SUMMARY OF THE PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of the medicinal product

FILSTATIN 10 (Atorvastatin Tablets 10 mg)

1.2 Strength

Each Film Coated Tablet Contains:
Atorvastatin Calcium Trihydrate BP
Equivalent to Atorvastatin 10 mg

1.3 Pharmaceutical form

Film Coated Tablets – Oral Solids

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

S. No	Name of the Ingredients	Specification	Qty per Tab (mg)	Reason for Inclusion
1	Atorvastatin Calcium	BP	10.840	Active Ingredient
2	Lactose monohydrate	BP	43.910	Diluent
3	Calcium carbonate	BP	34.375	Stabilizer
4	Croscarmellose sodium (Mixing)	BP	4.500	Disintegrant
5	Polysorbate 80	BP	0.750	Wetting agent
6	Hydroxypropylcellulose	BP	1.875	Binder
7	Microcrystalline cellulose	BP	48.500	Diluent
8	Croscarmellose sodium (Lub)	BP	4.500	Disintegrant
9	Magnesium stearate	BP	0.750	Lubricant
10	Purified water	BP	11.000	Solvent

FILM COATING MATERIALS (Batch Size: 210000 Tablets)

S. No	Name of the Ingredients	Specification	Qty / Batch (kg)	Reason for Inclusion
11	Hypromellose 15 cps	BP	0.298	Coating Polymer
12	Titanium dioxide	BP	0.149	Colourant
13	Purified Talc	BP	0.060	Glidant
14	Propylene glycol	BP	0.030	Plasticizer
15	Polysorbate 80	BP	0.030	Wetting agent
16	Purified water	BP	4.200 L	Solvent

3. PHARMACEUTICAL FORM

White, oblong, film coated tablets with 'F10' debossed on one side.

4. CLINICAL PARTICULARS

FILSTATIN is indicated as an adjunct to diet for reduction of elevated total-cholesterol, LDL-cholesterol, apolipoprotein-B, and triglyceride levels in patients with primary hypercholesterolaemia; mixed dyslipidaemia; and heterozygous familial hypercholesterolaemia.

FILSTATIN is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Therapy with lipid-lowering agents should be a component of multiple-risk-factor intervention in individuals at increased risk of atherosclerotic vascular disease due to hypercholesterolaemia.

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other non-pharmacological measures has been inadequate. Prior to initiating therapy with FILSTATIN , secondary causes for hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG.

Pediatric Patients (10-17 years of age) : Atorvastatin is indicated as an adjunct to diet to reduce total-C,LDL-C,and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolaemia if after an adequate trial of diet therapy the following findings are present:

a) LDL-C remains ≥ 190 mg/dL or
b) LDL-C remains ≥ 160 mg/dL and:

- there is a positive family history of premature cardiovascular disease or
- two or more other CVD risk factors are present in the pediatric patient

4.2 Posology and method of administration:

The patient should be placed on a standard cholesterol-lowering diet before receiving FILSTATIN and should continue on this diet during treatment with FILSTATIN. The usual starting dose is 10 mg or 20 mg once a day. The dosage range of FILSTATIN is 10 to 80 mg once daily. Starting and maintenance doses should be individualized according to baseline

LDL-C levels, the goal of therapy, and patient response. Adjustment of dosage should only be made after an interval of 4 weeks or more. The maximum recommended dose is 80 mg once a day. Doses may be given at any time of day with or without food. After initiation and/or upon titration of FILSTATIN, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Primary Hypercholesterolaemia including familial Hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Fredrickson Types IIa and IIb): Patients should be started with FILSTATIN 10 mg daily or 20 mg once daily. Patients who require a large reduction in LDL-C(more than 45%) may be started at 40 mg once daily. The dosage range of FILSTATIN is 10 to 80 mg once daily. FILSTATIN can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of FILSTATINshould be individualized according to patient characteristics such as goal of therapy and response.

After initiation and/or upon titration of FILSTATIN, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Homozygous Familial Hypercholesterolaemia: The dosage of FILSTATIN in patients with homozygous FH is 10 to 80 mg daily. FILSTATIN should be used as an adjunct to other lipid-lowering treatment (e.g. LDL apheresis) in these patients or if such treatments are unavailable. In a compassionate-use study of patients with homozygous familial hypercholesterolaemia, most patients responded to 80 mg of atorvastain with greater than 15% reduction in LDL-C.

Heterozygous Familial Hypercholesterolaemia in Pediatric Patients (10-17 years of age): The recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day.Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more.

Dosage in Patients with Renal Insufficiency: Renal disease has no influence on the plasma concentrations nor lipid effects of FILSTATIN; thus, no adjustment of dose is required.

Dosage in Patients with Hepatic Dysfunction: In patients with moderate to severe hepatic dysfunction, the therapeutic response to FILSTATIN is unaffected but serum levels of the drug are greatly increased. In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Child-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased,

respectively, in patients with Childs-Pugh B disease. Therefore, caution with dosage should be exercised in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Use in Children : Since safety and efficacy have not yet been established with the use of Atorvastatin Tablets through controlled clinical trial involving pre-pubertal patients or patients younger than 10 years of age use of Atorvastatin Tablets in children of this group (pre-pubertal patients or patients younger than 10 years of age) is contraindicated .

Use in Elderly : Efficacy and safety in patients older than 70 using recommended doses is similar to that seen in the general population.

Route of administration:

Oral.

4.3 Contraindications:

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases. FILSTATIN is contra-indicated in pregnancy, in breast feeding mothers and in women of childbearing potential not using adequate contraceptive measures. An interval of one month should be allowed from stopping FILSTATIN treatment to conception in the event of planning a pregnancy.

Children: Safety and efficacy have not yet been established in pre-pubertal patients or patients younger than 10 years of age. Hence FILSTATIN is contraindicated in this patient group.

4.4 Special warning and special precautions for use

Precautions:

General

Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Warnings:

Liver Dysfunction

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit

of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in 11 other patients were not associated with jaundice or other clinical signs or symptoms.

Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin.

Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin.

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in atorvastatin-treated patients.

Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals.

Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

4.5 Interaction with other medicinal product and other forms of interactions:

As with other HMG-CoA reductase inhibitors the risk of myopathy during treatment with FILSTATIN increases with concurrent administration of immunosuppressive drugs, fibric acid derivatives, macrolide antibiotics, e.g. erythromycin, azole antifungals, e.g. clotrimazole, or niacin (nicotinic acid) (see WARNINGS: Skeletal Muscle).

Antacid: Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides with FILSTATIN decreases plasma concentrations of atorvastatin approximately 35%; however, LDL-C reduction was not altered.

Antipyrine: Because FILSTATIN does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreases approximately by 25% when colestipol and FILSTATIN are co-administered. However, LDL-C reduction was greater when FILSTATIN and colestipol were co-administered than when either drug was given alone.

Cholestyramine: No data is available.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

Digoxin: Co-administration of multiple doses of FILSTAT and digoxin increases steady-state plasma digoxin concentrations by approximately 20%. Hence, patients taking digoxin should be monitored appropriately.

Erythromycin: In healthy individuals, plasma concentrations of FILSTATIN increases approximately 40% with co-administration of FILSTATIN and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle).

Oral contraceptives: Co-administration of FILSTATIN and an oral contraceptive increases the AUC values of norethindrone and ethinyl estradiol approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin: FILSTATIN had no clinically significant effect on prothrombin time when administered to patients receiving combined FILSTATIN and warfarin therapy for two weeks. Nevertheless, patients receiving FILSTATIN should be closely monitored when FILSTATIN is combined with warfarin therapy.

Other Concomitant Therapy: Use of FILSTATIN along with antihypertensive agents and oestrogen replacement therapy does not produce any clinically significant adverse interactions.

4.6. Pregnancy and lactation:

Women who are pregnant or may become pregnant. FILSTATIN may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of FILSTATIN use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. Filstatin 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 drug, Filstatin should be discontinued immediately and the patient apprised of the potential hazard to the fetus

Lactation: It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require Filstatin treatment should not breastfeed their infants

4.7. Effects on ability to drive and use machine:

Atorvastatin has negligible influence on the ability to drive and use machine

4.8. Undesirable effects:

The most frequent adverse effects associated with FILSTATIN therapy are: diarrhoea, constipation, flatulence, dyspepsia, abdominal pain, headache, nausea, myalgia, arthralgia, asthenia, insomnia and rash.

The following side-effects have also been reported: muscle cramps, myositis, myopathy, paraesthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, impotence, hyperglycaemia and hypoglycaemia. Allergic reactions have been reported rarely.

FILSTATIN may cause elevation of creatine phosphokinase and dose-related increase in transaminase levels may occur

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacological actions:

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

The liver is its primary site of action and the principal site of cholesterol synthesis and low-density lipoprotein cholesterol (LDL-C) clearance.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of LDL-C receptors on the cell-surface of liver cells, providing for enhanced uptake and catabolism of LDL-C. Atorvastatin reduces LDL-C production and the number of LDL-C particles. Depending on dose, atorvastatin reduces the number of apolipoprotein-B-containing particles in patients with hypercholesterolaemia. Atorvastatin produces a profound and sustained increase in LDL-C receptor activity coupled with a change in the quality of circulating LDL-C particle .

Atorvastatin reduces total cholesterol (total-C), LDL-C, apolipoprotein-B in normal volunteers, and in patients with heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia, mixed dyslipidaemia, and in some patients with homozygous familial hypercholesterolaemia. It also reduces serum triglycerides (TG) and produces variable increases

in high-density lipoprotein cholesterol (HDL-C) and apolipoprotein-A-1 in non-familial hypercholesterolaemia and mixed dyslipidaemias.

5.2. Pharmacokinetic properties:

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk.

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin.

Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation.

Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution

of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

5.3. Preclinical Safety Data
No data available.

6. Pharmaceutical Particulars

6.1. List of excipients:

S.No	Ingredients	Specification
1.	Lactose monohydrate	BP
2.	Calcium carbonate	BP
3.	Croscarmellose sodium	BP
4.	Polysorbate 80	BP
5.	Hydroxypropylcellulose	BP
6.	Microcrystalline cellulose	BP
7.	Magnesium stearate	BP
8.	Purified water	BP
9.	Hypromellose	BP
10	Titanium dioxide	BP
11	Purified Talc	BP
12	Propylene glycol	BP
13	Polysorbate 80	BP

6.2. Incompatibilities:

None known.

6.3. Shelf life:
2 years.

6.4. Special precautions for storage:
Store below 30°C in a dry place. Protect from light.

6.5 Nature and contents of container

3 Blister strips of ten tablets packed in a carton along with a packing insert.

6.6 Special precautions for disposal

No special requirements.

7 Registrant

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9 Date of revision of the text

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