SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ateroz (Atorvastatin) 40mg Film Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablets contains atorvastatin calcium equivalent to 40 mg atorvastatin.

Also contains titanium dioxide as coloring agent

3. PHARMACEUTICAL FORM

Film Coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ateroz is used for below cases:

1. Indicated as adjunct to diet for reduction elevated cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides and elevation of HDL-cholesterol in patients with primer hypercholesterolemia, heterozygote familial and non-familial hypercholesterolemia and combined (mixed) hyperlipidemia (Fredrickson Type IIa and IIb).
2. As an adjunct to diet for the treatment of patients with elevated serum levels (Fredrickson Type IV);
3. for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet;
4. to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable;

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. 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 nonpharmacological measures has been inadequate.

Prior to initiating therapy with Ateroz, secondary causes for hypercholesterolemia (eg, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, 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. For patients with TG <400

mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 × [TG] + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

Atorvastatin has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons *(Fredrickson* Types I and V).

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin calcium on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dl (6.5 mmol/l). Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/ 90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs 40 events in the atorvastatin group) or nonfatal MI (108 events in the placebo group vs 60 events in the atorvastatin group)] with a relative risk reduction of 36%.

Atorvastatin also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level, a favorable trend was observed with a 26% relative risk reduction. There was no significant difference between the treatment groups for death due to cardiovascular causes or noncardiovascular causes.

4.2 Posology and method of administration

Posology and Method of administration

Before starting Ateroz treatment hypercholestrolemia should be controlled with appropriate diet, exercise and weight loss should be controlled for obese patients. The patient should be continue on a standard cholesterol-lowering diet during treatment with Ateroz.

The recommended starting dose is 10 or 20 mg once daily. Doses should be individualized according to the LDL-C levels, the recommended goal of therapy and patient response. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range is 10 to 80 mg once daily. It can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin should be individualized according to patient characteristics such as goal of therapy and response(see *NCEP Guidelines)*. After initiation and/or upon titration of treatment, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly. Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response.

Primary Hypercholesterolaemia ve Mixed Hyperlipidemia

Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Following treatment guideline can be used for reaching treatment goals.

NCEP Guideline for Lipid Arrangement			
Defined Atherosclerotic Failure[a]	Other risk factors[b] (two or more)	LDL-C mg/dL	LDL-C mg/dL
		Starting level	Minimum Goal
No	No	≥190	<160
No	No	≥160	≥130
No	Yes/No	≥130 [c]	≥100

a Coronary heart disease, diabetes mellitus or peripheral venous disease (including sympthomatic carotid arterial disease and abdominal aort anevrism)

b Other risk factors for coronary heart disease : age (male ≥45, female ≥55 and earlymenapouse without ant estrogen replacement treatment), early coronary heart disease history in the family, current smoking, hypertension; approved HDL-C< 40 mg/dL. If HDL-C ≥60 mg/dL substract one risk factor.

c Coronary heart disease patients with LDL-C level 100-129 mg/dL, physician should decide about the initiation of the drug treatment.

□□ For patients with more than two risk factors, if 10 years CHD risk≥20%, LDL-C treatment goal should be <100 mg/dL.

Homozygous Familial Hypercholesterolemia

Adults: In a compassionate use study, patients with homozygous familial hypercholesterolaemia that received 80 mg of atorvastatin had responsed 15% reduction (18%-45%) in LDL.

Children: Experience in a pediatric population, treatment with up to 80 mg atorvastatin dosage has been limited. Doses up to 80 mg/day for 1 year have been evaluated for 8 patients with homozygous familial hypercholesterolemia**.** Usage of storvastation in the pediatric population is limited with this. For these patients no biochemical and clinical abnormalites were determined. All patients are over 9 years.

Use for Patients with Hepatic Insufficiency : (See. Contraindications and Special warnings and precautions for use)

Use for Patients with Hepatic Insufficiency: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary.

Geriatric Use

Efficacy and safety in older patients using recommended doses is similar to that seen in the general population (see Pharmacological properties – Special populations). Adequate treatment experience in adults age 70 or older with doses of atorvastatin up to 80 mg/day has been evaluated in 221 patients. The safety and the efficacy of atorvastation in this age group was found similar as compared to the patients less than 70 years of age.

4.3 Contraindications

ATEROZ is contraindicated in patients with hypersensitivity to any component of this medication, active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal, during pregnancy, while breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures. Atorvastatin can be used for in an age of fertile women who are not mainly possible to be pregrant or the patient apprised of the potential hazard to the fetus.

4.4 Special warnings and precautions for use

Liver Effects

Like some other lipid-lowering therapies, after atorvastatin treatment moderate elevations(>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases have been reported. Liver functions were observed in pre- and post-marketing clicical trials with atorvastation 10 mg, 20 mg, 40 mg and 80 mg. Persistent elevations in serum transaminases occurred in 0.7% of patients who received atorvastatin. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae.

It is recommended that liver function tests be performed prior to and following both the initiation of therapy. In patients who develop sings and symptoms of liver failure, liver fuction tests should be conducted. 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. In case of active liver disease or unexplained persistent transaminase elevations atorvastatin should not be used

Skeletal Muscle

Uncomplicated myalgia has been reported in atorvastatin-treated patients. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. Atorvastatin therapy should be discontinued if markedly elevated CPK levels(10 times greater then nomal upper limit (ULN)) 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(see Drug Interactions).

Atorvastatin may cause elevation of phosphokinase levels (see Side Effects).

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

Information for Patients:

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

Effects on Central Nervous System:

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

Pediatric Use

Clinical expeirence in this age group is limited with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients. No clinical or biochemical abnormality were reported in these patients. All of these patients were above 9 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals

Digoxin: When multiple doses of atorvastatin 10 mg and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Erythromycin / Clarithromycin: Plasma concentrations of atorvastatin is effected by the coadministration of atorvastatin and erythromycin(4 times a day, 500 mg) and clarithromycin

(2 times a day), known inhibitors of cytochrome P450 3A4. In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin (4 times a day, 500 mg), a known inhibitor of cytochrome P450 3A4 (see Warnings / Precautions, Skeletal muscle).

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Azithromycin: Plasma atorvastatin concentrations were not altered with the coadministration of atorvastatin 10 mg/day and azithromycin 500 mg/day.

Colestipol: Plasma concentrations of atorvastatin decreased (approximately 25%) when colestipol and atorvastatin were coadministered. However, lipid effects were greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Antacid: When atorvastatin and oral antacid suspension containing magnesium and aluminium were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

Warfarin: Interaction study was performed with warfarin and no clinically significant effect was determined. Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Cimetidine: Interaction study was performed with cimetidin and no clinically significant effect was determined. Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine

Amlodipine: Coadministration of atorvastatin 80 mg and amlodipine 10 mg did not affect the pharmacokinetics of atorvastatin.

Protease inhibitors: Coadministration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4 increased the plasma atorvastatin concentrations.

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

Terfenadine: Coadministration of atorvastatin and terfenadine did not effect the pharmacokinetics of atorvastatin.

Other drugs that are coadminitered with atorvastatin: In the clinical trials that antihypertansives and estrogen replacement therapy were coadministered, clinically significant drug interaction findings were not reported. Specific studies for all agent are not available.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

Since the plasma concentrations of atorvastatin may increase with the grapefruit juice, they should not be coadministered. Coadministration with the St. John's Wort may decrease the plasma concentrations of atorvastatin.

4.6 Fertility, pregnancy and lactation

Pregnancy Category X

Atorvastatin is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential should use appropriate contraceptive measures. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m2). In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100

mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. Atorvastatin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Ateroz, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking Ateroz should not breast-feed.

4.7 Effects on ability to drive and use machines

There is no pattern of reported adverse events suggesting that patients taking atorvastatin will have any impairment of ability to drive and use hazardous machinery.

4.8 Undesirable effects

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, abdominal pain, headache,nausea, myalgia, asthenia, diarrhoea and insomnia.

Clinical Adverse Experiences

Adverse experiences reported in >2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment are as following:

Body as a whole: Infection, headache, accidents, common cold, abdominal pain, back pain, alergic reactions, asthenia.

Digestive system: Constipation, diarrhea, dyspepsia, flatulance.

Respiratory system: Sinusitis, pharyngitis.

Skin: Rash.

Musculoskeletal system: Arthralgia, myalgia.

Below listed adverse reactions were reported during clinical trials, however, causal relationship was nor evaluated. These are the adverse reactions with the incidence of ≥%2:

Chest pain, nausea, bronchitis, rhinitis, sleeplessness, malaise, arthritis, urinary tract infections, pripheral edema.

Below listed adverse reactions were reported during clinical trials, however, causal relationship was nor evaluated. These are the adverse reactions with the incidence of <%2:

Body as a Whole: Facial edema, fever, neck stifness, malaise, photosensitivity reaction, generalized edema.

Digestive System: Gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System: Pneumonia, dyspnea, asthma, epistaxis, bronchitis, rhinitis.

Nervous System: Paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

Musculoskeletal System: Leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

Skin: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System: Urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: *Peripheral edema* , hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue, and tendon rupture.

Adverse experiences reported in placebo-controlled clinical studies of atorvastatin, are shown in Table 2.

Table-2: Adverse events in placebo-controlled clinical studies (% of Patients)

BODY SYSTEM/ Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidential Injury	3.7	4.2	0.0	1.3	3.2
Flu syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal pain	0.7	2.8	0.0	3.8	2.1
Back pain	3.0	2.8	0.0	3.8	1.1
Allergic reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					

Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Specific treatment is not available for Ateroz overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Atorvastatin is a selective, competitive inhibitor of HMGCoA reductase, the rate-limiting enzyme responsible for the conversion of 3hydroxy-3methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C a e associated with a decreased cardiovascular risk.

Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastation also reduces VLDL-C and TG and produces variable increases in HDL-C.

Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medication.

In a dose - response study, atorvastatin (10-80 mg) decreased the total cholesterol (30-46%), LDL-C (41-61%), apolipoprotein B (34-50%) and triglycerides (14-33%). These result are also coply to mixed hyperlipidemia patients including heterozygote familial hypercholesterolemia and non-insulin dependent diabetes mellitus.

Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

In patients with Fredrickson Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median percent changes from baseline in HDL-C for atorvastatin (10-80 mg) were 5,1% - 8,7%. Additionally, analysis of the pooled data demonstrated consistent, significant and dose-dependent decreases in total-C/HDL-C and LDL-C/HDL-C are -29% with 44 % and -37% with -55 % respectively.

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. Individualization of drug dosage should be based on therapeutic response The liver is the

primary site of action and the principal site of cholesterol synthesis and LDL clearance. LDL-C reduction is more related with dosage than systemic drug concentration. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. (see Dosage and Administration).

Clinical studies:

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Atorvastatin is effective in a wide variety of patient populations with hypercholesterolemia, with and without hypertriglyceridemia, in men and women, and in the elderly. Experience in pediatric patients has been limited to patients with homozygous FH.

In two multicenter, placebo-controlled, dose-response studies in patients with hypercholesterolemia, atorvastatin given as a single dose over 6 weeks significantly reduced total-C, LDL-C, apo B, and TG (Pooled results are provided in Table 3).

Table-3. Dose response in patients with primary hypercholestrolemia (Adjusted mean% change from baseline)[a]

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

[a] Results are pooled from 2 dose response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in HDL-C for atorvastatin 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7(0, 17), 7.8(0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hypercholesterolemia, atorvastatin was compared to other HMG-CoA reductase inhibitors. After randomization, patients were treated for 16 weeks with either atorvastatin 10 mg per day or a fixed dose of the comparative agent (Table 4).

Table-4. Mean percent change from baseline at end point
(Double blind, randomised, active controlled trials)

Treatment (Daily dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study1							
Atorvastatin 10mg	707	-27a	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20mg	191	-19	-27	-20	-6	+7	-28
%95 Cl Diff[1]		-9.2, -6.5	-10.7,-7.1	-10.0,-6.5	-15.2,-7,1	-1.7,-2.0	-11.1,-7.1
Study 2							
Atorvastatin 10mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Lovastatin 20mg	77	-17	-23	-17	-9	+8	-28
%95 Cl Diff[1]		-10.8,-6.1	-14.5,-8.2	-13.4,-7.4	-14.1,-0.7	-4.9,-1.6	-11.5,-4.1
Study 3							
Atorvastatin 10mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Lovastatin 20mg	45	-24	-30	-30	-15	+7	-33
%95 Cl Diff[1]		-8.7,-2.7	-10.1,-2.6	-8.0,-1.1	-15.1,-0.7	-4.3,-3.9	-9.6,-1.9

[1] A negative value for 95% CI for difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0,

this indicates a stistically significant difference.
[a] Significantly different from lovastatin, ANCOVA, p≤0.05
[b] Significantly different from pravastatin, ANCOVA, p≤0.05
[c] Significantly different from simvastatin, ANCOVA, p≤0.05

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 4 is not known. Table 4 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

In a wide clinical study included to NCEP-ATP II (National Cholesterol Education Program Adult Treatment Panel II) and 10 mg atorvastatin applied patient group is evalueted. After 16 weeks,for 156(93%) of 167patients which have CHD risk factor >2 and lower LDL-C value ≥190 mg/dl, ≤160 mg/dl treatment goals are reached. For 141(65%) of 218 patients which have CHD risk factor >2 and lower LDL-C value ≥160 mg/dl, LDL-C level decrease to ≤130 mg/dl and 21(19) % of 113 patients with CHD and LDL-C level ≥130 mg/dl, ≤100 mg/dl treatment goal for LDL-C are reached.

Hypertriglyceridemia (Fredrickson Type IV)

The response to atorvastatin in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below. For the atorvastatin-treated patients, median (min, max) baseline TG level was 565 (267-1502).

Table 5. Combined patients with isolated elevated TG: Median/min., max.) percent changes from baseline

	Placebo (n=12)	Atorvas. 10mg (n=37)	Atorvas. 20mg (n=13)	Atorvas. 80mg (n=14)
Triglycerides	-12. (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, 13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)

Non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4,3)

Dysbetalipoproteinemia (Fredrickson Type III)

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia *(Fredrickson* Type III) are shown in the table below.

Table 6. Open-label crossover study of 16 patients with dysbetalipoproteinemia (Fredrickson Type III)

	Median(min., max.) at baseline (mg/dl)	Median % cgange(min., max.)	
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C+VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)

Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous

FH received maximum daily doses of 20 to 80 mg of atorvastatin. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

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. Bioavailability of atorvastatin tablets versus solutions is 95%-99%. 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.

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. Coadministration of atorvastatin with terfenadine which is a compound that is metabolized in huge amounts with cytochrome P450 3A4 , does not affect the plasma concentration of terfenadine significantly. Therefore, atorvastation is not expected to affect the pharmacokinetics of other cytochrome P450 3A4 substrates.

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.

Special Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. LDL-C reduction at equivalent dose of drug in the elderly patient population is comparable to younger adults. The geriatric population was evaluated in the ACCESS study for reaching NCEP treatment goals. Study includes 1087 patients below 65 years, 815 patients above 65 and 185 patients above 75 years. For efficacy, safety and reaching treatment goals no significant difference was observed between older patients and all population.

Paediatric: Pharmacokinetic data in the paediatric population are not available.

Gender: Concentrations of atorvastatin in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin. Thus, dose adjustment in patients with renal dysfunction is not necessary.(See. Dosage and Administration).

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins

Hepatic Insufficiency: Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in Cmax and 11fold in AUC) in patients with chronic alcoholic liver disease (ChildsPugh B) (See.Contraindications).

5.3 Preclinical safety data

A series of tests (4 in vitro and 1 in vivo) have shown that atorvastatin has no mutagenic and clastogenic potential. Atorvastatin was not carcinogenic in rats, but hepatocellular adenomas in males and hepatocellular carcinomas in females were observed in mice at high doses (ending 6 to 11 times the AUC_{0-24} achieved at the highest recommended human dose).

There is evidence from experimental animal studies that HMG-CoA reductase inhibitors can affect embryo and fetal development. In rats, rabbits and dogs, atorvastatin had no effect on fertility and was not teratogenic. However, fetal toxicity was observed in rats and rabbits at maternally toxic doses. During maternal exposure to high doses of atorvastatin; rat pups had delayed development and decreased postnatal survival. In rats; There is evidence of placental transfer. In rats, plasma concentrations of atorvastatin were similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polisorbate 80

Hydroxypropylcellulose*

Calcium carbonate

Microcrystallin cellulose

Lactose monohydrate

Crosscarmellose sodium

Magnesium stearate

Ethyl alcohol

Methylene chloride

Opadry YS-I-7040 White

Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place below 30°C.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

White colored, two sided, oblong, biconvex, film coated tablet

30 film tablets are packaged in Al / Al blisters in a carton box with a leaflet.

6.6 Special precautions for disposal <and other handling>

Any unused medicinal product or waste material should be disposed of in accordance with "Regulation on Control of Medical Waste" and "Regulation on Control of Packaging and Packaging Wastes".

7. MARKETING AUTHORISATION HOLDER

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10. DATE OF REVISION OF THE TEXT

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