PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Bmd-ATORVASTATIN

Atorvastatin Calcium Tablets

Tablets, 10 mg, 20 mg, 40 mg and 80 mg atorvastatin (as atorvastatin calcium), Oral

USP

Lipid Metabolism Regulator

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RECENT MAJOR LABEL CHANGES

NA

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Bmd-ATORVASTATIN (atorvastatin calcium) is indicated in adults as an adjunct to lifestyle changes, including diet for:

- the reduction of elevated total cholesterol (total-C), LDL- C, triglycerides (TG), apolipoprotein B (apo B), the Total-C/HDL-C ratio and for increasing HDL-C in hyperlipidemic and dyslipidemic conditions, including:

    - Primary hypercholesterolemia (Type IIa);
    - Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern;
    - Dysbetalipoproteinemia (Type III);
    - Hypertriglyceridemia (Type IV);
    - Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, Bmd-ATORVASTATIN should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available.

- the prevention of Cardiovascular Disease, to reduce the risk of myocardial infarction in the following conditions:

    - hypertensive patients without clinically evident coronary heart disease, but with at least three additional risk factors for coronary heart disease such as age ≥55 years, male sex, smoking, type 2 diabetes, left ventricular hypertrophy, other specified abnormalities on ECG, microalbuminuria or proteinuria, ratio of plasma total cholesterol to HDL-cholesterol ≥6, or premature family history of coronary heart disease.
    - patients with type 2 diabetes mellitus and hypertension without clinically evident coronary heart disease, but with other risk factors such as age ≥55 years, retinopathy, albuminuria or smoking. It also reduced the risk of stroke in this population.
    - patients with clinically evident coronary heart disease.

1.1 Pediatrics

Pediatrics (10 to <18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of atorvastatin calcium in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls with heterozygous familial

hypercholesterolemia, if after an adequate trial of diet therapy the following findings are still present:

a. LDL-C remains ≥4.9 mmol/L (190 mg/dL) or

b. LDL-C remains ≥4.1 mmol/L (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.

(see 4.1 Dosing Considerations, 7.1.3 Pediatrics)

Pediatrics (< 10 years of age). The safety and efficacy in pediatric patients under the age of 10 has not been established, therefore, Health Canada has not authorized an indication for this age range.

1.2 Geriatrics

Geriatrics: Based on the data submitted and reviewed by Health Canada, atorvastatin calcium use in geriatric patients has been authorized for all indications (see 1 INDICATIONS). Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Atorvastatin calcium is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see 7 WARNINGS AND PRECAUTIONS, Hepatic / Bilary / Pancreatic).
- Pregnancy and breastfeeding women (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, 7.1.1 Pregnant Women, 7.1.2 Breast-feeding).
- Concomitant treatment with hepatitis C antivirals (9.4 Drug-Drug Interactions).
- Concomitant treatment with the immunosuppressant cyclosporine (see 9.4 Drug-Drug Interactions).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients should be placed on a standard cholesterol-lowering diet before receiving Bmd-ATORVASTATIN, and should continue on this diet during treatment with Bmd-ATORVASTATIN. If appropriate, a program of weight control and physical exercise should be implemented.
- Prior to initiating therapy with Bmd-ATORVASTATIN, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.
- Elevated serum triglycerides are most often observed in patients with the metabolic syndrome (abdominal obesity, atherogenic dyslipidemia {elevated triglycerides, small dense LDL particles and low HDL-cholesterol}, insulin resistance with or without glucose intolerance, raised blood pressure and prothrombic and proinflammatory states).
- When drugs are prescribed attention to therapeutic lifestyle changes (reduced intake of saturated fats and cholesterol, weight reduction, increased physical activity, ingestion of soluble fibers) should always be maintained and reinforced.
- The dosage of Bmd-ATORVASTATIN should be individualized according the baseline LDL-C, total-C/HDL-C ratio and/or TG levels to achieve the recommended desired lipid values at the lowest dose needed to achieve LDL-C desired level. Lipid levels should be monitored periodically and, if necessary, the dose of Bmd-ATORVASTATIN adjusted based on desired lipid levels recommended by guidelines.

4.2 Recommended Dose and Dosage Adjustment

- Primary Hypercholesterolemia and Combined (Mixed) Dyslipidemia, Including Familial Combined Hyperlipidemia

  The recommended starting dose of Bmd-ATORVASTATIN is 10 or 20 mg once daily, depending on patient's LDL-C reduction required. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of Bmd-ATORVASTATIN is 10 to 80 mg once daily. A significant therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 2-4 weeks. The response is maintained during chronic therapy. Adjustments of dosage, if necessary, should be made at intervals of 2 to 4 weeks. The maximum dose is 80 mg/day.

- Severe Dyslipidemias

  In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see 7 WARNINGS AND PRECAUTIONS, Pharmacokinetic Interactions, 7 WARNINGS AND PRECAUTIONS, Muscle Effects; 9 DRUG INTERACTIONS).

Patients with high or very high triglyceride levels, i.e. > 2.2 mmol/L (200 mg/dL) or > 5.6 mmol/L (500 mg/dL), respectively, may require triglyceride-lowering therapy (fenofibrate, bezafibrate or nicotinic acid) alone or in combination with Bmd-ATORVASTATIN.

In general, combination therapy with fibrates must be undertaken cautiously and only after risk-benefit analysis (see 7 WARNINGS AND PRECAUTIONS, Pharmacokinetic Interactions and 9.4 Drug-Drug Interactions).

- Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10- <18 years of age)

  The recommended starting dose of Bmd-ATORVASTATIN is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg/day have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see 1.1 Pediatrics and 14 CLINICAL TRIALS). Adjustments should be made at intervals of 4 weeks or more.
  Health Canada has not authorized an indication for pediatric use in a population under 10 years of age.

- Prevention of Cardiovascular Disease

  The recommended starting dose of Bm-dATORVASTATIN for the primary prevention of myocardial infarction is 10 mg/day.

  For secondary prevention of myocardial infarction, optimal dosing may range from 10 mg to 80 mg atorvastatin once daily, to be given at the discretion of the prescriber, taking into account the expected benefit and safety considerations relevant to the patient to be treated.

- Dosage in Patients with Renal Insufficiency

  Patients with a history of renal insufficiency of unknown severity and severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)] should be given lowest dose (10 mg/day) of Bmd-ATORVASTATIN. (see 7 WARNINGS AND PRECAUTIONS, Renal)

- Drug discontinuation

  If the patient becomes pregnant while taking Bmd-ATORVASTATIN, the drug should be discontinued immediately (see 7.1.1 Pregnant Women).

  If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

  Bmd-ATORVASTATIN therapy should be temporarily withheld or discontinued in any patient with

an acute serious condition suggestive of myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as sepsis, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures). Bmd-ATORVASTATIN therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal).

Bmd-ATORVASTATIN should be discontinued if hypersensitivity is suspected (7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).

If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued (see 8.5 Post-Market Adverse Reactions).If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with Bmd-ATORVASTATIN, promptly interrupt therapy (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

4.4 Administration

Doses can be given at any time of the day, preferably in the evening, with or without food.

4.5 Missed Dose

If patient misses a dose, it should be taken immediately unless the time is close to the next dose. In such an event, patient should wait for next scheduled dose and continue on the regular schedule. A double dose should not be taken to make up for a missed dose.

5 OVERDOSAGE

There is no specific treatment for atorvastatin 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, hemodialysis is not expected to significantly enhance atorvastatin clearance (see 8 ADVERSE REACTIONS).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets: 10 mg, 20 mg, 40 mg and 80 mg atorvastatin	calcium carbonate, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, polysorbate 80, magnesium stearate and opadry-YS-1-7040 white. The coating agent opadry-YS-1- 7040 white contains hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and Talc.

Bmd-ATORVASTATIN (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg, 40 mg and 80 mg atorvastatin per tablet.

10 mg: White, to off-white, oval shaped, biconvex, film-coated tablets, debossed with "FFI" on one side and plain on other side. Available in bottles of 90, 500 tablets and blister of 30 tablets (3 strips X 10).

20 mg: White, to off-white, oval shaped, biconvex, film-coated tablets, debossed with "FF2" on one side and plain on other side. Available in bottles of 90, 500 tablets and blister of 30 tablets (3 strips X 10).

40 mg: White, to off-white, oval shaped, biconvex, film-coated tablets, debossed with "FF3" on one side and plain on other side. Available in bottles of 90, 500 tablets and blister of 30 tablets (3 strips X 10).

80 mg: White, to off-white, oval shaped, biconvex, film-coated tablets, debossed with "FF4" on one side and plain on other side. Available in bottles of 90, 500 tablets and blister of 30 tablets (3 strips X 10).

7 WARNINGS AND PRECAUTIONS

General

Patients should be advised to inform health professionals of the prior use of Bmd-ATORVASTATIN or any other lipid-lowering agents.

Cardiovascular

Hemorrhagic Stroke in Patients with Recent Stroke or Transient Ischemic Attack (TIA)

The highest dose of atorvastatin calcium (80mg) was associated with an increased risk of hemorrhagic stroke in a post-hoc analysis of a clinical study in 4,731 patients without coronary heart disease (CHD) who had a stroke or TIA within the preceding six months compared to placebo.

Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke. The potential risk of hemorrhagic stroke should be carefully considered before initiating treatment with atorvastatin in patients with recent (1-6 months) stroke or TIA.

Effect on Ubiquinone (CoQ_{10}) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not 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. CoQ10 Levels should be measured when clinically indicated

Endocrine and Metabolism

Endocrine Function
HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, 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.

Patients treated with atorvastatin 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.

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.

Effect on Lipoprotein (a)
In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) lipoprotein concentrations. Present knowledge suggests the importance of high Lp(a) levels as an emerging risk factor for coronary heart disease. It is thus desirable to maintain and reinforce lifestyle changes in high risk patients placed on atorvastatin therapy.

Patients with Severe Hypercholesterolemia
Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see 7 WARNINGS AND PRECAUTIONS, Pharmacokinetic Interactions, Muscle Effects; 9.4 Drug-Drug Interactions; 4 DOSAGE AND ADMINISTRATION).

Hepatic/Biliary/Pancreatic

Hepatic Effects
In clinical trials, persistent increases in serum transaminases greater than three times the upper limit of normal occurred in <1% of patients who received atorvastatin calcium. When the dosage of atorvastatin calcium was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of atorvastatin calcium without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and repeated as clinically indicated. There have been rare post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If an alternate etiology is not found, do not restart Bmd-ATORVASTATIN.

Bmd-ATORVASTATIN, 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 Bmd-ATORVASTATIN; if such a condition should develop during therapy, the drug should be discontinued.

Musculoskeletal

Pharmacokinetic Interactions
The use of HMG- CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme (see 7 WARNINGS AND PRECAUTIONS, Muscle effects, and 9.2 Drug Interactions Overview).

Muscle Effects
Effects on skeletal muscle such as myalgia, myositis, myopathy and rarely, rhabdomyolysis have been reported in patients treated with atorvastatin calcium.

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

Myopathy, defined as muscle pain or muscle weakness in conjunction with increases in creatine kinase (CK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured.

Pre-disposing Factors for Myopathy/Rhabdomyolysis: Bmd-ATORVASTATIN, 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 > 65 years
- Renal impairment
- Hepatic impairment
- Diabetes with hepatic fatty change
- Surgery and trauma
- Frailty
- Situations where an increase in plasma levels of active ingredient may occur

The risk of myopathy and rhabdomyolysis is increased with concurrent administration of drugs

that increase the systemic concentration of atorvastatin via the inhibition of CYP 3A4 or transporter proteins Bmd-ATORVASTATIN (see 7 WARNING AND PRECAUTIONS, Pharmacokinetic Interactions; 9.4 Drug-Drug Interactions).

Although patients with renal impairment are known to be predisposed to the development of rhabdomyolysis with administration of HMG-CoA reductase inhibitors (also known as statins), those with a history of renal impairment may also be predisposed to the development of rhabdomyolysis. Such patients merit close monitoring for skeletal muscle effects.

There have been rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with statins (see 8.5 Post-Market Adverse Reactions). IMNM is clinically characterized by:

- persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment
- positive anti-HMG CoA reductase antibody
- muscle biopsy showing necrotizing myopathy without significant inflammation
- improvement with immunosuppressive agents.

Ophthalmologic

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

Renal

Plasma concentrations and LDL-C lowering efficacy of atorvastatin calcium was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of Bmd-ATORVASTATIN should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects; 9 DRUG INTERACTIONS; 4.2 Recommended Dose and Dosage Adjustment).

Sensitivity/Resistance

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous- like syndrome, polymyalgia rheumatica, vasculitis, purpura,

thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such.

Reproductive Health: Female and Male Potential
Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Bmd-ATORVASTATIN 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. 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 2 CONTRAINDICATIONS, 7.1.1 Pregnant Women)

Fertility -There is no available data on effect of atorvastatin on human fertility. Non-clinical studies did not show an effect on animal fertility (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1 Special Populations

7.1.1 Pregnant Women

Bmd-ATORVASTATIN is contraindicated during pregnancy (see 2 CONTRAINDICATIONS).

The extent of exposure in pregnancy during clinical trials: No experience.

Bmd-ATORVASTATIN 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 Bmd-ATORVASTATIN, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1.2 Breastfeeding

It is unknown if atorvastatin calcium is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking Bmd-ATORVASTATIN should not breast-feed (see 2 CONTRAINDICATIONS). In rats, milk concentrations of atorvastatin are similar to

those in plasma.

7.1.3 Pediatrics

Since the safety and tolerability profile of atorvastatin in pediatric patients (10-<18 years) is generally similar to the known safety profile of atorvastatin in adult patients, similar warning apply to this patient population. Patients should be particularly monitored for liver enzymes (AST/ALT) and creatine kinase, and adverse events of interest (e.g.: headache, gastrointestinal, musculoskeletal and connective tissue disorders). Doses greater than 20 mg have not been studied in this patient population.

Safety and effectiveness of atorvastatin calcium in pediatric patients has not been determined in the prevention of myocardial infarction.

Atorvastatin calcium had no effect on growth or sexual maturation in boys and in girls. The effects on menstrual cycle were not assessed [see 14 CLINICAL TRIALS; 8.2.1 Clinical Trial Adverse Reactions – Pediatrics; and 4.2 Recommended Dose and Dose Adjustment, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-<18years of age)].

Adolescent females should be counselled on appropriate contraceptive methods while on Bmd-ATORVASTATIN therapy (see 2 CONTRAINDICATIONS, 7.1.1 Pregnant Women).

Atorvastatin calcium has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. For this patient population, there are limited data available from uncontrolled, open label studies (see 1.1 Pediatrics, 8.2.1 Clinical Trial Adverse Reactions – Pediatrics, Heterozygous Familial Hypercholesterolemia in Pediatric and 10.3 Pharmacokinetics, Special Populations and Conditions: Pediatrics).

Doses of atorvastatin calcium up to 80 mg/day for 1 year have been evaluated in 8 pediatric patients with homozygous familial hypercholesterolemia (see 14 Clinical Studies - Heterozygous Familial Hypercholesterolemia in pediatric patients).

7.1.4 Geriatrics

Treatment experience in adults 70 years or older (N=221) with doses of atorvastatin calcium up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see 10.3 Pharmacokinetics, Special Populations and Conditions: Geriatrics).

Elderly patients may be more susceptible to myopathy (see 7 WARNINGS AND PRECAUTIONS, Pre-disposing Factors for Myopathy/Rhabdomyolysis).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most serious adverse reactions associated with atorvastatin calcium were rhabdomyolysis, with acute renal failure secondary to myoglobinuria, myalgia, myositis, myopathy (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal, 8.5 Post-Market Adverse Reactions). The most commonly reported adverse reactions in placebo controlled trials, that may be associated with atorvastatin therapy were nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and hyperglycemia (5.9%) (see 8.2 Clinical Trial Adverse Reactions).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse reactions with atorvastatin calcium have usually been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 atorvastatin calcium versus 7311 placebo) patients treated for a median period of 53 weeks , 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of atorvastatin calcium and reported to be possibly, probably or definitely drug related are shown in Table 1 below:

Table 1: Associated Adverse Events Reported in ≥1% of Patients in Placebo Controlled Clinical Trials

	Atorvastatin % (n=8755)	Placebo % (n=7311)
Gastrointestinal disorders:		
Diarrhea	6.8	6.3
Dyspepsia	4.6	4.3
Nausea	4.0	3.5
Constipation	3.9	4.3
Flatulence	1.2	1.0
General disorders and administration site conditions:		
Asthenia	1.1	1.1

	Atorvastatin % (n=8755)	Placebo % (n=7311)
Infections and Infestations:		
Nasopharyngitis	8.3	8.2
Metabolism and nutrition disorders:		
Hyperglycemia	5.9	5.5
Liver function test abnormal*	4.1	2.0
Blood creatine phosphokinase increased	1.9	1.8
Musculoskeletal and connective tissue disorders:		
Arthralgia	6.9	6.5
Pain in extremity	6.0	5.9
Musculoskeletal pain	3.8	3.6
Muscle spasms	3.6	3.0
Myalgia	3.5	3.1
Joint swelling	1.3	1.2
Nervous system disorders:		
Headache	6.5	6.7
Respiratory, thoracic and mediastinal disorders:		
Pharyngolaryngeal pain	2.3	2.1
Epistaxis	1.2	1.1

*alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic enzyme increased, liver function test abnormal and transaminases increased.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (ages 10-17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=187, where 140 patients received atorvastatin calcium), the safety and tolerability profile of atorvastatin calcium 10 to 20 mg daily was similar to that of placebo. The adverse events reported in ≥1% of patients were as follows: abdominal pain, depression and headache (see 14 CLINICAL TRIALS and 7.1.3 Pediatrics).

In an uncontrolled, open-label, 3-year study in children with heterozygous familial hypercholesterolemia ages 6 and above, physical growth (height, weight and BMI) and sexual maturation (Tanner Stage) appear to be consistent with the trend in the general pediatric population when atorvastatin was used as indicated. Patients should be evaluated for growth abnormalities if shifts in growth percentiles become evident. The safety and tolerability profile in pediatric patients had similar patterns to the known safety profile of atorvastatin in adult patients. Patients should be particularly monitored for liver enzymes (AST/ALT) and creatine kinase, and adverse events of interest (e.g.: headache, gastrointestinal, musculoskeletal and connective tissue disorders).

8.3 Less Common Clinical Trial Adverse Reactions

The following additional adverse events were reported in placebo-controlled clinical trials during atorvastatin calcium therapy: Muscle cramps, myositis, muscle fatigue, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, cholestasis, anorexia, vomiting, abdominal discomfort, alopecia, pruritus, rash, urticaria, erectile dysfunction, nightmare, vision blurred, tinnitus, eructation, neck pain, malaise, pyrexia and white blood cells urine positive.

In summary, the adverse events occurring at a frequency <1% are listed below:

Ear and labyrinth disorders: tinnitus

Eye disorders: vision blurred

Gastrointestinal disorders: abdominal discomfort, anorexia, eructation, pancreatitis, vomiting

General disorders and administration site conditions: malaise;

pyrexia **Hepatobiliary disorders**: hepatitis, cholestasis, cholestatic

jaundice

Investigations: white blood cells urine positive

Musculoskeletal and connective tissue disorders: muscle fatigue, neck pain, myopathy, myositis, muscle cramps

Neurological: peripheral neuropathy, paresthesia

Psychiatric disorders: nightmare

Skin and subcutaneous tissue disorders: alopecia, rash, pruritus, urticaria

Urogenital: erectile dysfunction

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial findings: The criteria for clinically significant laboratory changes were >3 X the upper limit of normal (ULN) for liver enzymes, and >5 X ULN for creatine kinase. A total of 8 unique subjects met one or more of these criteria during the double-blind phase. Hence, the incidence of patients who experienced abnormally high enzymatic levels (AST/ALT and creatine kinase) was > 4% (8/187).

Five atorvastatin and one placebo subjects had increases in CK >5 X ULN during the double-blind phase; two of the five atorvastatin treated subjects had increases in CK > 10 X ULN.

There were 2 subjects who had clinically significant increases in ALT.

Laboratory Tests: Increases in serum transaminase levels and serum glucose have been noted in clinical trials (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 8.2 Clinical Trial Adverse Reactions).

8.5 Post-Market Adverse Reactions

The following adverse events have also been reported during post-marketing experience with atorvastatin calcium, regardless of causality assessment:

Rare reports: severe myopathy with or without rhabdomyolysis (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects, 7 WARNINGS AND PRECAUTIONS, Renal and 9 DRUG INTERACTIONS).

There have been rare reports of immune-mediated necrotizing myopathy with statins (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects).

Isolated reports: Gynecomastia, thrombocytopenia, arthralgia and allergic reactions including urticaria, angioedema (angioneurotic edema), anaphylaxis and bullous rashes (including erytheme multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), fatigue, myositis, back pain, chest pain, malaise, dizziness, amnesia, peripheral edema, weight gain, abdominal pain, insomnia, hypoesthesia, tinnitus, tendon rupture, pancreatitis, dysgeusia and Ewing's sarcoma (pediatric).

Ophthalmologic observations: see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic.
Cases of erectile dysfunction have been reported in association with the use of statins.
The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares;
- Mood related disorders, including depression;
- Very rare cases of interstitial lung disease, especially with long term therapy.

Endocrine disorders: Increases in fasting glucose and HbA1c levels have been reported with atorvastatin calcium.

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).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant treatment with hepatitis C antivirals (see 9.4 Drug-Drug Interactions)
- Concomitant treatment with the cyclosporine (see 9.4 Drug-Drug Interactions)
- Concomitant treatment with HIV protease inhibitors (see 9.4 Drug-Drug Interactions)

9.2 Drug Interactions Overview

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see also 7 WARNINGS AND PRECAUTIONS, Renal; Patients with Severe Hypercholesterolemia; 7.1 Special Populations).

Concomitant Therapy with Other Lipid Metabolism Regulators: Based on post-marketing surveillance, increase in the risk of myopathy may be seen when given concomitantly with HMG-CoA reductase inhibitors (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects;, 9.4 Drug-Drug Interactions, Table 2 – Established or Potential Drug-Drug Interactions).

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Interaction may occur when atorvastatin calcium is administered with inhibitors of cytochrome P450 3A4. Concomitant administration can lead to increased plasma concentrations of atorvastatin (see 7 WARNINGS AND PRECAUTIONS, Pharmacokinetic Interactions, 7 WARNINGS AND PRECAUTIONS, Muscle Effects, 7 WARNINGS AND PRECAUTIONS , Renal and 7 WARNINGS AND PRECAUTIONS, Endocrine Function; 9.4 Drug-Drug Interactions, Table 2 – Established or Potential Drug-Drug Interactions).

Transporter Inhibitors: Atorvastatin is a substrate of the hepatic transporters (see section 9.4 Drug-Drug Interactions). Active liver disease or unexplained transaminase elevations are contraindications to the use of atorvastatin calcium; if treatment for active liver disease is necessary during therapy with Bmd-ATORVASTATIN, the drug should be discontinued (see 2 CONTRAINDICATIONS).

Inducers of cytochrome P450 3A: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 can lead to variable reductions in plasma concentrations of atorvastatin. (see 9.4 Drug-Drug Interactions).

9.3 Drug-Behavioural Interactions

Bmd-ATORVASTATIN, 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. Plasma concentrations of atorvastatin are markedly increased in patients with chronic alcoholic liver disease (See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)

9.4 Drug-Drug Interactions

Pharmacokinetic interaction studies have been conducted in healthy subjects with 3 macrolide antibiotics: erythromycin and clarithromycin (both of which inhibit CYP 3A4), and with azithromycin. Coadministration of atorvastatin with erythromycin or clarithromycin, resulted in moderately increased atorvastatin plasma levels but atorvastatin plasma levels were not altered by azithromycin. Twelve healthy subjects were administered atorvastatin 10 mg on days 1 and 15; erythromycin 500 mg QID was administered from days 8 to 19.

Erythromycin increased atorvastatin Cmax (ratio of Cmax: 1.38) and AUC (ratio of AUC: 1.33). In a second study, atorvastatin 10 mg was administered daily for 8 days; clarithromycin (500 mg BID) or azithromycin (500 mg QD) was coadministered from days 6 - 8 (N=12/treatment). Coadministration with clarithromycin increased atorvastatin AUC (ratio of AUC: 1.82) and Cmax (ratio of Cmax: 1.56), but atorvastatin plasma levels were not significantly altered by coadministration with azithromycin.

Steady-state, open-label, pharmacokinetic studies with digoxin have been performed in healthy subjects with both low and high doses of atorvastatin. Atorvastatin (10 mg or 80 mg QD; N=11 and N=12, respectively), was administered from days 1 - 20 and digoxin (0.25 mg QD) from days 11 - 20. At steady-state, atorvastatin 10 mg daily had no significant effect on steady-state digoxin pharmacokinetics. However, following co-administration with atorvastatin 80 mg QD, the mean steady-state digoxin AUC and Cmax increased (ratio of atorvastatin AUC: 1.15; ratio of atorvastatin Cmax: 1.20). Patients taking digoxin should be monitored appropriately.

The effect of amlodipine on the pharmacokinetics of atorvastatin was assessed at steady-state in a randomized, open-label, placebo-controlled, crossover study in healthy male subjects (N=16). Atorvastatin (80 mg QD) was administered with amlodipine (10 mg QD) or placebo from days 1 - 8. Following a 14 day washout, the alternate combination was administered from days 22 - 29. At steady-state, the coadministration of maximum doses of atorvastatin and amlodipine did not significantly alter the pharmacokinetics of atorvastatin and there were no apparent changes in blood pressure or heart rate.

The effect of quinapril on the pharmacokinetics of atorvastatin was assessed in a randomized, open-label study in healthy volunteers (N=22). Single doses of atorvastatin (10 mg) were administered on days 1 to 14, and single doses of quinapril (80 mg) were administered on days 1 to 7 or days 8 to 14. The mean Tmax value for atorvastatin during steady state quinapril

administration was shortened by 1.25 hours compared to that of atorvastatin administered alone but with no change in absorption/AUC or Cmax. No significant changes in blood pressure or heart rates were observed.

Concomitant administration of atorvastatin 20-40 mg and itraconazole 200 mg daily resulted in an increase in atorvastatin AUC (ratio of atorvastatin AUC:3.3 and ratio of atorvastatin Cmax: 1.20 for atorvastatin 40 mg only).

Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an increase in exposure to atorvastatin (ratio of atorvastatin AUC: 8.7 and ratio of atorvastatin C_{max}: 10.7).

The drugs listed in this table are based on either drug interactions, case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 2- Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
Antacids	↓ in plasma concentrations of atorvastatin calcium(ratio of atorvastatin AUC: 0.66 and ratio of atorvastatin Cmax: 0.67) following administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension. LDL-C reduction was not altered; TG-lowering effect of atorvastatin calcium may be affected.	This decrease in exposure should be considered when prescribing atorvastatin with antacids.

Proper name	Effect	Clinical comment
Antihypertensive Agents: Amlodipine Quinapril	In healthy subjects, atorvastatin PK were not altered by the coadministration of atorvastatin calcium 80 mg and amlodipine 10 mg at steady state. No apparent changes in BP or HR. In healthy volunteers, co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no clinical significant change in the AUC or C_{max} or T_{max} of atorvastatin (ratio of atorvastatin AUC: 1.18 and ratio of atorvastatin C_{max}: 0.91). Steady-state quinapril dosing of 80 mg QD did not significantly affect the PK profile of atorvastatin tablets 10 mg QD.	Close monitoring is required.
Antipyrine	Atorvastatin calcium had no effect on the PK of antipyrine Ratio of antipyrine AUC: 1.03 and ratio of antipyrine C_{max}: 0.89 with atorvastatin 80 mg QD and antipyrine 600 mg SD.	Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). Interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Proper name	Effect	Clinical comment
Bile Acid Sequestrants	Patients with mild to moderate HC: ↑ LDL-C reduction (-45%) when atorvastatin calcium 10 mg and colestipol 20 g were coadministered than when either drug was administered alone (-35% for atorvastatin calcium and -22% for colestipol). Patients with severe HC: LDL-C reduction was similar (-53%) when atorvastatin calcium 40 mg and colestipol 20 g were coadministered when compared to that with atorvastatin calcium 80 mg alone. ↓ plasma atorvastatin concentration (ratio of 0.74) when atorvastatin calcium 40 mg plus colestipol 20 g were coadministered compared with atorvastatin calcium 40 mg alone. However, the combination drug therapy was less effective in lowering TG than atorvastatin calcium monotherapy in both types of hypercholesterolemic patients.	When Bmd-ATORVASTATIN is used concurrently with colestipol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of atorvastatin calcium may be impaired by the resin.
Cimetidine	No effect on plasma concentrations (ratio of atorvastatin AUC: 1.00 and ratio of atorvastatin C_{max}: 0.89) or LDL-C lowering efficacy of atorvastatin calcium ↓ in TG-lowering effect of atorvastatin calcium from 34% to 26%	This decrease in TG-lowering should be considered when prescribing atorvastatin with cimetidine.
Colchicine	Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administrated with colchicine.	Caution should be exercised when prescribing atorvastatin with colchicine (7 WARNINGS AND PRECAUTIONS, Muscle Effects).

Proper name	Effect	Clinical comment
Coumarin Anticoagulants	No clinically significant effect on prothrombin time	Atorvastatin calcium had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.
Cyclosporine	Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an increase in exposure to atorvastatin (ratio of atorvastatin AUC: 8.7; ratio of atorvastatin C_{max}: 10.7).	Concomitant use is contraindicated. (See 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS, Muscle Effects)
Digoxin	In healthy subjects, digoxin PK at steady-state were not significantly altered by coadministration of digoxin 0.25 mg and atorvastatin calcium 10 mg daily. ↑ in digoxin steady-state concentrations (ratio of atorvastatin AUC:1.15 and ratio of atorvastatin C_{max}: 1.20) following coadministration of digoxin 0.25 mg and atorvastatin calcium 80 mg daily.	Patients taking digoxin should be monitored appropriately.
Diltiazem Hydrochloride	Steady-state diltiazem increases the atorvastatin exposure, based on AUC_{LASTs}, of a single dose of atorvastatin by approximately 50% (ratio of atorvastatin AUC: 1.51 and ratio of atorvastatin C_{max}: 1.00).	
Efavirenz	Ratio of AUC: 0.59 and ratio of C_{max}: 1.01 with atorvastatin 10 mg and Efavirenz 600 mg daily.	This decrease in exposure should be considered when prescribing atorvastatin with efavirenz.

Proper name	Effect	Clinical comment
Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (nicotinic acid)	↑ in the risk of myopathy during treatment with other drugs in this class, including atorvastatin. Ratio of atorvastatin AUC: 1.35 and ratio of atorvastatin C_{max}: 1.00 with atorvastatin 40 mg SD and Gemfibrozil 600 mg BID. Ratio of atorvastatin AUC: 1.03 and ratio of atorvastatin C_{max}: 1.02 with atorvastatin 40 mg SD and Fenobibrate 160 mg BID.	The concomitant therapy with Bmd-ATORVASTATIN and gemfibrozil should be avoided. The benefits and risks of combined therapy with Bmd-ATORVASTATIN and fenofibrate, bezafibrate and niacin should be carefully considered; lower starting and maintenance doses of atorvastatin should be considered (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects).
Fusidic Acid	Although interaction studies with atorvastatin and fusidic acid have not been conducted, rhabdomyolysis resulting in fatal outcome has been reported in patients receiving a combination of statins, including atorvastatin, and fusidic acid. The mechanism of this interaction is not known.	The concurrent use of atorvastatin and fusidic acid should be avoided. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. Statin therapy may be re-introduced at least seven days after the last dose of fusidic acid. Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects).

Proper name	Effect	Clinical comment
Hepatitis C virus inhibitors: Telaprevir Boceprevir Glecaprevir / Pibrentasvir	 Ratio of atorvastatin AUC: 7.9 and ratio of atorvastatin Cmax: 10.6 with atorvastatin 20 mg SD and Telaprevir 750 mg q8h, 10 days* Ratio of atorvastatin AUC: 2.3 and ratio of atorvastatin Cmax: 2.7 with atorvastatin 40 mg SD and Boceprevir 800 mg TID, 7 days Ratio of atorvastatin AUC: 8.3 and ratio of atorvastatin Cmax: 22.0 with atorvastatin 10 mg QD for 7 days and Glecaprevir 400 mg QD/Pibrentasvir 120 mg QD for 7 days*	Concomitant use of atorvastatin and drugs used for the treatment of active liver disease, such as HCV inhibitors, is contraindicated. (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS) Discontinue Bmd-ATORVASTATIN if treatment for active liver disease is necessary.
Elbasvir / Grazoprevir Simeprevir Ledipasvir / Sofosbuvir	Ratio of atorvastatin AUC: 1.95 and ratio of atorvastatin Cmax: 4.3 with atorvastatin 10 mg SD and Elbasvir 50 mg QD/Grazoprevir 200 mg QD for 13 days* Ratio of atorvastatin AUC: 2.12 and ratio of atorvastatin Cmax: 1.70 with atorvastatin 40 mg SD and Simeprevir 150 mg QD for 10 days* Although interaction studies with atorvastatin and ledipasvir/sofosbuvir have not been conducted, cases of myopathy and rhabdomyolysis have been reported with atorvastatin co-administrated with ledipasvir/sofosbuvir.	

Proper name	Effect	Clinical comment
Velpatasvir / Sofosbuvir	Co-administration of atorvastatin (40 mg) with velpatasvir (100 mg)/sofosbuvir (400 mg) resulted in increased exposure to atorvastatin by 1.68-fold for C_{max} and 1.54-fold for AUC.	
Itraconazole	Concomitant administration of atorvastatin 20-40 mg and itraconazole 200 mg daily resulted in an increase in atorvastatin (ratio of atorvastatin AUC: 3.3 and ratio of atorvastatin C_{max}: 1.20 for atorvastatin 40 mg only).	The dose of Bmd-ATORVASTATIN used in combination with itraconazole should not exceed 20 mg daily
Letermovir	Concomitant administration of atorvastatin 20 mg SD and letermovir 480 mg daily resulted in an increase in exposure to atorvastatin (ratio of AUC 3.29 and ratio of atorvastatin C_{max}: 2.17).	The dose of Bmd-ATORVASTATIN used in combination with letermovir should not exceed 20 mg daily. Patients should be closely monitored for statin-associated adverse events such as myopathy or rhabdomyolysis (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects).
Macrolide Antibiotics (azithromycin, clarithromycin, erythromycin). Clarithromycin and erythromycin are both CYP3A4 inhibitors	In healthy adults, coadministration of atorvastatin calcium (10 mg QD) and azithromycin (500 mg QD) did not significantly alter the plasma concentrations of atorvastatin. Ratio of atorvastatin AUC: 1.33 and ratio of atorvastatin C_{max}: 1.38 with erythromycin (500 mg QID) when coadministered with atorvastatin (10 mg QD) Ratio of atorvastatin AUC: 1.82 and ratio of atorvastatin C_{max}: 1.56 with clarithromycin (500 mg BID) when coadministered with atorvastatin (10 mg QD)	See 7 WARNINGS AND PRECAUTIONS, Muscle Effects.
Oral Contraceptives and Hormone Replacement Therapy	↑ plasma concentrations (AUC levels) of norethindone (ratio of atorvastatin AUC: 1.28 and ratio of atorvastatin C_{max}: 1.23) and ethinyl estradiol (ratio of atorvastatin AUC: 1.19 and ratio of atorvastatin C_{max}: 1.30) following coadministration of	These increases should be considered when selecting an oral contraceptive.

Proper name	Effect	Clinical comment
	atorvastatin with an oral contraceptive containing 1 mg norethindone and 35 µg ethinyl estradiol. In clinical studies, atorvastatin calcium was used concomitantly with estrogen replacement therapy without evidence to date of clinically significant adverse interactions.	
Protease Inhibitors (nelfinavir mesylate, lopinavir/ritonavir, tipranavir/ritonavir, saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, fosamprenavir)	↑ plasma concentrations of atorvastatin when atorvastatin 10 mg QD is coadministered with nelfinavir mesylate 1250 mg BID. Ratio of atorvastatin AUC: 1.74 and ratio of atorvastatin C_{max}: 2.2. Ratio of atorvastatin AUC: 5.9 and ratio of atorvastatin C_{max}: 4.7 with atorvastatin 20 mg QD and Lopinavir 400 mg / Ritonavir 100 mg BID Ratio of atorvastatin AUC: 9.4 and ratio of atorvastatin C_{max}: 8.6 with atorvastatin 10 mg SD and Tipranavir 500 mg BID / Ritonavir 200 mg BID, 7 days. Atorvastatin 10 mg SD had no effect on the PK of Tripanavir 500mg BID / Ritonavir 200 mg BID, 7 days Ratio of atorvastatin AUC: 3.9 and ratio of atorvastatin C_{max}: 4.3 with atorvastatin 40 mg QD for 4 days and Ritonavir 400 mg BID, 15 days / Saquinavir 400 mg BID†	The dose of Bmd-ATORVASTATIN used in combination with nelfinavir should not exceed 40 mg daily. The concomitant therapy with Bmd-ATORVASTATIN and the combination of lopinavir/ritonavir should be used with caution and lowest Bmd-ATORVASTATIN dose necessary. (See7 WARNINGS AND PRECAUTIONS, Muscle Effects) The concomitant therapy with Bmd-ATORVASTATIN and the combination of tipranavir/ritonavir or Bmd-ATORVASTATIN and telaprevir should be avoided. The dose of Bmd-ATORVASTATIN should be restricted to 20 mg daily when used in combination with saquinavir/ritonavir, darunavir/ ritonavir, fosamprenavir alone or fosamprenavir/ritonavir. † The dose of saquinavir/ritonavir in this study is not the clinically used dose. The increase in

Proper name	Effect	Clinical comment
	Ratio of atorvastatin AUC: 3.4 and ratio of atorvastatin C_{max}: 2.2 with atorvastatin 10 mg QD for 4 days and Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days Ratio of atorvastatin AUC: 2.5 and ratio of atorvastatin C_{max}: 2.8 with atorvastatin 10 mg QD for 4 days and Fosamprenavir 700 mg BID/ritonavir 100 mg BID,14 days Ratio of atorvastatin AUC: 2.3 and ratio of atorvastatin C_{max}: 4.0 with atorvastatin 10 mg QD for 4 days and Fosamprenavir 1400 mg BID, 14 days. Atorvastatin 10 mg QD for 4 days had the following effect on the PK of Fosamprenavir 1400 mg BID, 14 days: Ratio of atorvastatin AUC: 0.73 and ratio of atorvstatin C_{max}: 0.82 Atorvastatin 10 mg QD, 4 days had no effect on the PK of Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days (ratio of atorvastatin AUC: 0.99 and ratio of atorvastatin C_{max}: 0.94)	atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore caution should be applied and the lowest dose necessary should be used
Rifampin	<u>Co-administration</u>: Ratios of AUC and C_{max} are 1.12 and 2.9, respectively, for co-administered atorvastatin 40 mg single dose and 7 day Rifampin 600 mg daily vs. atorvastatin 40 mg single dose alone. <u>Separate administration</u> Ratio of atorvastatin AUC: 0.20 and ratio of atorvastatin C_{max}: 0.60 with atorvastatin 40 mg single dose and Rifampin 600 mg daily (doses separated)	Due to the dual interaction mechanism of rifampin (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co- administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Legend: HC = hypercholesterolemia; TG = Triglycerides; PK = pharmacokinetics; BP = Blood Pressure; HR = Heart Rate; AUC = Area under the curve
Ratio of AUC and C_{max} represent ratio treatments (co-administered drug plus atorvastatin versus atorvastatin alone).

9.5 Drug-Food Interactions

Bmd-ATORVASTATIN may be taken with or without food. Do not take with grapefruit juice. Coadministration of grapefruit juice has the potential to increase plasma concentrations of HMG CoA reductase inhibitors including atorvastatin calcium. The equivalent of 1.2 litres per day resulted in an increase in AUC (ratio of AUC up to 2.5) and Cmax (ratio of Cmax up to 1.71) of atorvastatin.

For 240 ml of grapefruit juice, the ratio of AUC was 1.37 and the ratio of Cmax was 1.16 for atorvastatin 40 mg.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Bmd-ATORVASTATIN may elevate serum transaminase and creatine kinase levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with Bmd-ATORVASTATIN, cardiac and noncardiac fractions of these enzymes should be determined.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Atorvastatin calcium is a synthetic lipid-lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Atorvastatin calcium lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake and catabolism of Low Density Lipoprotein (LDL).

Atorvastatin calcium reduces LDL-Cholesterol (LDL-C) and the number of LDL particles. Atorvastatin calcium also reduces Very Low Density Lipoprotein-Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-

Cholesterol (HDL-C). Elevated serum cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Low serum concentration of HDL-C is also an independent risk factor. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

Epidemiologic, clinical and experimental studies have established that high LDL-C, low HDL-C and high plasma TG promote human atherosclerosis and are risk factors for developing cardiovascular disease. Some studies have also shown that the total (TC):HDL-C ratio (TC:HDL-C) is the best predictor of coronary artery disease. In contrast, increased levels of HDL-C are associated with decreased cardiovascular risk. Drug therapies that reduce levels of LDL-C or decrease TG while simultaneously increasing HDL-C have demonstrated reductions in rates of cardiovascular mortality and morbidity.

10.2 Pharmacodynamics

The lowering of total cholesterol, LDL-C and ApoB have been shown to reduce the risk of cardiovascular events and mortality.

Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA reductase. In both subjects and in patients with homozygous and heterozygous familial hypercholesterolemia, nonfamilial forms of hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia, and dysbetalipoproteinemia, atorvastatin calcium has been shown to reduce levels of total cholesterol (total-C), LDL-C, apo B and total TG, and raises HDL-C levels.

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. Like LDL, cholesterol-enriched 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 (metabolic syndrome). Clinical studies have also shown that serum triglycerides can be an independent risk factor for CAD. CAD risk is especially increased if the hypertriglyceridemia is due to increased intermediate density lipoproteins (IDL) or associated with decreased HDL or increased LDL-C. In addition, high TG levels are associated with an increased risk of pancreatitis. Although epidemiological and preliminary clinical evidence link low HDL-C levels and high triglyceride levels with coronary artery disease and atherosclerosis, the independent effect of raising HDL or lowering TG on the risk of coronary and cerebrovascular morbidity and mortality has not been demonstrated in prospective, well-controlled outcome studies. 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. Regardless of the intervention used (low-fat/low-cholesterol diet, partial ileal bypass surgery or pharmacologic therapy), effective treatment of hypercholesterolemia/ dyslipidemia has consistently been shown to reduce the risk of CAD.

Atorvastatin calcium reduces LDL-C and the number of LDL particles, lowers Very Low Density Lipoprotein-Cholesterol (VLDL-C) and serum triglyceride, reduces the number of apo B containing particles, and also increases HDL-C. Atorvastatin calcium is effective in reducing LDL-C in patients with homozygous familial hypercholesterolemia, a condition that rarely responds to any other lipid- lowering medication. In addition to the above effects, atorvastatin calcium reduces IDL-C and apolipoprotein E (apo E) in patients with dysbetalipoproteinemia (Type III).

In patients with type II hyperlipidemia, atorvastatin improved endothelial dysfunction. Atorvastatin significantly improved flow-mediated endothelium-dependent dilatation induced by reactive hyperemia, as assessed by brachial ultrasound ($p<0.01$).

10.3 Pharmacokinetics

Absorption
Atorvastatin is rapidly absorbed after oral administration; maximal plasma concentrations occur within 1 to 2 hours. Extent of absorption and plasma atorvastatin concentrations increases in proportion to atorvastatin dose. Atorvastatin tablets are 95-99% bioavailable compared to solutions. The absolute bioavailability (parent drug) of atorvastatin is approximately 12% 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 first-pass metabolism in the liver. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, as assessed by Cmax and AUC respectively, LDL-C reduction and HDL-C elevation are similar when atorvastatin is given with and without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following drug administration in the evening compared with morning dosing. However, LDL-C reduction and HDL-C elevation are the same regardless of the time 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 para-hydroxylated derivatives by cytochrome P-450 3A4 (CYP 3A4) and to various beta-oxidation products. In vitro, inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation. Atorvastatin and its metabolites are eliminated by biliary excretion.

Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of

OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters MDR1 and BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

Elimination
Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life for inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of longer-lived active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations and Conditions

Pediatrics: Assessment of pharmacokinetic parameters such as Cmax, AUC and bioavailability of atorvastatin calcium in pediatric patients (>10-<17 years old, postmenarche) was not performed during the 6-month, placebo-controlled trial referred to earlier (see 14 Clinical Studies - Heterozygous Familial Hypercholesterolemia in Pediatric Patients and 7.1.3 Pediatric).

In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage ≥2 (N=24) pediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolemia and baseline LDL-C ≥4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film-coated atorvastatin tablets once daily, respectively. Population PK analyses indicated that variability in atorvastatin PK was primarily affected by body weight. Allometric scaling by body weight was used to describe the changes in the apparent oral clearance of atorvastatin in the pediatric subjects. Apparent oral clearance (CL/F) of atorvastatin in pediatric subjects with the reference covariates Tanner Stage ≥ 2 and body weight of 70Kg appeared similar to adults however the value of CL/F is expected to be relatively lower for a lower weight individual. Consistent decreases in LDL-C and TC (at week 8, 40% and 30% from baseline, respectively) were observed over the range of atorvastatin and o-hydroxyatorvastatin simulated exposures.

Geriatrics: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age 65 years or older) compared with younger individuals. LDL-C reduction, however, is comparable to that seen in younger patient populations.

Sex: Plasma concentrations of atorvastatin in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men; however, there is no clinically significant difference in LDL-C reduction between men and women.

Ethnic Origin: Plasma concentrations of atorvastatin are similar in black and white subjects.

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

disease (Childs-Pugh B).

Renal Insufficiency: Plasma concentrations and LDL-C lowering efficacy of atorvastatin calcium are similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of Bmd-ATORVASTATIN should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see 7 WARNINGS AND PRECAUTIONS, Muscle Effects; 9 DRUG INTERACTIONS; 4.2 Recommended Dose and Dosage Adjustment).

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature 15 to 30°C. Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

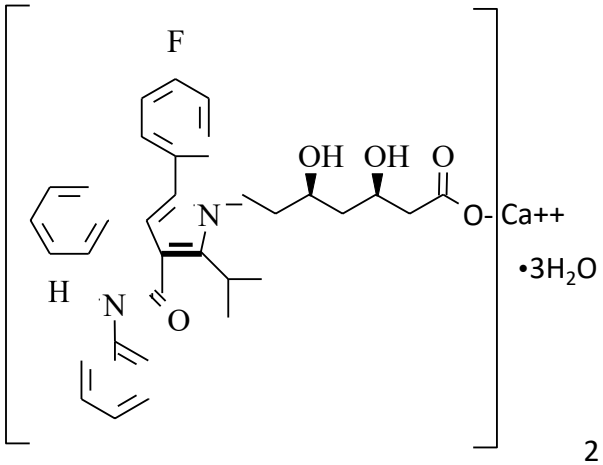
Proper name: Atorvastatin calcium

Chemical name: [R-(R*,R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)- 3- phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Molecular Formula: $(C_{33}H_{34}FN_2O_5)_2Ca \bullet 3H_2O$

Molecular mass: 1209.42 g/ mol

Structural formula:



Physicochemical properties: Atorvastatin calcium is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Primary Hypercholesterolemia

Atorvastatin calcium has been shown to significantly improve lipid profiles in a variety of dyslipidemic conditions. Atorvastatin calcium has been shown to be highly effective in reducing total and LDL-cholesterol, and triglycerides and apolipoprotein B in patients with primary hypercholesterolemia.

Combined Hyperlipidemia

Atorvastatin calcium has been shown to significantly improve lipid profiles in a variety of dyslipidemic conditions. Atorvastatin calcium has been shown to be highly effective in reducing total and LDL-cholesterol, and triglycerides and apolipoprotein B in patients with mixed hyperlipidemia.

Dysbetalipoproteinemia

Atorvastatin calcium has been shown to significantly improve lipid profiles in a variety of dyslipidemic conditions. Atorvastatin calcium has been shown to be highly effective in reducing total and LDL- cholesterol, and triglycerides and apolipoprotein B in patients with familial combined hyperlipidemia.

Hypertriglyceridemia

Atorvastatin calcium has been shown to significantly improve lipid profiles in a variety of dyslipidemic conditions. Atorvastatin calcium has been shown to be highly effective in reducing total and LDL-cholesterol, and triglycerides and apolipoprotein B in patients with hypertriglyceridemia (Type IV). Atorvastatin calcium (10 to 80 mg daily) reduced TG (25 - 56%) and LDL-C levels (23 - 40%). Atorvastatin calcium has not been studied in conditions where the major abnormality is elevation of chylomicrons (TG levels > 11 mmol/L), i.e. types I and V.

Familial Hypercholesterolemia

Atorvastatin calcium has been shown to significantly improve lipid profiles in a variety of dyslipidemic conditions. Atorvastatin calcium has been shown to be highly effective in reducing total and LDL-cholesterol, and triglycerides and apolipoprotein B in patients with familial hypercholesterolemia.

Prevention of Cardiovascular Disease

Atorvastatin calcium significantly reduced the rate of coronary events [either fatal coronary heart disease or nonfatal MI. The risk reduction was consistent regardless of age, smoking status, obesity or presence of diabetes or renal dysfunction. The effect of Atorvastatin calcium was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.In 2 multicenter, placebo-controlled, double-blind dose-response studies in patients with mild to moderate hypercholesterolemia (Fredrickson types IIa and IIb), atorvastatin calcium given as a single daily dose over 6 weeks reduced total-C, LDL-C, apo B, and TG; HDL-C was increased (Table 3). A therapeutic response was evident within 2 weeks, and the maximum response was usually achieved within 2-4 weeks.

Table 3. Dose-Response in Patients with Mild to Moderate Hypercholesterolemia (Fredrickson Types IIa and IIb)
(Mean Percent Change from Baseline)[a]

Atorvastatin calcium Dose (mg/day)	N	Total-C	LDL-C	Apo B	TG	HDL-C
Placebo	21	+4	+4	+3	+10	-3
10	22	-29	-39	-32	-19	+6
20	20	-33	-43	-35	-26	+9
40	21	-37	-50	-42	-29	+6
80	23	-45	-60	-50	-37	+5

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

In a pooled data set from 24 controlled clinical trials in patients with primary hypercholesterolemia (type IIa) and mixed (combined) dyslipidemia (type IIb), atorvastatin calcium increased HDL C by 5% to 8% from baseline at each dose tested (10, 20, 40, and 80 mg QD) (Table 4). In patients with HDL C < 0.9 mmol/L (a condition often observed in persons with the metabolic syndrome) [see 1 INDICATIONS], atorvastatin calcium raised HDL-C 7% to 14%. These changes were independent of the dose administered. Atorvastatin calcium also decreased total-C/HDL-C, LDL-C/HDL-C, and non-HDL-C/HDL-C ratios from baseline in a dose dependent manner (Table 4). Atorvastatin calcium (10, 20, 40 and 80 mg QD) increased HDL-C levels from baseline for both men and women.

Table 4. Adjusted[a] Mean Percent Changes from Baseline in HDL-C, Total-C/HDL-C, LDL-C/HDL- C, Non-HDL-C/HDL-C, and HDL-C ≤ 0.9 mmol/L for Patients[b] With Mild to Moderate Hypercholesterolemia (Fredrickson Types IIa and IIb)

Atorvastatin calcium Dose (mg/day)	N (all patients)	HDL-C	Total-C/ HDL-C	LDL-C/ HDL-C	Non HDL-C/ HDL-C	HDL-C (baseline ≤ 0.9 mmol/L) (N)
Placebo	250	+0.2‡	+2.8‡	+3.8‡	+3.5‡	+6.2* (17)
10	1871	+6.4	-29.3†	-37.0†	-35.5†	+13.8 (248)
20	147	+7.8	-36.0†	-44.1†	-43.0†	+8.3 (20)
40	115	+7.1	-38.9†	-49.6†	-47.1†	+8.6 (8)
80	318	+5.0	-43.5†	-55.3†	-52.4†	+7.1 (58)

[a] Least squares means from ANCOVA model with study, treatment and baseline
[b] Data pooled from 24 controlled studies
†significant linear dose trend
‡ significantly different from atorvastatin calcium 10 mg ($p<0.01$)
* significantly different from atorvastatin calcium 10 mg ($p<0.05$)

In another multicenter, placebo controlled, double blind trial in patients with hypertriglyceridemia, atorvastatin calcium lowered triglycerides in a dose related manner, without causing a redistribution of triglycerides into various lipoprotein fractions (Table 5).

Table 5. Efficacy in Patients with Hypertriglyceridemia (Mean Percent Change from Baseline)

Atorvastatin calcium Dose (mg/day)	N	VLDL-C	Total-C	VLDL-TG	LDL-C	TG	HDL-C	Apo B
Placebo	12	-2.0	+0.3	-6.6	+1.4	-5.3	+2.4	+2.7
5	11	-34.0*	-19.9*	-28.7	-12.7*	-27.3	+7.1	-15.4*
20	12	-46.0*	-33.1*	-35.7*	-31.1*	-33.7*	+10.6	-32.7*
80	11	-54-2*	-41.3*	-43.6*	-36.1*	-42.4*	+11.8*	-38.7*

* Significantly different from placebo, $p<0.05$

Comparison of pooled data by Fredrickson types shows similar reductions for Type IIa and IIb patients in total-C, LDL-C and apo B; however, Type IIb patients, and Types IV patients experience a greater percent decrease in VLDL-C and TG levels (Table 6).

Table 6. Efficacy in Patients by Fredrickson Type[a] (Mean Percent Change from Baseline)

Lipid Parameter	Atorvastatin calcium 10 mg/day		
	Type IIa (N = 935)	Type IIb (N = 550)	Type IV (N = 29)
LDL-C	-36	-35	-26
Apo B	-28	-28	-25
Total-Cl	-27	-27	-25
TG	-14	-24	-29
VLDL-C	-15	-28	-41
HDL-C	+6	+10	+13
Apo B/HDL-C	-31	-34	-33
Non-HDL-C/HDL-C	-37	-38	-38

[a] Pooled dataset

In a pilot study of 8 patients with homozygous familial hypercholesterolemia, the mean decrease in LDL-C with 80 mg/day atorvastatin calcium was 30% for patients not on plasmapheresis, and 31% for patients who continued plasmapheresis. A LDL-C lowering of 35% was observed in receptor defective patients (n=6) and of 19% in receptor negative patients (n=2). All patients also experienced decreases in total-C, apo B, LDL-C/HDL-C and non-HDL-C/HDL-C ratios (Table 7).

Table 7. Patients with Homozygous FH (Mean Percent Change from Baseline After 8 Weeks)

Lipid Parameter	Atorvastatin calcium 80 mg/day		
	All Patients (N=8)	Patients Not on Plasmapheresis (N=3)	Patients on Plasmapheresis (N=5)
Total-C	-29	-29	-29
LDL-C	-31	-30	-31
Apo B	-28	-17	-34
TG	-20	-41	-8
LDL-C/HDL-C Ratio	-23	-19	-25
Non HDL-C/HDL-C Ratio	-22	-19	-24

In an open label study, 69 patients (2-61 years of age) with homozygous familial hypercholesterolemia, and 92 patients with severe hypercholesterolemia who had ≤15% response to maximum combination therapy, received atorvastatin calcium 10 to 80 mg/day. Most patients began atorvastatin calcium treatment with 40 mg/day, but severely debilitated and very young patients began treatment with 10 mg/day. Atorvastatin calcium was titrated at 4-week intervals to ≤80 mg/day. The mean reduction in LDL-C for 69 patients diagnosed with homozygous familial hypercholesterolemia was 22%. Table 8 shows the mean percent change in lipid parameters. In 2 receptor-negative patients mean LDL-C reduction was 19%. Six patients had less than a 10% response to treatment.

Table 8. Patients with Homozygous FH or Severe Nonresponsive Hypercholesterolemia (Mean Percent Change from Baseline after 8 Weeks)

Lipid Parameter	Atorvastatin calcium 80 mg/day	
	Homozygous FH (N=69[a])	Severe Unresponsive Hypercholesterolemia (N=92)
Total-C	-21%	-34%
LDL-C	-22%	-39%
TG	-9%	-29%
HDL-C	+3%	+6%

[a] Data available from 68 patients

In a 1-year study in patients with heterozygous familial hypercholesterolemia, atorvastatin calcium monotherapy (80 mg/day) was compared with combination therapy of colestipol (10 g BID) plus atorvastatin calcium (40 mg/day. The 2 treatments produced similar effects on total-C, LDL-C, TG, VLDL-C, apo B and HDL-C; however, atorvastatin calcium monotherapy was more effective than atorvastatin calcium plus colestipol in decreasing TG levels (Table 9).

Table 9. Efficacy in Patients with Heterozygous Familial Hypercholesterolemia (Mean Percent Change from Baseline after 52 Weeks)

Lipid Parameter	Atorvastatin calcium 80 mg/day (N=189)	Atorvastatin calcium 40 mg/day Plus Colestipol 10 g BID (N=124)
TOTAL-C	-44	-42
LDL-C	-53	-53
VLDL-C	-33	-17
HDL-C	+7	+9
TG	-33[a]	-17
non-HDL/HDL-C Ratio	-53	-52
Apo B	-46	-45

[a] Significantly different from Atorvastatin calcium plus colestipol ($p < 0.05$), ANCOVA.

A comparison of results in patients with heterozygous familial and non-familial hypercholesterolemia shows similar magnitudes of reductions in LDL-C, apo B and non-HDL- C/HDL-C ratio, in both patient populations (Table 10).

Table 10. Efficacy in Heterozygous FH and Non FH Patients† (Mean Percent Change from baseline)

Lipid Parameter	Phenotype	Atorvastatin calcium	
		10/mg/day	80 mg/day
LDL-C	Heterozygous FH Non FH	-36 (N=140) -36 (N=1215)	-53 (N=154) -52 (N=166)
Apo B	Heterozygous FH Non FH	-27 (N=134) -28 (N=1149)	-46 (N=153) -46 (N=144)
Non HDL-C/HDL-C Ratio	Heterozygous FH Non FH	-37 (N=140) -37 (N=1215)	-53 (N=132) -54 (N=166)

†Data from several studies

Comparison of results in patients with and without familial combined hyperlipidemia (FCH) demonstrated that atorvastatin calcium lowered LDL-C, apo B, total-C, VLDL-C, TG, and the non- HDL-C/HDL-C ratio to a similar extent in both patient populations (Table 11).

Table 11. Efficacy in Patients With and Without FCH†,[a] (Mean Percent Change from Baseline)

Lipid Parameter	Atorvastatin calcium 10 mg/day	
	FCH (N = 78-84)	Non-FCH (N = 1084-1224)
Total-C	-26%	-27%
LDL-C	-34%	-36%
TG	-21%	-17%
HDL-C	+8%	+7%
Apo B	-26%	-28%
VLDL-C	-25%	-18%
Non HDL-C/HDL-C Ratio	-36%	-37%
LDL-C/Apo B ratio	-9%	-11%

†Data from several studies

[a] The following criteria were used to define patients with FCH: first degree relative with lipid disorder, TG >250 mg/dL (>2.8 mmol/L), VLDL >45 mg/dL (>1.16 mmol/L), HDL <35 mg/dL (<0.9 mmol/L) (men) or <45 mg/dL (<1.16 mmol/L) (women).

In an open-label, randomised, cross-over study in patients with dysbetalipoproteinemia (Type III), atorvastatin calcium 80 mg/day resulted in a significantly greater reduction in serum lipids than either atorvastatin calcium 10 mg/day or gemfibrozil 1200 mg/day (Table 12).

Table 12. Efficacy in Patients with Type III Hyperlipoproteinemia (Familial Dysbetalipoproteinemia) Mean Percent Change from Baseline

Lipid parameter	Atorvastatin calcium 10 mg/day N = 15	Atorvastatin calcium 80 mg/day N = 16	Gemfibrozil 1200 mg/day N = 16
Total-C	-40	-57[a]	-34
LDL-C	+20[a]	-6[a]	+86
TG	-40[a]	-56	-52
VLDL-C	-32	-59[a]	-35
IDL-C	-28[a]	-50[a]	-13
IDL-C + VLDL-C	-34	-58[a]	-33
HDL-C	+3	+13	+11
Apo B (total)	-47	-66[a]	-53
Apo-C III	-16	-31	-12
Apo-E	-27	-41[a]	-24

[a]significantly different from gemfibrozil, $p<0.05$ (ANOVA)

In a 6-month, double-blind, study in patients with hyperlipidemia and non-insulin dependent diabetes mellitus (NIDDM), Atorvastatin calcium (10 or 20 mg/day) lowered total cholesterol by 27%, LDL-C by 34%, apo B by 30%, TG by 24%, and increased HDL-C by 12% (Table 13)

Table 13. Efficacy in Patients with NIDDM (Mean Percent Change From Baseline)

Lipid Parameter	Atorvastatin calcium 10 or 20 mg/day N=84
Total-C	-27
LDL-C	-34
VLDL-C	-35
TG	-24
VLDL-TG	-26
HDL-C	+12
Apo B	-30

In three, double-blind, multicenter studies in patients with mild to moderate hypercholesterolemia, the number of patients meeting NCEP target LDL-C levels on atorvastatin calcium was assessed over a 1-year period. After 16 weeks, between 46-74% of patients receiving 10 mg/day atorvastatin calcium reached target LDL-C levels. The efficacy of atorvastatin calcium (10 or 20 mg/day) was maintained over 52 weeks, with between 50-78% of patients achieving their LDL-C target levels.

The effect of atorvastatin calcium was evaluated in comparative clinical trials with lovastatin, simvastatin and pravastatin.

In a 1-year study in postmenopausal women with primary hyperlipidemia, atorvastatin calcium monotherapy (10 mg/day) was compared with estradiol monotherapy (1 mg/day) and with combination therapy of atorvastatin calcium 10 mg/day plus estradiol 1 mg/day (Table 14). Atorvastatin calcium monotherapy (10 mg/day) was significantly more effective in lowering total- C, LDL-C, VLDL- C, TG, apo B and non-HDL-C/HDL-C ratio than estradiol monotherapy (1 mg/day). For combination therapy (atorvastatin calcium plus estradiol), reductions in total-C, LDL-C, VLDL-C, Lp(a), apo B and non HDL-C/HDL-C ratio were similar compared with atorvastatin calcium monotherapy. However, HDL-C levels were significantly higher for combination therapy compared with atorvastatin calcium monotherapy. TG levels were lower with atorvastatin calcium monotherapy compared with combination therapy. Adverse reactions were similar in type and incidence following combination therapy (atorvastatin calcium plus estradiol) compared with estradiol monotherapy.

Table 14. Efficacy in Post-menopausal Women (Mean Percent Change from Baseline After 52 Weeks)

Lipid Parameter	Atorvastatin calcium 10 mg/day (N=38)	Estradiol 1 mg/day (N=16)	Atorvastatin calcium 10 mg/day Plus Estradiol (1mg/day) (N=21)
TOTAL-C	-29	-1[a]	-27
LDL-C	-40	-5[a]	-42
VLDL-C	-32	+13[a]	-20
HDL-C	+8	+11	+20[a]
TG	-27	+5[a]	-13[a]
non-HDL/HDL-C Ratio	-43	-12[a]	-48
Apo B	-34	-3[a]	-34

[a]Significantly different from atorvastatin calcium monotherapy (p <0.05), ANCOVA.

In a comparative study with niacin in patients with hypercholesterolemia and mixed hyperlipidemia (Fredrickson types IIa and IIb) and hypertriglyceridemia (Frederickson Type IV), atorvastatin calcium (10 mg/day) had greater cholesterol-lowering efficacy (greater decreases in LDL-C, apo B, LDL-apo B), while niacin (3 g/day) had greater triglyceride- lowering efficacy (greater decreases in TG, VLDL-TG, HDL-TG, VLDL-apo B). Atorvastatin calcium was better tolerated by patients compared with niacin (Table 15).

Table 15. Atorvastatin calcium versus Niacin (Mean Percent Change from Baseline)

Parameter	Fredrickson Types IIa and IIb		Fredrickson Type IV	
	Atorvastatin 10 mg (N = 43)	Niacin 3 g/day (N = 39)	Atorvastatin 10 mg (N = 11)	Niacin 3 g/day (N = 12)
LDL-C	-33*	-8	-15*	+14
Apo B	-30*	-16	-23*	-3
Total-C	-28*	-11	-26*	0
TG	-16	-29*	-36	-29
HDL-C	+4	+27*	+4	+25
VLDL-C	-28	-39	-43	-36
Non-HDL-C/HDL-C	-34	-32	-34	-19
Apo B/HDL	-32	-31	-28	-18

* Significant difference between treatments, ANCOVA p <0.05.

In a comparative study with fenofibrate in patients with combined hyperlipidemia or hypertriglyceridemia, atorvastatin calcium (20 mg/day) was more effective in lowering LDL-C, apo B and total cholesterol levels compared to fenofibrate (100 mg TID). Treatment with atorvastatin calcium also resulted in clinically significant reductions in TG and VLDL-C, and increases in HDL-C levels, although not to the same extent as was

seen with fenofibrate. Atorvastatin calcium therapy resulted in a better reduction of the non-HDL-C/HDL-C ratio, which may be a good indicator of overall lipid- regulating benefit. Atorvastatin calcium was also better tolerated compared with fenofibrate (Table 16).

Table 16. Atorvastatin calcium versus Fenofibrate Mean Percent Change From Baseline After 24 Weeks

Parameter	Fredrickson Types IIa and IIb		Fredrickson Type IV	
	Atorvastatin 20 mg (N = 36)	Fenofibrate 300 mg (N = 33)	Atorvastatin 20 mg (N = 9)	Fenofibrate 300 mg (N = 8)
LDL-C	-39*	-7	-28*	+27
Apo B	-36*	-17	-27	-9
Total-C	-34*	-14	-26	-13
TG	-27	-39	-34	-57*
HDL-C	+9	+22*	+8	+30*
VLDL-C	-39	-50	-36	-73*
Non-HDL-C/HDL-C	-44*	-32	-36	-35

Significant difference between treatments, ANCOVA p <0.05.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients:

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia were randomized to atorvastatin calcium (n=140) or placebo (n=47) for 26 weeks after that, all received atorvastatin calcium for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level > 4.9 mmol/L (190 mg/dL) or 2) a baseline > 4.1 mmol/L (160 mg/dL) and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative.

Table 17. Effect of Atorvastatin calcium on LDL-C, TC and TG in a controlled trial of 6 months duration in adolescent boys and postmenarchal girls 10-17 years of age (N=187) with heterozygous familial hypercholesterolemia at a dose of 10 and 20 mg.

N	Age	Dose	% Change		
			LDL-C	TC	TG
22	10-13	10 mg	-37.85	-29.3	-9.2
40	14-17	10 mg	-38.2	-29.4	-6.9
33	10-13	20 mg	-42.1	-34.0	-13.3
43	14-17	20 mg	-40.3	-33.0	-18.3

The mean baseline LDL-C value was 5.7 mmol/L (218.6 mg/dL) (range: 3.6-10.0 mmol/L [138.5-385.0 mg/dL]) in the atorvastatin calcium group compared to 5.9 mmol/L (230.0 mg/dL) (range: 4.1-8.4 mmol/L [160.0-324.5

mg/dL]) in placebo group. The dosage of atorvastatin calcium (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was >3.4 mmol/L (130 mg/dL). The number of atorvastatin calcium - treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 78 (55.7%).

Atorvastatin calcium significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see Table 17, and Table 18).

Table 18. Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia
(Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

Dosage	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12	-34

The mean achieved LDL-C value was 3.8 mmol/L (130.7 mg/dL) (range: 1.8-6.3 mmol/L [70.0-242.0 mg/dL]) in the atorvastatin calcium group compared to 5.9 mmol/L (228.5 mg/dL) (range: 3.9-10.0 mmol/L [152.0-385.0 mg/dL]) in the placebo group during the 26 week double-blind phase. The safety and tolerability profile of atorvastatin calcium 10 to 20 mg daily was similar to that of placebo.

In this controlled study, there was no effect on growth or sexual maturation in boys and in girls, as measured by Tanner staging during 26 weeks. The proportion of subjects who had an increase in Tanner stage between baseline and week 26 of the double-blind phase was similar for the atorvastatin and placebo groups (28% and 31%, respectively; P = 0.7). No specific documentation of menstrual cycle was recorded. Atorvastatin calcium had no effect on plasma levels of LH, FSH, cortisol, testosterone and dehydroepiandrosterone. Effect of treatment on cognitive function was not captured during the course of this study.

Atorvastatin calcium has not been studied in controlled clinical trials involving pre pubertal patients or patients younger than 10 years of age. The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children.

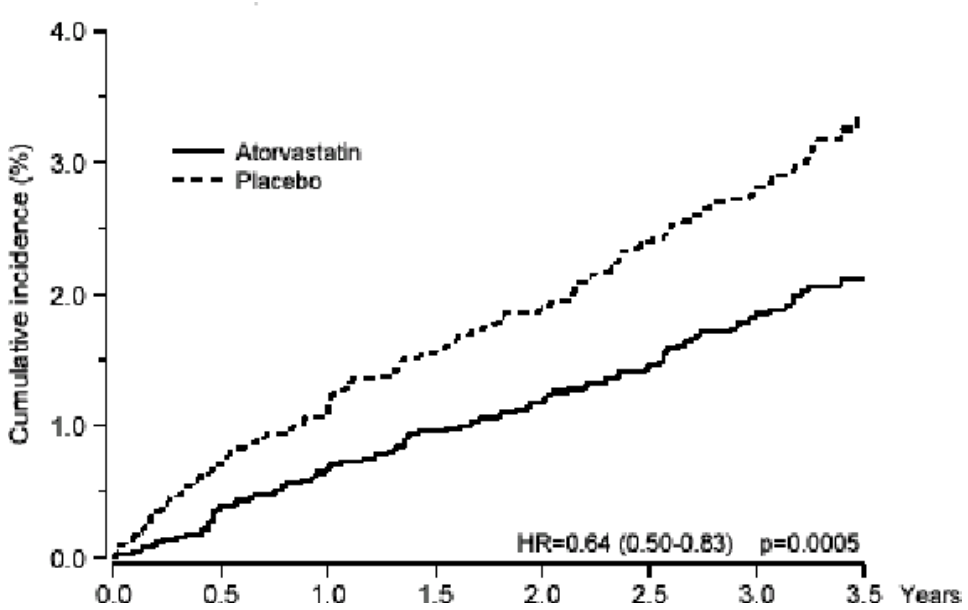
Prevention of Cardiovascular Disease
In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin calcium on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels <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 calcium 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 calcium on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin calcium significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs 40 events in the atorvastatin calcium group) or nonfatal MI (108 events in the placebo group vs 60 events in the atorvastatin calcium group)] with an absolute risk reduction of 1.1% and a relative risk reduction of 36% (based on incidences of 1.9% for atorvastatin calcium vs 3.0% for placebo), p=0.0005 (see Figure 1)]. This risk reduction yields a Number Needed to Treat of 311 patients per year. The risk reduction was consistent regardless of age, smoking status, obesity or presence of renal dysfunction. The effect of atorvastatin calcium was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 1. Effect of Atorvastatin calcium 10 mg/day on Cumulative Incidence of Nonfatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



In the Collaborative AtoRvastatin Diabetes Study (CARDS), the effect of atorvastatin calcium on coronary heart disease (CHD) and non-CHD endpoints was assessed in 2838 men (68%) and women (32%), ages 40-75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL < 4.14 mmol/L and TG < 6.78 mmol/L. In addition to type 2 diabetes, subjects had one or more of the following CHD risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), microalbuminuria (9%) or macroalbuminuria (3%). In this multicenter, placebo-controlled, double blind clinical trial of primary prevention of fatal and nonfatal cardiovascular and cerebrovascular disease in subjects with type 2 diabetes and 1 other CHD risk factor, patients were randomly allocated to either atorvastatin calcium 10 mg daily (1429) or placebo (1411) in a 1:1 ratio.

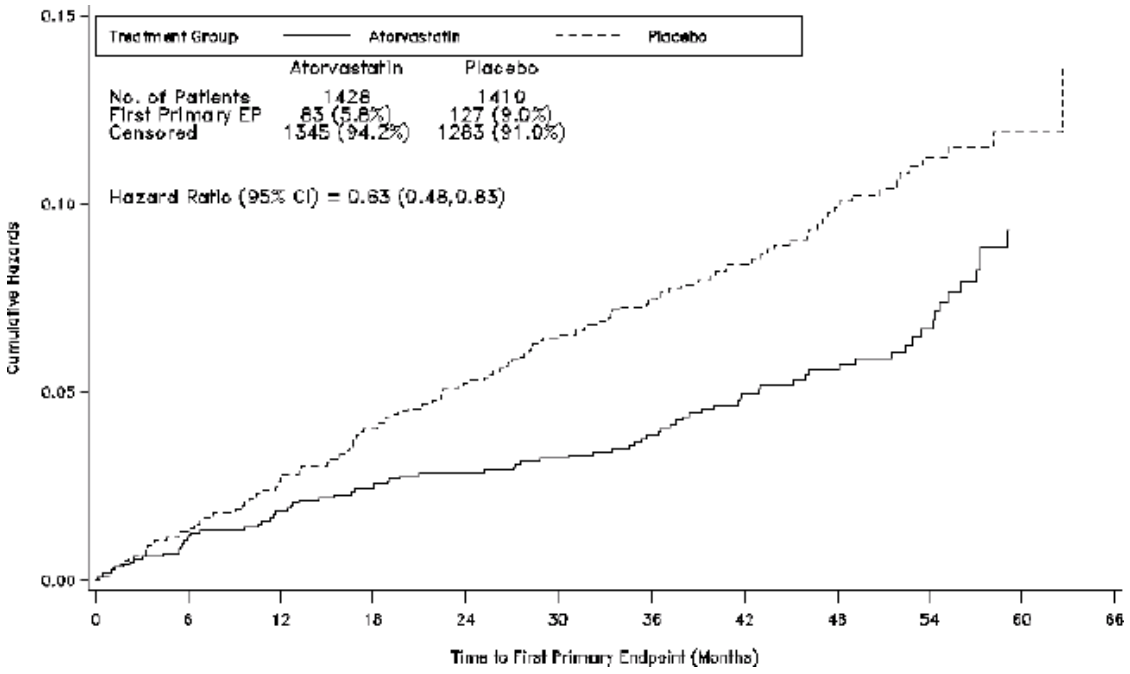
Patients were followed for a median duration of 3.9 years. Due to significant treatment benefits (p<0.0005, one-sided, in favor of atorvastatin calcium) seen early in the study, the study was stopped by the CARDS Steering Committee two years earlier than anticipated.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA1c 7.7%; median LDL-C 3.10 mmol/L; median TC 5.35 mmol/L; median TG 1.70 mmol/L; median HDL-C 1.34 mmol/L.

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

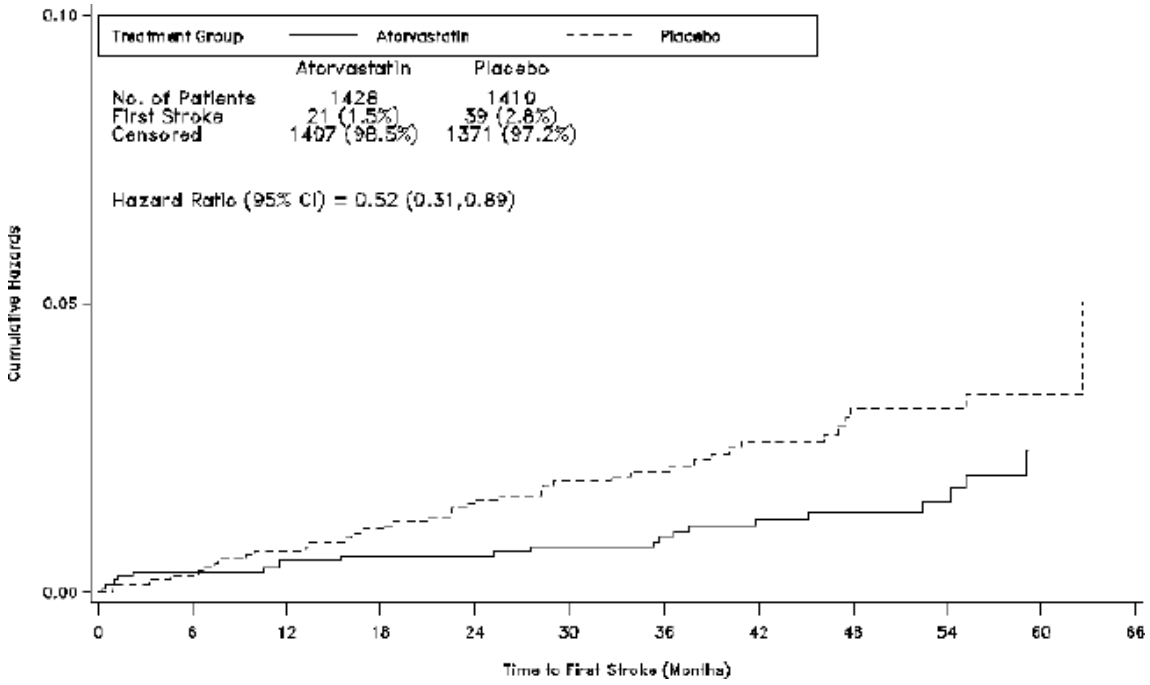
Treatment with atorvastatin calcium was associated with a statistically significant 37% relative risk reduction (RRR), or 3.2% absolute risk reduction (ARR) in the rate of major cardiovascular events. Efficacy analysis showed that 83 (5.8%) of atorvastatin calcium treated patients and 127 (9.0%) of placebo treated patients experienced their first primary clinical endpoint. Comparison of the time to the first primary endpoint in the two groups yielded the hazard ratio (HR) of 0.63 with 95% CI 0.48, 0.83 and p=0.001 in favour of atorvastatin calcium. The number needed to treat (NNT) for one year to prevent one case experiencing the primary clinical endpoint, based on the ARR 3.2% yields 125 patients. The effect of atorvastatin calcium was seen regardless of age, sex, or baseline lipid levels.

Figure 2. Time to Occurrence of First Primary Endpoint



When cardiovascular events were evaluated separately, atorvastatin calcium significantly reduced the relative risk of stroke by 48% (ARR of 1.3%). There were 21 cases of stroke (1.5%) in the atorvastatin calcium group vs 39 cases (2.8%) in the placebo group, HR 0.52, 95% CI 0.31, 0.89, p=0.016. To prevent one case of stroke 307 patients are needed to be treated for one year.

Figure 3. Time to Occurrence of First Stroke



Relative risk of myocardial infarction was reduced by 42%, or ARR by 1.8%, with 38 cases (2.7%) in the atorvastatin calcium group vs 64 cases (4.5%) in the placebo group, HR 0.58, 95% CI 0.39, 0.86, p = 0.007. To prevent one case of myocardial infarction 222 patients have to be treated for one year.

No significant risk reduction was observed in the time to first CABG, PTCA or other coronary revascularization procedure, time to first unstable angina or time to acute CHD death. No significant reduction was observed in time to death due to all causes (61 deaths in the atorvastatin calcium group vs 82 deaths in the placebo group, HR 0.73, 95% CI 0.52, 1.01, p=0.059), cardiovascular causes, or non-cardiovascular causes.

14.3 Comparative Bioavailability Studies

A double blind, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, oral bioequivalence study was conducted to determine the bioavailability of Atorvastatin administered as 1 x 80 mg Atorvastatin Calcium Tablets (Biomed Pharma) and Lipitor® (Atorvastatin Calcium) 1 x 80 mg tablets (Pfizer Canada Inc.) in 68 healthy, adult, human male subjects under fasting conditions.

Atorvastatin (1×80 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	258.707 291.833 (57.0)	267.463 300.511 (59.6)	96.7	91.7 - 102.1
AUC_I (ng.h/mL)	262.296 295.396 (56.6)	270.711 303.852 (59.4)	96.9	91.9 - 102.2
C_{max} (ng/mL)	63.715 73.273 (59.3)	70.593 80.315 (53.8)	90.3	82.8 - 98.4
T_{max}§ (h)	0.667 (0.333 - 4.000)	0.667 (0.333 - 5.000)		
$T_{½}$ € (h)	9.053 (23.0)	9.041 (26.6)		

* Atorvastatin Calcium Tablets 80 mg– Manufactured by Biomed Pharma.

† Lipitor® (Atorvastatin Calcium) tablets 80 mg – Manufactured by: Pfizer Ireland Pharmaceuticals, Pfizer Canada Inc., were purchased in Canada

§ Expressed as the median (min - max)

€ Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

The acute toxicity of atorvastatin following single doses was evaluated in mice, rats and dogs by oral and intravenous routes, and the results are summarized below:

Table 19. Acute Oral and Intravenous Toxicity Studies with Atorvastatin

Species	Sex	Route	Dose Range (mg/kg)	Results
Mouse	Male/Female	Oral	200 - 5000	No Deaths
Mouse	Male/Female	IV	0.4 - 4	No Deaths
Rat	Male/Female	Oral	200 - 5000	No Deaths
Rat	Male/Female	IV	0.4 - 4	No Deaths
Dog	Male/Female	Oral	10 - 400	No Deaths
Dog	Male/Female	IV	0.4 - 4	No Deaths

The acute toxicity of atorvastatin in rodents and dogs is low. Oral median lethal doses in mice and rats are greater than 5000 mg/kg.

The target organs affected by atorvastatin in multiple dose toxicity studies in rats (2 weeks to 52 weeks), and dogs (2 weeks to 104 weeks) are summarized in the table below. The spectrum of effects observed is not unexpected in view of the magnitude of the dose levels used, potency of atorvastatin in inhibiting mevalonate synthesis and the essential role of HMG-CoA reductase in maintaining cellular homeostasis.

Table 20. Atorvastatin: Target Organs Affected in Animal Studies

Rat	Dog
Liver	Liver
Stomach (non-glandular)	Gallbladder
Skeletal Muscle	Skeletal Muscle
	Intestine
	Brain/Optic Nerve*

* Occurred after administration of high, intolerable doses (280 mg/kg)

The following table summarizes the significant adverse changes observed during long-term toxicology studies in rats (52 weeks) and dogs (104 weeks):

Table 21. Atorvastatin: Significant Adverse Changes in Chronic Studies

Species/Results	Minimal Toxic Dose (mg/kg/day)	No-Effect Dose (mg/kg/day)
RAT		
Hepatocellular atypia	70	5
Bile Duct hyperplasia[1]	125	70
Nonglandular stomach acanthosis	125	70
DOG		
Death[2]	120	40
Hepatocellular granulomata[3]	10	ND
Hepatocellular necrosis[3]	120	40
Gallbladder edema/hemorrhage[3]	120	40
Bile duct hyperplasia[3]	120	10
Intestinal ulcers and single cell necrosis[3]	120	40
Skeletal muscle (tongue) necrosis[2]	120	40

[1] Present only at Week 26; not observed at Week 52.

[2] Findings occurred in Week 7 or 9.

[3] Findings occurred at Week 52 or in moribund dogs, were less pronounced after a 12- week withdrawal period (Week 64), and were not observed after 104 weeks of dosing.

ND = Not determined

The results of the long-term toxicology studies with atorvastatin indicated that similar to other HMG-CoA reductase inhibitors, the liver is the primary target organ. This is expected since the liver is the primary site of the pharmacologic action of atorvastatin and it is subject to the greatest drug exposure following oral administration. In both the rat and dog studies, the hepatic changes diminished with time (i.e. effects were less pronounced at the end of the 52-week and 104-week studies) suggesting an adaptive response.

Brain hemorrhage, optic nerve degeneration, lenticular opacities and testicular degeneration were not seen in dogs treated for 104-weeks with atorvastatin up to 120 mg/kg/day

Carcinogenicity:

Atorvastatin was not carcinogenic in rats given 10, 30 or 100 mg/kg/day for 2 years. The 100 mg/kg dose is 63-fold higher than the maximum recommended human dose of 80 mg (1.6 mg/kg, based on a 50 kg human) and AUC (0-24 hr) values were 8- to 16-fold higher.

In a 2-year study in mice given 100, 200 or 400 mg/kg/day, incidences of hepatocellular adenoma in males and hepatocellular carcinoma in females were increased at 400 mg/kg. This dose is 250 times the maximum recommended human dose on a mg/kg basis and systemic exposure based on AUC (0-24 hr) was 6 to 11 times higher. There was no evidence of treatment-related increases in tumor incidences at the lower doses of 100 and 200 mg/kg/day (i.e. up to 125 times the maximum recommended human dose on a mg/kg basis and systemic exposures of 3 times higher based on AUC (0-24 hr).

Genotoxicity:
Atorvastatin did not demonstrate mutagenic or clastogenic potential in four in vitro tests with and without metabolic activation or in one in vivo assay. It was negative in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, and in the in vitro HGPRT forward mutation assay in Chinese hamster lung cells. Atorvastatin did not produce significant increases in chromosomal aberrations in the in vitro Chinese hamster lung cell assay and was negative in the in vivo mouse micronucleus test.

Reproductive and Developmental Toxicology:

No adverse effects on fertility or reproduction were observed in male rats given doses of atorvastatin up to 175/mg/kg/day or in female rats given doses up to 225 mg/kg/day. These doses are 100 to 140 times the maximum recommended human dose on a mg/kg basis. Atorvastatin did not cause any adverse effects on sperm or semen parameters, or in reproductive organ histopathology in dogs given doses of 10, 40 or 120 mg/kg for 2 years. Atorvastatin was not teratogenic in either rats or rabbits.

17 SUPPORTING PRODUCT MONOGRAPHS

1. [Pr] LIPITOR® (atorvastatin calcium) Tablets 10 mg, 20 mg, 40 mg and 80 mg, submission control 253694, Product Monograph, Upjohn Canada ULC. (November 10, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Bmd-ATORVASTATIN

Atorvastatin Calcium Tablets

Read this carefully before you start taking **Bmd-ATORVASTATIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Bmd-ATORVASTATIN**.

Serious Warnings and Precautions

- Bmd-ATORVASTATIN may cause muscle disorders, such as:
  - **Myalgia** (muscle pain)
  - **Rhabdomyolysis** (breakdown of damaged muscle)
  - **Immune-Mediated Necrotizing Myopathy (IMNM)** (a type of autoimmune disease that causes muscle cell death)

  They may not go away even after you stop taking Bmd-ATORVASTATIN.

- Tell your healthcare professional **right away** if you have any muscle pain, tenderness, soreness or weakness while taking Bmd-ATORVASTATIN.

What Bmd-ATORVASTATIN is used for?

Bmd-ATORVASTATIN is used along with changes in lifestyle, including diet, to lower the level of cholesterol and other fats (such as triglycerides) in the blood in:

- adults with high blood cholesterol
- boys and girls (who already started their period) who are 10 to less than 18 years of age with heterozygous familial hypercholesterolemia. This is a genetic condition where high blood cholesterol is inherited from one of the parents. These children have high blood cholesterol when dieting and have:
  - a family history of premature cardiovascular disease (heart and blood vessel problems); or
  - two or more other cardiovascular risk factors as determined by their healthcare professional.

Bmd-ATORVASTATIN is also used to lower the risk of heart attack in adults with:

- coronary heart disease. This is a heart condition that happens when the arteries of the heart become narrower and cannot deliver enough blood to the heart. This is due to a buildup of plaque (fatty deposits) inside the artery walls.

- high blood pressure who have no evidence of coronary heart disease, but have three or more risk factors as determined by their healthcare professional

Bmd-ATORVASTATIN is used to lower the risk of heart attack and stroke in adults with:

- type 2 diabetes and high blood pressure who have no evidence of coronary heart disease, but have other risk factors as determined by their healthcare professional.

Bmd-ATORVASTATIN is just part of the treatment the healthcare professional will plan with you to help keep you or your child healthy. Depending on your/your child's health and lifestyle, the healthcare professional may recommend:

- a change in diet to:
  - control your/your child's weight
  - reduce your/your child's intake of cholesterol and saturated fats
  - increase your/your child's intake of fiber
- exercise that is right for you or your child
- quitting smoking or avoiding smoky places
- giving up alcohol or drinking less

Follow the instructions of your/your child's healthcare professional carefully.

How does Bmd-ATORVASTATIN work?

Bmd-ATORVASTATIN belongs to a class of medicines known as "statins", more specifically called HMG-CoA reductase inhibitors. Statins block an enzyme called HMG-CoA reductase in your liver, which is involved in the production of cholesterol in your body. ACH-ATORVASTATIN is used along with changes to your lifestyle to help control the amount of cholesterol in your blood.

Bmd-ATORVASTATIN can help your body:

- Decrease LDL (bad) cholesterol, triglyceride levels and other fats in the blood
- Increase HDL (good) cholesterol
- Decrease the Total Cholesterol HDL-Cholesterol Ratio (TC-HDL-C Ratio). This ratio represents the balance between good and bad cholesterol.

This in turn also reduces the risk of heart attack and stroke in adults who:

- have multiple risk factors for developing cardiovascular problems
- have coronary heart disease

What are the ingredients in Bmd-ATORVASTATIN?

Medicinal ingredients: atorvastatin calcium.

Non-medicinal ingredients: calcium carbonate, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, polysorbate 80, magnesium stearate and opadry-YS-1-7040 white. The coating agent opadry-YS- 1-7040 white contains hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and talc.

Bmd-ATORVASTATIN comes in the following dosage forms:
Tablets: 10 mg, 20 mg, 40 mg and 80 mg.

Do not use Bmd-ATORVASTATIN if you/your child:

- are allergic to atorvastatin calcium or any other ingredients in Bmd-ATORVASTATIN or its packaging
- have active liver disease or unexplained increases in liver enzymes
- are pregnant or think you/they might be pregnant
- are breast-feeding
- are taking medicines used to treat hepatitis C, such as telaprevir, boceprevir, glecaprevir/pibrentasvir, elbasvir/grazoprevir, simeprevir, velpatasvir/sofosbuvir, ledipasvir/sofosbuvir.
- are taking cyclosporine, a medicine used to suppress your immune system

To help avoid side effects and ensure proper use, talk to your healthcare professional before you/your child take Bmd-ATORVASTATIN. Talk about any health conditions or problems you/your child may have, including if you/your child:

- have previously taken any cholesterol-lowering medicines in the past. This includes:
  - statins, such as atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin
  - fibrates such as gemfibrozil, fenofibrate and bezafibrate
  - niacin (nicotinic acid)
- have had a stroke or a mini stroke
- are currently taking any other medicines
- have kidney or liver problems
- are above 65 years of age
- regularly drink **three or more** alcoholic drinks daily
- have a family history of muscular disorders
- had any past problems with the muscles (pain, tenderness) after using medicines such as atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin.
- have thyroid problems
- do excessive physical exercise
- have diabetes
- have undergone surgery or other tissue injury
- feel weak or frail

Other warnings you should know about:

Bmd-ATORVASTATIN can cause serious side effect, including:

- **Hyperglycemia** (high blood sugar):

- This may lead to the development of type 2 diabetes.
- Your healthcare professional will monitor your blood sugar level regularly and may adjust your dose during treatment.
- If you have diabetes, closely monitor your blood sugar while taking Bmd-ATORVASTATIN and report any unusual results to your healthcare professional.

- **Liver failure** (serious disturbances of liver function)

- **Allergic reactions**

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Pregnancy:

- Bmd-ATORVASTATIN should **not** be taken during pregnancy. It could harm an unborn baby. Your healthcare professional will discuss the potential risks with you.
- If you are a woman who could become pregnant, your healthcare professional will ask you to use a highly effective birth control method while taking Bmd-ATORVASTATIN.
- If you discover that you are pregnant while taking Bmd-ATORVASTATIN, **stop** taking the medicine and contact your healthcare professional **as soon as possible**.

Breastfeeding:

- It is not known whether Bmd-ATORVASTATIN can pass into breast milk and harm a breastfed baby. As such, Bmd-ATORVASTATIN is **not** recommended during breastfeeding.
- Talk to your healthcare professional about ways to feed your baby while taking Bmd-ATORVASTATIN.

Check-ups and testing: Your healthcare professional may do blood tests before you start Bmd-ATORVASTATIN and regularly during your treatment. These tests will check:

- the level of CoQ10 (an antioxidant) in your blood.
- the amount of cholesterol and other fats in your blood.
- that your liver or muscles are working properly.
- the amount of sugar (glucose) in your blood.

Depending on your test results, your healthcare professional may adjust your dose, temporarily stop or discontinue your treatment with Bmd-ATORVASTATIN.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do not take Bmd-ATORVASTATIN with:

- Medicines used to treat hepatitis C. These include telaprevir, boceprevir, glecaprevir/pibrentasvir, elbasvir/grazoprevir, simeprevir, ledipasvir/sofosbuvir and velpatasvir/sofosbuvir.
- Cyclosporine, a medicine used to suppress the immune system.

Inform your healthcare professional before taking Bmd-ATORVASTATIN with:

- Medicines used to treat HIV/AIDS. These include efavirenz, nelfinavir, lopinavir/ritonavir, tipranavir, ritonavir, saquinavir, darunavir and fosamprenavir.

Taking Bmd-ATORVASTATIN with any of these medicines may cause serious drug interactions. Ask yourhealthcare professional if you are unsure.

The following may interact with Bmd-ATORVASTATIN:

- Medicines used to lower blood cholesterol. These include niacin (nicotinic acid), fibrates, such as gemfibrozil, fenofibrate, and bezafibrate, and bile acid resins, such as cholestyramine and colestipol.
- Medicines used to treat bacterial infections. These include erythromycin, clarithromycin, azithromycin, fusidic acid and rifampin.
- Letermovir – used to treat a viral infection caused by the cytomegalovirus (CMV)
- Itraconazole, ketoconazole – used to treat fungal infections
- Nefazodone – used to treat depression
- Digoxin – used to treat heart conditions
- Amlodipine, quinapril, diltiazem – used to treat high blood pressure and other heart conditions
- Antacids – used to treat heartburn (indigestion)
- Cimetidine – used to treat ulcers of the stomach and intestines
- Colchicine – used to treat gout
- Birth control medication
- Hormone replacement therapy
- Grapefruit juice

How to take Bmd-ATORVASTATIN:

Take Bmd-ATORVASTATIN:

- exactly as your healthcare professional tells you
- once a day
- preferably in the evening
- with or without food. However, do not drink grapefruit juice while taking Bmd-ATORVASTATIN. Grapefruit juice increases the level of Bmd-ATORVASTATIN in your

blood and makes side effects more likely.

Follow the plan your healthcare professional is recommending for diet, exercise and weight control while taking Bmd-ATORVASTATIN.

Usual dose:

The dose of Bmd-ATORVASTATIN prescribed to you will depend on your condition and/or your blood cholesterol level. Your healthcare professional may change your dose depending on your response to Bmd-ATORVASTATIN.

To lower blood cholesterol

Adults:

- The recommended starting dose is 10 mg or 20 mg once daily, depending on your required cholesterol reduction.
- Patients who need a large reduction in blood cholesterol (more than 45%) may start at 40 mg once daily.
- The dosage range for Bmd-ATORVASTATIN is 10 to 80 mg once daily.
- The maximum dose is 80 mg per day.

Children and adolescents (10 to less than 18 years of age):

- The recommended starting dose is 10 mg once daily.
- The maximum recommended dose is 20 mg per day.

To prevent heart attack and stroke

Adults: The recommended dose is 10 to 80 mg once daily.

Overdose:

If you think you, or a person you are caring for, have taken too much Bmd-ATORVASTATIN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, take it as soon as you remember. If you do not remember until it is almost time for your next dose, skip the missed dose and take the next dose as scheduled. Do not double the dose.

What are possible side effects from using Bmd-ATORVASTATIN?

These are not all the possible side effects you/your child may have when taking Bmd-ATORVASTATIN. If you/your child experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Diarrhea
- Abdominal pain or discomfort
- Nausea
- Vomiting
- Gas
- Sore throat or stuffy nose
- Nosebleeds
- Dizziness
- Memory loss or confusion
- Loss of sensation in part of your body
- Tingling sensation or pain in the hands, arms, legs or feet
- Nightmares
- Difficulty falling sleeping
- Hair loss
- Skin rash or itch
- Joint pain
- Impotence (inability to get or keep an erection)
- Breast growth in males

Bmd-ATORVASTATIN can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Cholestasis (decrease in bile flow from the liver): jaundice (yellowing of the skin or whites of eyes), dark urine, light coloured stools		√	
RARE			
Allergic Reactions: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			√
Chest Pain			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Liver failure (serious disturbance of liver function): yellow colour to skin, whites of the eyes (jaundice), bleeding easily, swollen abdomen, mental disorientation or confusion, sleepiness, coma			√
Muscle Disorders: - **Myalgia** (muscle pain): aching muscles, tenderness or weakness that you cannot explain – **Rhabdomyolysis** (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea- coloured) urine – **Immune-Mediated Necrotizing Myopathy (IMNM)** (a type of autoimmune disease that causes muscle cell death): progressive muscle weakness in forearms. thighs, hips, shoulders, neck and back, difficulty standing up, climbing stairs or lifting arms over the head, falling and difficulty getting up from a fall, general feeling of tiredness These muscle disorders can be accompanied with fever or feeling unwell.		√ √	√
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heartbeat, nausea, vomiting, tenderness when touching the abdomen			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Tendon rupture: popping or snapping sound when injury occurs, feeling of being kicked in the calf, very painful calf, difficulty walking, inability to stand on the toes on the injured leg, swollen or bruised calf			√
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness			√
VERY RARE			
Ewing's Sarcoma in children (a type of tumour that forms in bone or soft tissue): Presence of a lump, pain, swelling or tenderness near the tumour, bone pain, unexplained broken bone, feeling tired, fever with no cause, weight loss		√	
Hepatitis (inflammation of the liver): abdominal pain, fatigue, fever, itchiness, light coloured stool, trouble thinking clearly, yellowing of the skin		√	
Interstitial lung disease (disease that inflame or scar lung tissue): shortness of breath when rest that gets worse with exertion, dry cough			√
UNKNOWN			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Depression (sad mood that won't go away)**:** difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse		√	
Hyperglycemia: (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax;
- Or by calling toll-free at 1-866-234-2345.

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.

Storage:

- Store Bmd-ATORVASTATIN at room temperature (15 - 30°C).

- Keep out of reach and sight of children.

If you want more information about Bmd-ATORVASTATIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by contacting Biomed Pharma.

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