פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

1. NAME OF THE MEDICINAL PRODUCT

LIPITOR 10, 20, 40, 80mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains atorvastatin calcium equivalent to 10, 20, 40, or 80 mg atorvastatin.

Excipients:

For a full list of excipients, see section **6.1 List of excipients**

3. PHARMACEUTICAL FORM

Film coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

LIPITOR is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL-cholesterol in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.
LIPITOR is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

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

a. LDL-C remains ≥ 190 mg/dL or
b. LDL-C remains ≥ 160 mg/dL and:
   - there is a positive family history of premature cardiovascular disease or
   - two or more other CVD risk factors are present in the pediatric patient

Prevention of cardiovascular disease

Prevention of cardiovascular and/or cerebrovascular events such as MI or stroke: as an adjunct to correction of other risk factors such as hypertension in patients with three or more additional risk factors or diabetes with one additional risk factors.

In patients with clinically evident coronary heart disease, LIPITOR is indicated to:
- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

4.2 Posology and method of administration

General - Before instituting therapy with LIPITOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise and weight reduction in obese patients, and to treat underlying medical problems. The

patient should continue on a standard cholesterol lowering diet during treatment with LIPITOR. (see National Cholesterol Education Program (NCEP) Guidelines, summarized in Table 1).
The usual starting dose is 10 mg or 20 mg once daily. The dosage range of LIPITOR is 10 to 80 mg once daily. Starting and maintenance doses should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.
Doses may be given at any time of day with or without food.
After initiation and/or upon titration of LIPITOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.
Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia.

TABLE 1. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD [a] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional) [b]
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥ 160
0-1 Risk factor [c]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease
[b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of < 100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Prior to initiating therapy with LIPITOR, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 x [TG] + HDL-C). For TG levels >400 mg/dL (<4.5 mmol/L) this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

LIPITOR has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson Types I and V).
NCEP (National Cholesterol Education Program) Pediatric Panel Guidelines
Classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

Primary Hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Fredrickson Types IIa and IIb)
Patients should be started with LIPITOR 10 mg dailyA therapeutic response is evident within two weeks, and the maximum response is usually achieved within four weeks. The response is maintained during chronic therapy.Doses should be individualized and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg LIPITOR.

Homozygous Familial Hypercholesterolaemia
The dosage of LIPITOR in patients with homozygous FH is 10 to 80 mg daily. LIPITOR should be used as an adjunct to other lipid-lowering treatment (e.g. LDL apheresis) in these patients or if such treatments are unavailable.
In a compassionate-use study of patients with homozygous familial hyper-cholesterolaemia, most patients responded to 80mg of atorvastatin with a greater than 15% reduction in LDL-C (18%-45%).

Severe dyslipidemias in Pediatric Patients -
Experience in pediatrics is limited to a small number of patients (age 4-17 years) with severe dyslipidemias, such as familial hypercholesterolemia. The recommended starting dose in this population is 10mg of LIPITOR per day. The dose may be increased to 80mg daily, according to the response and tolerability. Doses should be individualized according to the recommended goal of therapy (see **section 4.1 Therapeutic indications, and section 5.1 Pharmacodynamic properties**). Adjustments should be made at intervals of 4 weeks or more.

Prevention of cardiovascular or cerebrovascular events
In the primary prevention trials the dose was 10 mg/day. Higher dosages may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

Use in Patients with Hepatic Insufficiency
(See sections **4.3 Contraindications** and **4.4 Special warnings and precautions for use)**

Dosage in Patients with Renal Insufficiency
Renal disease has no influence on the plasma concentrations or on the LDL-C reduction with LIPITOR ; thus, no adjustment of dose is required. (see ***section* 4.4 Special warnings and precautions for use**).

Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors
In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with LIPITOR should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with LIPITOR should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed.In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with LIPITOR should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed (see *section* **4.4 Special warnings and precautions for use – Skeletal Muscle Effects** and *section* **4.5 Interaction with other medicinal products and other forms of interaction - Transporter Inhibitors).**

Use in Elderly
Efficacy and safety in patients older than 70 using recommended doses is similar to that seen in the general population. (see **section 5.2 Pharmacokinetic properties: Special Populations**).

4.3 Contraindications

LIPITOR is contraindicated in patients:
- with hypersensitivity to any component of this medication
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- with myopathy
- during pregnancy
- while breastfeeding
- in women of child-bearing potential not using appropriate contraceptive measures.

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

4.4 Special warnings and precautions for use

Hepatic Effects

Liver function tests should be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically (e.g. semi-annually) thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) is (are) resolved. Should an increase in transaminases of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of LIPITOR is recommended. Atorvastatin can cause an elevation in transaminases (see ***section* 4.8 Undesirable effects**).

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of LIPITOR (see **section 4.3 Contraindications**).

As with other lipid-lowering agents of the same class, moderate (>3 x upper limit of normal [ULN] elevations of serum transaminases have been reported following therapy with LIPITOR. Liver function was monitored during pre-marketing as well as post-marketing clinical studies of atorvastatin given at doses of 10, 20, 40 and 80mg.

LIPITOR can cause an elevation in transaminases (see section **4.8 Undesirable effects**).

Persistent increases in serum transaminases (>3 x ULN on two or more occasions) occurred in 0.7% of patients who received atorvastatin in these clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6% and 2.3% for 10, 20, 40 and 80mg respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels returned to pretreatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of LIPITOR (see section **4.3 CONTRAINDICATIONS**).

Skeletal Muscle Effects

Myalgia has been reported in LIPITOR-treated patients (see **section 4.8 Undesirable effects**). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 x ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, azole antifungals, colchicine, the hepatitis C protease inhibitor telaprevir, boceprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir. Many of these drugs inhibit cytochrome P450 3A4 metabolism and/or drug-transport. CYP 3A4 is the primary hepatic isozymes known to be involved in the biotransformation of atorvastatin. Physicians considering combined therapy with LIPITOR and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Therefore, lower starting and maintenance doses of LIPITOR should also be considered when taken concomitantly with the aforementioned drugs. Temporary suspension of LIPITOR may be appropriate during fusidic acid therapy (See section **4.5 Interaction with other medicinal products and other forms of interaction**). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. LIPITOR may cause an elevation of creatine phosphokinase (see section **4.8 Undesirable effects**).

Prescribing recommendations for interacting agents are summarized in Table 2 (see *sections* **4.2 Posology and method of administration, 4.5 Interaction with other medicinal products and other forms of interaction and 5.2 Pharmacokinetic Properties)**

Table 2. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

* Use with caution and with the lowest dose necessary

As with other drugs in this class, rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects. LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Children aged 10-17 years
In patients aged <18 years efficacy and safety have not been studied for treatment periods>52 weeks' duration and effects on long-term cardiovascular outcomes are unknown. The effects of LIPITOR in children aged <10 years and premenarchal girls have not been investigated.
Long term effects on cognitive development, growth and pubertal maturation are unknown.

Hemorrhagic Stroke
A post-hoc analysis of a clinical study in 4,731 patients without CHD who had a stroke or TIA within the preceding 6 months and were initiated on atorvastatin 80 mg, revealed a higher incidence of hemorrhagic stroke in the atorvastatin 80 mg group compared to placebo (55 atorvastatin vs 33 placebo). Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke (7 atorvastatin vs 2 placebo). However, in patients treated with atorvastatin 80 mg there were fewer strokes of any type (265 vs 311) and fewer CHD events (123 vs 204). (See section **5.1 Pharmacodynamic Properties – Recurrent Stroke**)

Adolescent females and women of childbearing potential should be counseled on appropriate contraceptive methods while on LIPITOR therapy **(**see **section Pregnancy and lactation *4.6*).**

Patients with rare hereditary problems of galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Endocrine Function - Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, lipid-modifying doses of niacin or cytochrome P450 3A4 inhibitors (eg erythromycin (see below), and azole antifungals) (see also ***section* 4.2 Posology and method of administration: Use in Combination with Other Medicinal Compounds and *section* 4.4 Special warnings and Special precautions for use: Skeletal Muscle Effects**).

Inhibitors of cytochrome P450 3A4: Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4.

- ***Transporter Inhibitors:*** Atorvastatin and atorvastatin - metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in a 7.7 fold increase in exposure to atorvastatin. (See also *section* **4.2 Posology and method of administration** - **Use in Combination with Other Medicinal Compounds)**

- ***Erythromycin/Clarithromycin:*** Co-administration of atorvastatin and erythromycin (500 mg four times daily), or clarithromycin (500 mg twice daily) known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin (see ***section* 4.4 Special warnings and precautions for use: Skeletal Muscle Effects**).

- ***Protease inhibitors***: Coadministration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin. (See section 5.2 Pharmacokinetic properties).

- ***Diltiazem hydrochloride***: Co-administration of atorvastatin (40mg) with Diltiazem (240mg) was associated with higher plasma concentrations of atorvastatin.

- ***Cimetidine:*** An atorvastatin interaction study with cimetidine was conducted, and no clinically significant interactions were seen.

- ***Itraconazole*:** Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with an increase in atorvastatin AUC.

- ***Grapefruit juice*:** Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of drugs metabolized by CYP3A4. Intake of one 240 ml glass of grapefruit juice resulted in an increase in atorvastatin AUC of 37 % and a decreased AUC of 20.4 % for the active orthohydroxy metabolite. However, large quantities of grapefruit juice (over 1.2L daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold. Concomitant intake of large quantities of grapefruit juice and atorvastatin is therefore not recommended.

Inducers of cytochrome P450 3A: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous coadministration 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.

Digoxin
When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady - state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. Patients taking digoxin should be monitored appropriately.

Azithromycin
Co-administration of atorvastatin (10 mg once daily) and azithromycin (500 mg once daily) did not alter the plasma concentrations of atorvastatin.

Oral contraceptives

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

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

Colestipol
Plasma concentrations of atorvastatin and its active metabolites were lower (approximately 25%) when colestipol was coadministered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Antacids
Coadministration of Lipitor with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin by approximately 35%; however, LDL-C reduction was not altered.

Warfarin
Atorvastatin interaction studies with warfarin was conducted, and no clinically significant interactions were seen. Nevertheless, patients receiving warfarin should be closely monitored when atorvastatin is added to their therapy

Colchicine: Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

Phenazone
Coadministration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.

Amlodipine
In a drug-drug interaction study in healthy subjects, co-adminstration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful.

Fusidic acid
Although interaction studies with atorvastatin and fusidic acid have not been conducted, severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

Other Concomitant Therapy
In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with all specific agents have not been conducted.

4.6 Fertility , pregnancy and lactation

LIPITOR is contraindicated in pregnancy and while breast feeding. Women of childbearing potential should use appropriate contraceptive measures. The safety of LIPITORin pregnancy and lactation has not yet been proven.
There is evidence from animal studies that HMG-CoA reductase inhibitors may influence the development of embryos or fetuses. The development of rat offspring was delayed and post-natal survival reduced during exposure of the dams to atorvastatin at doses of about 30 times (rat) or 20 times (rabbit) mg/kg/day the human exposure based on surface area (mg/m2).Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy.

LIPITOR 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 to the fetus. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

-In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.
Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for Lipitor.

Estimated frequencies of reactions are ranked according to the following convention: common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (≤ 1/10,000).

Infections and infestations:
Common: nasopharyngitis.

Blood and lymphatic system disorders
Rare: thrombocytopenia.

Immune system disorders
Common: allergic reactions.
Very rare: anaphylaxis.

Metabolism and nutrition disorders
Common: hyperglycaemia.
Uncommon: hypoglycaemia, weight gain, anorexia

Psychiatric disorders
Uncommon: nightmare, insomnia.

Nervous system disorders
Common: headache.
Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.
Rare: peripheral neuropathy.

Eye disorders
Uncommon: vision blurred.
Rare: visual disturbance.

Ear and labyrinth disorders
Uncommon: tinnitus
Very rare: hearing loss.

Respiratory, thoracic and mediastinal disorders:
Common: pharyngolaryngeal pain, epistaxis.

Gastrointestinal disorders
Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.

Hepatobiliary disorders
Uncommon: hepatitis.
Rare: cholestasis.
Very rare: hepatic failure.

Skin and subcutaneous tissue disorders
Uncommon: urticaria, skin rash, pruritus, alopecia.
Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders
Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.
Uncommon: neck pain, muscle fatigue.
Rare: myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture.

Reproductive system and breast disorders
Very rare: gynecomastia.

General disorders and administration site conditions
Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.
Investigations
Common: liver function test abnormal, blood creatine kinase increased.
Uncommon: white blood cells urine positive.

As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving Lipitor. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on Lipitor. These elevations were dose related and were reversible in all patients.
Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on Lipitor, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% Lipitor-treated patients (see section 4.4).

Paediatric Population
The clinical safety database includes safety data for 249 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the age range of 10 to 17.
Nervous system disorders
Common: Headache
Gastrointestinal disorders
Common: Abdominal pain
Investigations
Common: Alanine aminotransferase increased, blood creatine phosphokinase increased
Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.

The following adverse events have been reported with some statins:
• Sexual dysfunction.
• Depression.
• Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).
• Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m2, raised triglycerides, history of hypertension).

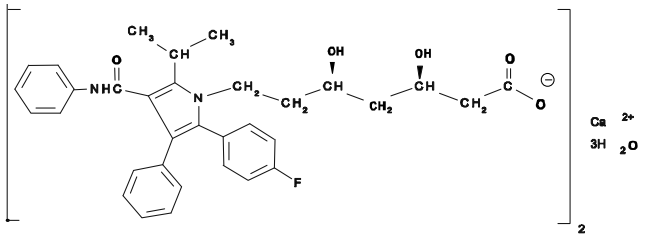
4.9 Overdose

Specific treatment is not available for LIPITOR overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests and serum CPK levels should be monitored. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance LIPITOR clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Atorvastatin calcium is a synthetic lipid-lowering agent, which is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.
The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \bullet 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



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

Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. In patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia, atorvastatin reduces total-C (total cholesterol), LDL-C (low-density lipoprotein cholesterol), and apoB (apolipoprotein B). Atorvastatin also reduces VLDL-C (very-low-density lipoprotein cholesterol) and TG (triglycerides) and produces variable increases in HDL-C (high-density lipoprotein cholesterol).
Triglycerides and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabloized primarily through the high affinity LDL receptor. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease.

As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.
Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

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

In a dose-response study, atorvastatin (10-80 mg) reducedtotal-C (30%-46%), LDL-C (41%-61%), apolipoprotein B (34%-50%), and triglycerides (14%-33%) while producing variable increases in HDL-C and apolipoprotein A in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

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

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality. Mortality and morbidity studies with atorvastatin have not yet been completed.

In patients with Fredrickson Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median percent increases from baseline in HDL-C for atorvastatin (10-80 mg) were 5.1-8.7% in a non-dose-related manner. Additionally, analysis of this pooled data demonstrated significant dose related decreases in total-C/HDL-C and LDL-C/HDL-C ratios, ranging from -29 to -44% and -37 to -55%, respectively.

The effects of atorvastatin on ischemic events and total mortality were studied in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study (MIRACL). This multicenter, randomized, double-blind, placebo-controlled study followed 3086 patients with acute coronary syndromes; unstable angina or non-Q wave myocardial infarction. Patients were treated with standard care, including diet, and either atorvastatin 80 mg daily or placebo for a median duration of 16 weeks. The final LDL-C, total-C, HDL-C and TG levels were 72, 147, 48, 139 mg/dL in the atorvastatin group, respectively, and 135, 217, 46, and 187 mg/dL, respectively, in the placebo group. Atorvastatin significantly

reduced the risk of ischemic events and death by 16%. The risk of experiencing rehospitalization for angina pectoris with documented evidence of myocardial ischemia was significantly reduced by 26%. Atorvastatin reduced the risk of ischemic events and death to a similar extent across the range of baseline LDL-C. In addition, atorvastatin reduced the risk of ischemic events and death to similar extents in patients with non-Q wave MI and unstable angina, as well as in males and females and in patients <65 years of age and >65 years of age.

Atorvastatin and some of its metabolites are pharmacologically active in humans. The primary site of action of atorvastatin is the liver, which is the principal site of cholesterol synthesis and LDL clearance. LDL-C reduction correlates better with drug dose than it does with systemic drug concentration. Individualization of drug dosage should be based on therapeutic response (see section **4.2 (Posology and method of administration)**).

Recurrent Stroke
In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (mean 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.
Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15%
(HR 0.85; 95% CI, 0.72-1.00; p=0.05 or 0.84; 95% CI, 0.71-0.99; p=0.03 after adjustment for
baseline factors) compared to placebo. Atorvastatin 80 mg significantly reduced the risk of major coronary events (HR 0.67; 95% CI, 0.51-0.89; p=0.006), any CHD event (HR 0.60; 95% CI, 0.48-0.74; p<0.001), and revascularization procedures (HR 0.57; 95% CI, 0.44-0.74; p<0.001).
In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365,
9.2% vs. 274/2366, 11.6%, p=0.01) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin vs. 18 placebo). Reduction in the risk of cardiovascular events with atorvastatin 80 mg was demonstrated in all patient groups except in patients who entered the study with a hemorrhagic stroke and had a recurrent hemorrhagic stroke (7 atorvastatin vs 2 placebo).

In patients treated with atorvastatin 80 mg there were fewer strokes of any type (265 atorvastatin vs 311 placebo) and fewer CHD events (123 atorvastatin vs 204 placebo). Overall mortality was similar across treatment groups (216 atorvastatin vs 211 placebo). The overall incidence of adverse events and serious adverse events was similar between treatment groups.

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 age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia were randomized to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative.
The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5-385.0 mg/dL) in the atorvastatin group compared to 230.0 mg/dL (range: 160.0-324.5 mg/dL) in placebo group. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see Table 3).

TABLE 3
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	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the Atorvastatin group compared to 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26 week double-blind phase.

In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls. Atorvastatin 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. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

Atherosclerosis
In the Reversing Atherosclerosis with Aggressive Lipid- Lowering Study (REVERSAL), the effect of intensive lipid lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomized, double- blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

The median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin the effects of atorvastatin were statistically significant (p=0.02). The effect of intensive lipid lowering on cardiovascular endpoints (e. g. need for revascularisation, non fatal myocardial infarction, coronary death) was not investigated in this study.
In the atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/L ± 0.8 (78.9 mg/dl ± 30) from baseline 3.89 mmol/l ± 0.7 (150 mg/dl ± 28) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/l ± 0.7 (110 mg/dl ± 26) from baseline 3.89 mmol/l ± 0.7 (150 mg/dl ± 26) (p<0.0001). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG levels by 20% (pravastatin: -6.8%, p<0.0009), and mean apolipoprotein B by 39.1% (pravastatin: -22.0%, p<0.0001). Atorvastatin increased mean HDL-C by 2.9% (pravastatin: +5.6%, p=NS). There was a 36.4% mean reduction in CRP in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).

Study results were obtained with the 80 mg dose strength. Therefore, they cannot be extrapolated to the lower dose strengths.

The safety and tolerability profiles of the two treatment groups were comparable.

Prevention of cardiovascular disease
In the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), theeffect of atorvastatin 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 or treatment for angina, and with TC levels <6.5 mmol/l (251 mg/dl). Additionally all patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.
Patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).
As the effect of atorvastatin treatment compared to placebo exceeded the significance threshold during an interim analysis, the ASCOT-LLA was terminated early at 3.3 years instead of 5 years. Additionally, blood pressure was well controlled and similar in patients assigned atorvastatin and placebo. These changes persisted throughout the treatment period.
atorvastatin reduced the rate of the following events:

Event	Relative Risk Reduction (%)	No. of Events (Atorva vs Placebo)	Absolute Risk Reduction1 (%)	p-value
Coronary events (fatal CHD plus non-fatal MI)	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular events and revascularization procedures	20%	389 vs. 483	1.9%	0.0008
Total coronary events	29%	178 vs 247	1.4%	0.0006
Fatal and non-fatal stroke*	26 %	89 vs. 119		0.0332

*Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction.
CHD = coronary heart disease; MI = myocardial infarction.

Total mortality and cardiovascular mortality were not significantly reduced (185 vs. 212 events, p=0.17 and 74 vs. 82 events, p=0.51) although a favorable trend was observed. In the subgroup analyses by gender (81% males, 19% females), a beneficial effect of atorvastatin was seen in males but could not be established in females possibly due to the low event rate in the female subgroup. Overall and cardiovascular mortality were numerically higher in the female patients (38 vs. 30 and 17 vs. 12), but this was not statistically significant.
There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD plus non-fatal MI) was significantly reduced by atorvastatin in patients treated with Amlodipine (HR 0.47 (0.32-0.69), p=0.00008), but not in those treated with Atenolol (HR 0.83 (0.59-1.17), p=0.287).

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomized, double-blind, multicenter, placebo-controlled trial, the Collaborative atorvastatin Diabetes Study (CARDS) in 2838 patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤4.14 mmol/l (160 mg/dl) and TG ≤6.78 mmol/l (600 mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.
Patients were treated with either atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410) for a median follow-up of 3.9 years. As the effect of atorvastatin treatment on the primary endpoint reached the predefined stopping rules for efficacy, CARDS was terminated 2 years earlier than anticipated.
The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative Risk Reduction (%)	No. of Events (Atorva vs Placebo)	Absolute Risk Reduction1 (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37 %	83 vs. 127	3.2 %	0.0010
MI (fatal and non-fatal AMI, silent MI)	42 %	38 vs 64	1.9 %	0.0070
Strokes (Fatal and non-fatal)	48 %	21 vs. 39	1.3 %	0.0163

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level. A relative risk reduction in death of 27% (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group, p=0.0592) has been observed with a borderline statistical significance (p=0.0592). The overall incidence of adverse events or serious adverse events was similar between the treatment groups.

In the Treating to New Targets Study (TNT), the effect of atorvastatin 80 mg/day vs. atorvastatin 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98 and 47 mg/dL during treatment with 80 mg of atorvastatin and 99, 177, 152, 129 and 48 mg/dL during treatment with 10 mg of atorvastatin.

Treatment with atorvastatin 80 mg/day significantly reduced the rate of MCVE (434 events in the 80mg/day group vs 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69,0.89), p=0.0002 (see Figure 1 and Table 4). The overall risk reduction was consistent regardless of age (<65, ≥65) or gender.

Figure 1. Effect of Atorvastatin 80 mg/day vs.10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

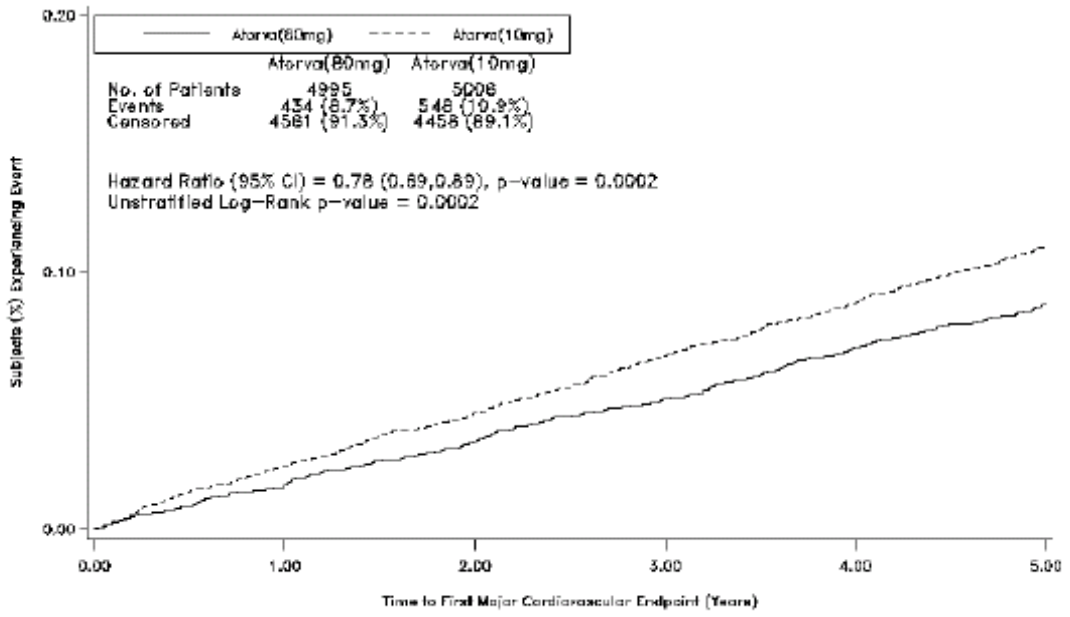


TABLE 4. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR[a] (95%CI)
PRIMARY ENDPOINT*	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Nonfatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS**					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure[b]	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of all cause mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

a Atorvastatin 80 mg: atorvastatin 10 mg
b component of other secondary endpoints
* major cardiovascular endpoint (MCVE) = death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke
** secondary endpoints not included in primary endpoint
HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft

Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin 80 mg/day significantly reduced the rate of nonfatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 4). Of the predefined secondary endpoints, treatment with atorvastatin 80 mg/day significantly reduced the rate of coronary revascularization, angina and hospitalization for heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only observed in the 8% of patients with a prior history of CHF.

There was no significant difference between the treatment groups for all-cause mortality (Table 4): 282 (5.6%) in the atorvastatin 10 mg/day group vs. 284 (5.7%) in the atorvastatin 80 mg/day group. The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke were numerically smaller in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study
(IDEAL), treatment with atorvastatin 80 mg/day was compared to treatment with simvastatin 20-40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45 and 100 mg/dL during treatment with 80 mg of atorvastatin and 105, 179, 142, 47 and 132 mg/dL during treatment with 20-40 mg of simvastatin.

There was no significant difference between the treatment groups for the primary endpoint, the rate of first major coronary event (fatal CHD, nonfatal MI and resuscitated cardiac arrest): 411 (9.3%) in the atorvastatin 80 mg/day group vs. 463 (10.4%) in the simvastatin 20-40 mg/day group, HR 0.89, 95% CI (0.78,1.01), p=0.07.

There were no significant differences between the treatment groups for all-cause mortality: 366 (8.2%) in the atorvastatin 80 mg/day group vs. 374 (8.4%) in the simvastatin 20-40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the atorvastatin 80 mg group and the simvastatin 20-40 mg group.

5.2 Pharmacokinetic Properties

Pharmacokinetics and Drug Metabolism
Absorption*:* Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption and plasma atorvastatin concentrations increase in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions. The absolute bioavailability of atorvastatin is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9% respectively, as assessed by Cmax and AUC, LDL C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL C reduction is the same regardless of the time of day of drug administration8 (see **section 4.2 Posology and method of administration**).

Distribution: Mean volume of distribution of atorvastatin is approximately 381 L.
Atorvastatin is $\geq$ 98% bound to plasma proteins. A red blood cell/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. In-vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity of HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by hepatic cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme. *In vitro* studies also indicate that atorvastatin is a weak inhibitor of cytochrome P450 3A4. Atorvastatin coadministration did not produce a clinically significant effect in plasma concentrations of terfenadine, a compound predominantly metabolized by cytochrome P450 3A4; therefore, it is unlikely that atorvastatin will significantly alter the pharmacokinetics of other cytochrome P450 3A4 substrates (see ***section*** **4.5 Interaction with other medicinal products and other forms of interaction**). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are 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. The half-life of inhibitory activity of HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

Elderly: Plasma concentrations of atorvastatin and its active metabolites are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (aged ≥65 years) than in young adults. The ACCESS study specifically evaluated elderly patients with respect to reaching their NCEP treatment goals. The study included 1087 patients under 65 years of age, 815 patients over 65 years of age, and 185 patients over 75 years of age. No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population.

Children: Pharmacokinetic data in the paediactic population are not available.

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

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites. Thus, dose adjustment in patients with renal dysfunction is not necessary (see **section 4.2 Posology and Method of Administration**).

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

Hepatic Insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approximately 16-fold in Cmax and 11-fold in AUC) in patients with chronic alcohol liver disease (Childs-Pugh B).

Drug Interactions - The effect of co-administered drugs on the pharmacokinetics of atorvastatin as well as the effect of atorvastatin on the pharmacokinetics of co-administered drugs are summarized below (see ***section*** **4.4 Special warnings and precautions for use**, and ***section*** **4.5 Interaction with other medicinal products and other forms of interaction** and **Table 5 and 6**).

Table 5. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	**Atorvastatin**		
	Dose (mg)	**Change in AUC[&]**	**Change in Cmax[&]**
#Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑8.7 fold	↑10.7 fold
#Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 9.4 fold	↑ 8.6 fold
#Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.88 fold	↑ 10.6 fold
# Boceprevir 800 mg TID, 7 days	40 mg SD	↑ 2.30 fold	↑ 2.66 fold
#Lopinavir 400 mg BID/ ritonavir 100 mg BID, 14 days	20 mg QD for 4 days	↑ 5.9 fold	↑ 4.7 fold
#, ‡Saquinavir 400 mg BID/ ritonavir 400mg BID, 15 days	40 mg QD for 4 days	↑ 3.9 fold	↑ 4.3 fold
#Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑4.4 fold	↑ 5.4 fold
#Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
#Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑20%
#Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold

Co-administered drug and dosing regimen	Atorvastatin		
days			
#Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑2.3 fold	↑4.04 fold
#Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑2.2 fold
#Grapefruit Juice, 240 mL QD *	40 mg, SD	↑ 0.37 fold	↑ 0.16 fold
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 0.51 fold	0 fold
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 0.33 fold	↑ 0.38 fold
Amlodipine 10 mg, single dose	80 mg, SD	↑ 0.15 fold	↓ 0.12 fold
Cimetidine 300 mg QID, 2 weeks	10 mg QD for 2 weeks	↓ 0.001 fold	↓ 0.11 fold
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 0.26 fold**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 0.33 fold	↓ 0.34 fold
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 0.41 fold	↓ 0.01 fold
#Rifampin 600 mg QD, 7 days (co-administered) †	40 mg SD	↑ 0.30 fold	↑ 1.72 fold
#Rifampin 600 mg QD, 5 days (doses separated) †	40 mg SD	↓ 0.80 fold	↓ 0.40 fold
#Gemfibrozil 600mg BID, 7 days	40mg SD	↑ 0.35 fold	↓ 0.004 fold
#Fenofibrate 160mg QD, 7 days	40mg SD	↑ 0.03 fold	↑ 0.02 fold

& "fold" change = change ratio [(I-B)/B], where I = pharmacokinetic value during the Interaction phase, and B = pharmacokinetic value during the Baseline phase;
# See Section 4.4 and 4.5 for clinical significance
* Greater increases in AUC (up to 1.5 fold) and/or Cmax (up to0.71 fold have been reported with excessive grapefruit consumption (≥ 750 mL - 1.2 liters per day).
** Single sample taken 8-16 h post dose
† Due to the dual interaction mechanism of rifampin, 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.
‡ The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in 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.

Table 6. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	**Change in AUC&**	**Change in Cmax&**
80 mg QD for 15 days	Antipyrine, 600mg SD	↑ 0.03 fold	↓ 0.11 fold
80 mg QD for 14 days	#Digoxin 0.25mg QD, 20 days	↑ 0.15 fold	↑ 0.20 fold
40 mg QD for 22 days	Oral contraceptive QD, 2 months - norethindrone 1mg -ethinyl estradiol 35µg	 ↑ 0.28 fold ↑ 0.19 fold	 ↑ 0.23 fold ↑ 0.30 fold
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg, QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 0.27 fold	↓ 0.18 fold
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

& "fold" change = change ratio [(I-B)/B], where I = pharmacokinetic value during the Interactions phase, and B = pharmacokinetic value during the baseline phase
# See Section 4.5 for clinical significance

5.3 Preclinical Safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility - Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on AUC (0-24) values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenomas in males and hepatocellular carcinomas in females were increased at the maximum dose used, which was 250-fold higher than the highest human dose on mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on AUC (0-24).
All other chemically similar drugs in this class have induced tumors in both mice and rats at multiples of 12 to 125 times their highest recommended clinical doses, on a mg/kg body-weight basis.
Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 *in vitro* tests with and without metabolic activation and in 1 *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.

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 caused no adverse effects on sperm or semen parameters, or on reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium carbonate
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Polysorbate 80
Hydroxypropyl cellulose
Magnesium stearate

Film coating:
Opadry white
Simethicone emulsion

6.2 Incompatibilities
None

6.3 Special Precautions for Storage
In a dry place below 25°C.

6.4 Instructions for Use/Handling
No special instructions needed.

6.5 Manufactured by:
Pfizer manufacturing, Germany

License holder: Pfizer Pharmaceuticals Israel Ltd. 9 Shenkar St. Herzlya Pituach 46725.