*For the use of registered medical practitioner only*

# STORVAS C TABLETS

**(Atorvastatin Tablets 10/20/40/80 mg)**

## COMPOSITION

**STORVAS C 10**
Each film coated tablet contains:
Atorvastatin Calcium equivalent to Atorvastatin .....10 mg

**STORVAS C 20**
Each film coated tablet contains:
Atorvastatin Calcium equivalent to Atorvastatin .....20 mg

**STORVAS C 40**
Each film coated tablet contains:
Atorvastatin Calcium equivalent to Atorvastatin .....40 mg

**STORVAS C 80**
Each film coated tablet contains:
Atorvastatin Calcium equivalent to Atorvastatin .....80 mg

## PRODUCT DESCRIPTION

**STORVAS C 10**
White to off-white film-coated capsule shaped tablets debossed 'SB' on one side and other side "1" and "0" on either side of breakline.

**STORVAS C 20**
White to off-white film-coated capsule shaped tablets debossed 'SB' on one side and other side "2" and "0" on either side of breakline.

**STORVAS C 40**
White to off-white film-coated capsule shaped tablets debossed 'SB' on one side and other side "4" and "0" on either side of breakline.

**STORVAS C 80**
White to off-white film-coated capsule shaped tablets debossed 'SB' on one side and other side "8" and "0" on either side of breakline

## PHARMACOLOGY

- **Pharmacodynamic properties**

Pharmacotherapeutic group: **C10AA05 -** Lipid modifying agents, HMG-CoA-reductase inhibitors

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response (see **DOSAGE AND ADMINISTRATION**).

**Mechanism of Action**

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts HMG-Co-A to mevalonate, a precursor of sterols, including cholesterol. In patients with homozygous and heterozygous familial hypercholesterolemia, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia, atorvastatin reduces total-C, LDL-C, and apo B. Atorvastatin also reduces very low-density lipoprotein cholesterol (VLDL-C) and TG and produces variable increases in HDL-C. 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 hypercholesterolemia, a population that has not normally responded to lipid-lowering medication. 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.

- **Pharmacokinetics**

*Absorption*

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

of atorvastatin metabolism by hepatic cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme. In vitro studies also indicate that atorvastatin is a weak inhibitor of cytochrome P450 3A4. Atorvastatin co-administration 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.

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

**Pharmacokinetics in Special Populations**

*Elderly*
Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Reported clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults.

*Pediatrics*
In a reported study, paediatric 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. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were reported over the range of atorvastatin and o-hydroxyatorvastatin exposures.

*Gender*
Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

*Renal Insufficiency*
Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

*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 Impairment*
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 Class B) (see **CONTRAINDICATIONS**).

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

**Table: Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin**

| **Co-administered drug and dosing regimen** | **Atorvastatin** | | |
|---|---|---|---|
| | **Dose (mg)** | **Ratio of AUC[&]** | **Ratio of $C_{max}$[&]** |
| #Cyclosporine 5.2 mg/kg/day, stable dose | 10 mg QD[a] for 28 days | 8.7 | 10.7 |
| Tipranavir 500 mg BID[b]/ritonavir 200 mg BID[b], 7 days | 10 mg SD[c] | 9.4 | 8.6 |
| Glecaprevir 400 mg QD[a]/Pibrentasvir 120 mg QD[a], 7 days[102] | 10 mg QD[a] for 7 days | 8.3 | 22.0 |
| #Telaprevir 750 mg q8h[f], 10 days | 20 mg SD[c] | 7.9 | 10.6 |
| #Elbasvir 50 mg QD[a]/grazoprevir 200 mg QD[a], 13 days | 10 mg SD[c] | 1.95 | 4.3 |
| #Boceprevir 800 mg TID[d], 7 days | 40 mg SD[c] | 2.3 | 2.7 |
| #Simeprevir 150 mg QDa, 10 days | 40 mg SD[c] | 2.12 | 1.7 |
| #Lopinavir 400 mg BID[b]/ ritonavir 100 mg BID[b], 14 days | 20 mg QD[a] for 4 days | 5.9 | 4.7 |
| #,‡Saquinavir 400 mg BID[b]/ ritonavir 400 mg BID[b], 15 days | 40 mg QD[a] for 4 days | 3.9 | 4.3 |
| #Clarithromycin 500 mg BID[b], 9 days | 80 mg QD[a] for 8 days | 4.5 | 5.4 |
| #Darunavir 300 mg BID[b]/ ritonavir 100 mg BID[b], 9 days | 10 mg QD[a] for 4 days | 3.4 | 2.2 |
| #Itraconazole 200 mg QD[a], 4 days | 40 mg SD[c] | 3.3 | 1.20 |
| #Letermovir 480 mg QD[a], 10 days | 20 mg SD[c] | 3.29 | 2.17 |
| #Fosamprenavir 700 mg BID[b]/ ritonavir 100 mg BID[b], 14 days | 10 mg QD[a] for 4 days | 2.5 | 2.8 |
| #Fosamprenavir 1400 mg BID[b], 14 days | 10 mg QD[a] for 4 days | 2.3 | 4.0 |
| *Nelfinavir 1250 mg BID[b], 14 days | 10 mg QD[a] for 28 days | 1.74 | 2.2 |
| #Grapefruit Juice, 240 mL QD[a] * | 40 mg SD[c] | 1.37 | 1.16 |
| Diltiazem 240 mg QD[a], 28 days | 40 mg SD[c] | 1.51 | 1.00 |
| Erythromycin 500 mg QID[e], 7 days | 10 mg SD[c] | 1.33 | 1.38 |
| Amlodipine 10 mg, single dose | 80 mg SD[c] | 1.18 | 0.91 |
| Cimetidine 300 mg QID[e], 4 weeks | 10 mg QD[a] for 2 weeks | 1.00 | ↓0.89 |
| Colestipol 10 mg BID[b], 24 weeks | 40 mg QD[a] for 8 weeks | NA | 0.74** |

| | | | |
|---|---|---|---|
| Antacid suspension containing magnesium hydroxide & aluminum hydroxide 30 mL QD, 17 days | 10 mg QD[a] for 15 days | 0.66 | 0.67 |
| Efavirenz 600 mg QD[a], 14 days | 10 mg for 3 days | 0.59 | 1.01 |
| #Rifampin 600 mg QD[a], 7 days (coadministered) † | 40 mg SD[c] | 1.12 | 2.9 |
| #Rifampin 600 mg QD[a], 5 days (doses separated) † | 40 mg SD[c] | 0.20 | 0.60 |
| #Gemfibrozil 600 mg BID[b], 7 days | 40 mg SD[c] | 1.35 | 1.00 |
| #Fenofibrate 160 mg QD[a], 7 days | 40 mg SD[c] | 1.03 | 1.02 |

& Represents ratio treatments (co-administered drug plus atorvastatin vs. atorvastatin alone).

# see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**

* Greater increases in AUC (ratio of AUC up to 2.5) and/or $C_{max}$ (ratio of $C_{max}$ up to 1.71) have been reported with excessive grapefruit consumption (≥ 750 mL - 1.2 liters per day).

** Ratio based on 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 / 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 exercised and the lowest dose necessary should be used.

[a] Once daily

[b] Twice daily

[c] Single dose

**Table: Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs**

| **Atorvastatin** | **Co-administered drug and dosing regimen** | | |
|---|---|---|---|
| **Drug/Dose (mg)** | **Drug/Dose (mg)** | **Ratio of AUC[&]** | **Ratio of Cmax[&]** |
| 80 mg QD[a] for 15 days | Antipyrine, 600 mg SD[c] | 1.03 | 0.89 |
| 80 mg QD[a] for 10 days | # Digoxin 0.25 mg QD, 20 days | 1.15 | 1.20 |
| 40 mg QD for 22 days | Oral contraceptive QD[a], 2 months<br>- norethindrone 1mg<br>- ethinyl estradiol 35µg | <br>1.28<br>1.19 | <br>1.23<br>1.30 |
| 10 mg SD[c] | Tipranavir 500 mg BID[b]/ritonavir 200 mg BIDb ,7 days | 1.08 | 0.96 |
| 10 mg QDa for 4 days | Fosamprenavir 1400 mg BID[b], 14 days | 0.73 | 0.82 |
| 10 mg QD[a] for 4 days | Fosamprenavir 700 mg BID[b]/ritonavir 100 mg BID[b], 14 | 0.99 | 0.94 |

[&]Represents ratio treatments (co-administered drug plus atorvastatin vs. atorvastatin alone)

#see **DRUG INTERACTIONS** for clinical significance.

[a] Once daily

[b] Twice daily

[c] Single dose

## INDICATIONS

Atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG) and to increase high density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial hypercholesterolemia), combined (mixed) hyperlipidemia (*Fredrickson* Types IIa and IIb), elevated serum TG levels (*Fredrickson* Type IV), and for patients with dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet. Atorvastatin is also indicated for the reduction of total-C and LDL-C in patients with homozygous familial hypercholesterolemia.

*Prevention of Cardiovascular Disease*
In adult patients without clinically evident cardiovascular disease (CVD), but with multiple risk factors for coronary heart disease (CHD) such as age, smoking, hypertension, low HDL-C, or a family history of early CHD, STORVAS C is indicated to:

- Reduce the risk of myocardial infarction (MI)
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident CHD, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident CHD, atorvastatin is indicated to:

- Reduce the risk of non-fatal MI
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for congestive heart failure (CHF)
- Reduce the risk of angina

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

- LDL-C remains ≥190 mg/dL or
- LDL-C remains ≥160 mg/dL and

    - There is a positive family history of premature CVD or
    - Two or more other CVD risk factors are present in the pediatric patient

## DOSAGE AND ADMINISTRATION

**General -** Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise and weight reduction in obese patients, and to treat underlying medical problems. The patient should continue on standard cholesterol lowering diet during treatment with atorvastatin. The dosage range is 10 to 80 mg once daily. Doses may be given any time of the day, with or without food. Starting and maintenance dosage should be

individualized according to baseline LDL-C levels, the goa of therapy and patient response. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks, and dosage adjusted accordingly

**Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia -** The majority of patients are controlled with 10 mg atorvastatin once a day. A therapeutic response is evident within two weeks and the maximum response is usually achieved within four weeks. The response is maintained during chronic therapy.

**Homozygous Familial Hypercholesterolemia -** In a compassionate-use study of patients with homozygous familial hypercholesterolemia, most patients responded to 80 mg of atorvastatin with a greater than 15% reduction in LDL-C (18% - 45%).

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

**Severe Dyslipidemias in Pediatric Patients**
For patients aged 10 years and above, the recommended starting dose is 10 mg atorvastatin once daily. The dose may be increased to 80 mg daily, according to the response and tolerability. Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more.

**Use in Patients with Hepatic Insufficiency -** (see **WARNINGS AND PRECAUTIONS** and **CONTRAINDICATIONS**).

**Use in Patients with Renal Insufficiency -** Renal disease has no influence on the plasma concentrations or on the LDL-C reduction with atorvastatin. Thus no adjustment of the dose is required.

**Use in the Elderly-** No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population.

**Use in Children (Homozygous Familial Hypercholesterolemia) -** Treatment experience in a pediatric population is limited to doses of atorvastatin up to 80 mg/day for one year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients.

**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 atorvastatin should be avoided.

In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin 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 atorvastatin should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with atorvastatin should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

## CONTRAINDICATIONS

Atorvastatin is contraindicated in patients who have:

Hypersensitivity to any component of this medication,

Active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal (ULN) or who are:

Pregnant, breast-feeding, or of childbearing potential who are not using adequate contraceptive measures. 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 to the fetus.

## WARNINGS AND PRECAUTIONS

### Hepatic Effects

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

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 the 10 mg, 20 mg, 40 mg and 80 mg doses 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 pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggesting liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality (ies) resolve(s). Should an increase in ALT or AST of >3 x ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin can cause an elevation in transaminases.

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

### Skeletal Muscle Effects

Myalgia has been reported in atorvastatin-treated patients (see **ADVERSE REACTIONS**). Myopathy, defined as muscle ache 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. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or if 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, telaprevir, boceprevir or the combination of tipranavir/ritonavir. Many of these drugs inhibit cytochrome P450 3A4 (CYP 3A4) metabolism and/or drug transport. CYP 3A4 is the primary hepatic isozyme known to be involved in the biotransformation of atorvastatin. Physicians considering combined therapy with atorvastatin and fibrates, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin (≥1g/day) 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 atorvastatin should also be considered when taken concomitantly with the aforementioned drugs. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. Atorvastatin may cause an elevation of CPK (see **ADVERSE REACTIONS**).

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins (see **ADVERSE REACTIONS**). IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment, muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

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. Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or with 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).

**Hemorrhagic Stroke**
A higher incidence of hemorrhagic stroke has been reported in patients without CHD who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and were initiated on atorvastatin 80 mg. Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke. However, in patients treated with atorvastatin 80 mg there were fewer strokes of any type and fewer CHD events.

**Endocrine Function**
Increases in hemoglobin A1c (HbA1c) and fasting serum glucose levels have been reported with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, including atorvastatin. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins

and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/$m^2$, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

**Myasthenia Gravis/ Ocular Myasthenia**
In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). Atorvastatin should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

**Paediatric population**
No clinically significant effect on growth and sexual maturation has been reported based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight (see **ADVERSE REACTIONS**).

## USE IN SPECIAL POPULATIONS

**Pregnancy**
Atorvastatin is contraindicated in pregnancy. Women of child-bearing potential should use appropriate contraceptive measures. 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 to the fetus.

**Lactation**
Atorvastatin is contraindicated while breast feeding. It is not known whether this drug or its metabolites is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking atorvastatin should not breast-feed.

**Pediatrics**
See **DOSAGE AND ADMINISTRATION**

**Geriatric Use**
Adequate treatment experience in adults age 70 or older with doses of atorvastatin up to 80 mg/day has been obtained. Efficacy and safety in older patients using recommended doses is similar to that seen in the general population. Since advanced age (≥65 years) is a predisposing factor for myopathy, atorvastatin should be prescribed with caution in the elderly.

**Hepatic Impairment**
Atorvastatin is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels (see **WARNINGS AND PRECAUTIONS**; **CONTRAINDICATIONS** and **PHARMACOLOGY**).

**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.

## DRUG INTERACTIONS

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, lipid-modifying doses of niacin or CYP 3A4 inhibitors (e.g. erythromycin and azole antifungals) (see **WARNINGS AND PRECAUTIONS**).

**Inhibitors of CYP 3A4:**
Atorvastatin is metabolized by CYP3A4. Concomitant administration of atorvastatin with inhibitors of cytochrome CYP3A4 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 CYP3A4.

**Erythromycin/Clarithromycin:** Co-administration of atorvastatin with erythromycin (500 mg four times daily) or clarithromycin (500 mg twice daily), known inhibitors of CYP3A4, was associated with higher plasma concentrations of atorvastatin (see **WARNINGS AND PRECAUTIONS and Pharmacokinetics**).

**Protease Inhibitors:** Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P4503A4, was associated with increased plasma concentrations of atorvastatin (see **Pharmacokinetics**).

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

**Cimetidine:** No clinically significant interactions have been reported when atorvastatin was co-administered with cimetidine (see **Pharmacokinetics**)

**Itraconazole:** Concomitant administration of atorvastatin (20-40 mg) with itraconazole (200 mg) have been reported to be associated with an increase in atorvastatin AUC (see **Pharmacokinetics**)

**Grapefruit Juice:** Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day) (see **Pharmacokinetics**)

**Transport inhibitors**
Atorvastatin is a substrate of the hepatic transporters (see **Pharmacokinetics**).

Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day have been reported to result in an increase in exposure to atorvastatin (ratio of AUC: 8.7; see **Pharmacokinetics**). Cyclosporine is an inhibitor of organic anion-transporting polypeptide 1B1 (OATP1B1), OATP1B3, multi-drug resistance protein 1 (MDR1), and breast cancer resistance protein (BCRP) as well as CYP3A4, thus it increases exposure to atorvastatin.

Glecaprevir and pibrentasvir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Do not exceed 10 mg atorvastatin daily.

Concomitant administration of atorvastatin 20 mg and letermovir 480 mg daily have been reported to result in an increase in exposure to atorvastatin (ratio of AUC: 3.29; see **Pharmacokinetics**). Letermovir inhibits efflux transporters P-gp, BCRP, MRP2, OAT2 and hepatic transporter OATP1B1/1B3, thus it increases exposure to atorvastatin. Do not exceed 20 mg atorvastatin daily.

The magnitude of CYP3A- and OATP1B1/1B3-mediated drug interactions on co-administered drugs may be different when letermovir is co-administered with cyclosporine. Use of atorvastatin should be avoided in patients taking letermovir co-administered with cyclosporine.

Elbasvir and grazoprevir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Use with caution and lowest dose necessary. Dose of atorvastatin should not exceed 20 mg daily in patients receiving concomitant medications with products containing elbasvir and grazoprevir.

**Inducers of CYP3A4:** Concomitant administration of atorvastatin with inducers of CYP3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin (CYP 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.

**Antacids:** Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxides decreased atorvastatin plasma concentrations (ratio of AUC: 0.66); however, LDL-C reduction was not altered.

**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 were lower (ratio of concentration: 0.74) when colestipol was administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were administered together than when either drug was given alone.

**Digoxin:** When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased (ratio of AUC: 1.15) 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) with azithromycin (500 mg once daily) did not alter the plasma concentrations of atorvastatin.

**Oral Contraceptives:** Co-administration of atorvastatin with an oral contraceptive containing norethindrone and ethinyl estradiol increased the area under the concentration vs. time curve (AUC) values for norethindrone (ratio of AUC: 1.28) and ethinyl estradiol (ratio of AUC: 1.19). These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

**Warfarin:** Atorvastatin had no clinically significant interactions when administered to patients receiving chronic warfarin treatment.

**Colchicine:** Cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

**Amlodipine:** Co-administration of atorvastatin 80 mg with amlodipine 10 mg have been reported to result in an increase in exposure to atorvastatin (ratio of AUC: 1.18) which was not clinically meaningful.

**Fusidic acid:** There is an increased risk of rhabdomyolysis in patients receiving a combination of statins, including atorvastatin, and fusidic acid. The mechanism of this interaction is not known. 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 seven days after the last dose of fusidic acid.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of atorvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

**Fibrates**: Concurrent use of fibrates may cause severe myositis and myoglobinuria.

**Other Concomitant Therapy:** No clinically significant adverse interactions have been reported when atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy.

**Gemfibrozil/fibric acid derivatives:** The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored.

**Ezetimibe:** The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.

**Effect of co-administered medicinal products on atorvastatin**
Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin. Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe.

## ADVERSE REACTIONS

Atorvastatin is generally well tolerated. Adverse reactions have usually been mild and transient.

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 3 weeks). Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

The most frequent adverse effects reported with atorvastatin therapy are:

**Infections and infestations**: nasopharyngitis

**Blood and lymphatic system disorders**: thrombocytopenia

**Immune system disorders**: allergic reactions (including anaphylaxis)

**Metabolism and nutrition disorders**: hyperglycaemia, hypoglycaemia, weight gain, anorexia

**Injury, poisoning, and procedural complications:** tendon rupture

**Psychiatric disorders**: insomnia, nightmare,

**Nervous system disorders**: headache, dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia, peripheral neuropathy

**Eye disorders**: vision blurred, visual disturbance, ocular myasthenia

**Ear and labyrinth disorders**: tinnitus, hearing loss

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

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

**Hepatobiliary disorders**: hepatitis, cholestasis, hepatic failure

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

**Musculoskeletal disorders:**
Frequency not known: Immune-mediated necrotizing myopathy

**Musculoskeletal and connective tissue disorders**: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain, neck pain, muscle fatigue, myopathy, myositis, rhabdomyolysis, muscle rupture, tendonopathy, sometimes complicated by rupture, lupus-like

syndrome

**Reproductive system and breast disorders**: gynecomastia

**General disorders and administration site conditions**: asthenia, malaise, chest pain, peripheral oedema, fatigue, pyrexia.

**Investigations**: liver function test abnormal, blood creatine kinase increased, white blood cells urine positive.

Elevated serum ALT levels have been reported. Elevations in serum ALT levels are dose related and reversible. Elevated serum CPK levels (>3 times upper normal limit) have been reported.

***Pediatric Patients***
Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences reported in both groups, regardless of causality assessment, were infections.

No clinically significant effect on growth and sexual maturation was reported in a 3-year study in children ages 6 and above based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight. The safety and tolerability profile in pediatric patients was similar to the known safety profile of atorvastatin in adult patients.

**OVERDOSAGE**
There is no specific treatment for atorvastatin over dosage. In the event of an overdose, 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, hemodialysis is not expected to significantly enhance atorvastatin clearance.

**STORAGE**
Store below 30°C, protect from moisture

**SHELF LIFE**: 36 Months

**KEEP ALL MEDICINES OUT OF REACH OF CHILDREN**

**PACKING**
Blister strips of 3 x 10's, 6 x 10's and 10 x 10's

**Manufactured by/Product Registration Holder:**
**RANBAXY (MALAYSIA) SDN. BHD.**
Lot 23, Bakar Arang Industrial Estate,
08000 Sungai Petani, Kedah,
Malaysia

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