistent cough and/or shortness of breath or fever, depression, erectile dysfunction, sleep disturbances, including insomnia and nightmares.

If any of these affect you severely, tell your doctor.

TEVA-FLUVASTATIN can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Stop taking drug and seek immediate medical attention
		Only if severe	In all cases	
Rare	Muscle pain that you cannot explain, muscle tenderness or muscle weakness		√	
	Skin rash, hives, swelling of the face, eyelids and lips			√
Very rare	Brownish or discoloured urine		√	
	Generalized weakness, especially if you do not feel well (i.e. fever or fatigue)		√	
	Myositis (muscle inflammation), rhabdomyolysis (a muscle wasting disease)		√	
	Unusual tiredness or fever, yellowing of the skin and eyes, dark coloured urine (hepatitis)			√
	Severe abdominal pain (inflamed pancreas)		√	
	Skin swelling, rash, hives, dizziness, sensitivity to light (signs of severe allergic reaction)			√
	Difficulty in breathing, swelling of the lips, throat, mouth, tongue or face (signs of severe allergic reaction)			√
Unknown	**Increased Blood Sugar:** frequent urination, thirst and hunger	√		
	Unexplained muscle pain, tenderness or weakness	√		

This is not a complete list of side effects. For any unexpected effects while taking TEVA-FLUVASTATIN, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature between 15 and 30°C in a tight container. Protect from light and humidity.

Keep all medicines out of the reach of children. This medicine is prescribed for your specific medical problem and for your own use only. Do not give to other people.

Do not use outdated medicines. Discard them safely out of the reach of children or take them to your pharmacist who will dispose of them for you.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited by:
Phone: 1-800-268-4127 ext. 3;
Email: druginfo@tevacanada.com; or
Fax: 1-416-335-4472

This leaflet was prepared by:
Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

Last revised: November 7, 2016