Generic Name: Atorvastatin
Trade Name: Lipitor
CDS Effective Date: December 15, 2020
Supersedes: January 24, 2020

DESCRIPTION

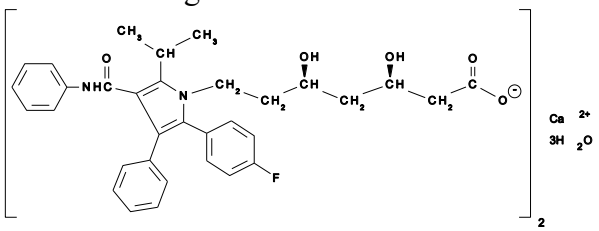
Atorvastatin tablets for oral administration contain 10 mg, 20 mg, 40 mg and 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, polysorbate 80, hydroxypropyl cellulose, magnesium stearate, Opadry White YS-1-7040, Antifoam AF Emulsion Medical.

PHARMACOLOGICAL PROPERTIES

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 that converts HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. In patients with homozygous and heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, and mixed dyslipidemia, atorvastatin reduces total-C (total cholesterol), LDL-C (low-density lipoprotein cholesterol), and apo B (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).

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 (see section **Posology and Method of Administration**).

In a dose-response study, atorvastatin, (10 mg-80 mg) reduced total-C (30%-46%), LDL-C (41%-61%), apo B (34%-50%), and TG (14%-33%). These results are consistent in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, and mixed hyperlipidemia, including patients with non-insulin-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 intermediate density lipoprotein cholesterol (IDL-C).

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 mg-80 mg) were 5.1% to 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 (MI). 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 mg/dL, 147 mg/dL, 48 mg/dL, 139 mg/dL, respectively, in the atorvastatin group, and 135 mg/dL, 217 mg/dL, 46 mg/dL, 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.

Prevention of Cardiovascular Complications

In the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), the effect of atorvastatin on fatal and non-fatal coronary heart disease (CHD) was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean age 63 years), without a previous MI and with total-C levels <6.5 mmol/L (251 mg/dL). Additionally all patients had at least three of the following cardiovascular (CV) risk factors: male gender, age >55 years, smoking, diabetes, history of CHD in a first-degree relative, total-C: HDL >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific electrocardiogram (ECG) abnormality, proteinuria/albuminuria. In this double-blind, placebo-controlled study, patients were treated with antihypertensive therapy (goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137). 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 significantly reduced the rate of the following events:

Event	**Risk Decrease (%)**	**No. of Events (Atorvastatin vs. Placebo)**	**p-value**
Coronary events (fatal CHD[a] plus non-fatal MI[b])	36%	100 vs. 154	0.0005
Total cardiovascular events and revascularization procedures	20%	389 vs. 483	0.0008
Total coronary events	29%	178 vs. 247	0.0006

Fatal and non-fatal stroke*	26%	89 vs. 119	0.0332

[a] Coronary Heart Disease.
[b] Myocardial infarction.
* 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.

The total mortality and CV mortality have not been significantly reduced although a favorable trend was observed.

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on fatal and non-fatal cardiovascular disease (CVD) was assessed in 2838 patients with type 2 diabetes 40 to 75 years of age, without prior history of CVD and with LDL ≤4.14 mmol/L (160 mg/dL) and TG ≤6.78 mmol/L (600 mg/dL). Additionally, all patients had at least one of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

In this randomized, double-blind, multicenter, placebo-controlled trial, patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) 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 effects of atorvastatin are as follows:

Event	**Relative Risk Reduction (%)**	**No. of Events (atorvastatin vs. placebo)**	**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	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs. 64	0.0070
Stroke (fatal and non-fatal)	48%	21 vs. 39	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 compared to 61 deaths in the treatment arm) 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.

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 to 17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia 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 familial hypercholesterolemia or documented premature CVD 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 the 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 78 (55.7%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, TG, and apo B during the 26-week double-blind phase (see Table 1).

Table 1. 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

Total-C=total cholesterol; LDL-C=low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol; TG=triglycerides

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.

Pharmacokinetic Properties

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within one to two hours. The extent of absorption increases in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by 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 to morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see section **Posology and Method of Administration**).

Distribution: Mean volume of distribution of atorvastatin is approximately 381 Liters. Atorvastatin is ≥98% bound to plasma proteins. A red 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 (see section **Contraindications**, and section **Fertility, Pregnancy and Lactation**).

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by hepatic CYP 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 CYP 3A4. Atorvastatin co-administration did not produce a clinically significant effect in plasma concentrations of terfenadine, a compound predominantly metabolized by CYP 3A4; therefore, it is unlikely that atorvastatin will significantly alter the pharmacokinetics of other CYP 3A4 substrates (see section **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 extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters MDR1 and BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

Special Populations

Elderly - Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy, elderly subjects (age ≥65 years) than in young adults. The ACCESS study specifically evaluated elderly patients with respect to reaching their National Cholesterol Education Program (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 studies have not been conducted in the pediatric population.

Gender - Plasma concentrations of atorvastatin in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men. However, there were no clinically significant differences in lipid effects between men and women.

Renal Insufficiency - Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin. Thus, dose adjustment in patients with renal dysfunction is not necessary (see section **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 are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh Class B) (see section **Contraindications**). C_{max} and AUC are each 4-fold greater in patients with Child-Pugh Class A disease.

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 **Special Warnings and Precautions for Use**, and section **Interaction with Other Medicinal Products and Other Forms of Interaction).**

Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered Drug and Dosing Regimen	**Atorvastatin**		
	Dose (mg)	**Ratio of AUC[&]**	**Ratio of**

Co-administered Drug and Dosing Regimen	Atorvastatin		
			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	10 mg QD[a] for 7 days	8.3	22.0
[#] Telaprevir 750 mg q8h[f], 10 days	20 mg, SD	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 QD[a], 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, 10 days[a]	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

Co-administered Drug and Dosing Regimen	Atorvastatin		
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], 2 weeks	10 mg QD[a] for 2 weeks	1.00	0.89
Colestipol 10 g BID[b], 24 weeks	40 mg QD[a] for 8 weeks	NA	0.74**
Maalox TC® 30 mL QID[e], 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 (co-administered)†	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 section **Special Warnings and Precautions for Use** and section **Interaction with Other Medicinal Products and Other Forms of Interaction** for clinical significance.
* 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 L/day).
** Ratio based on a 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
[d] Three times daily
[e] Four times daily
[f] Every 8 hours

Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered Drug and Dosing Regimen		
	Drug/Dose (mg)	Ratio of AUC&	Ratio of

			C_{max}[&]
80 mg QD[a] for 15 days	Antipyrine, 600 mg SD[c]	1.03	0.89
80 mg QD[a] for 14 days	Digoxin 0.25 mg QD[a], 20 days[#]	1.15	1.20
40 mg QD[a] for 22 days	Oral contraceptive QD[a], 2 months - Norethindrone 1 mg - Ethinyl estradiol 35 µg	 1.28 1.19	 1.23 1.30
10 mg SD[c]	Tipranavir 500 mg BID[b]/ritonavir 200 mg BID[b], 7 days	1.08	0.96
10 mg QD[a] 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, 14 days	0.99	0.94

[&] Represents ratio treatment (co-administered drug plus atorvastatin vs. atorvastatin alone)
[#] See section **Interaction with Other Medicinal Products and Other Forms of Interaction** for clinical significance.
[a] Once daily
[b] Twice daily
[c] Single dose

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. In a 2-year study in mice, the 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 biggest human dose on a 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 four *in vitro* tests with and without metabolic activation or in one *in vivo* assay. It was negative in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, and *in vitro*

hypoxanthine-guanine phosphoribosyltransferase (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 mg/kg, 40 mg/kg, or 120 mg/kg for 2 years.

CLINICAL PARTICULARS

Therapeutic Indications

Atorvastatin is indicated as an adjunct to diet for the reduction of elevated total-C, LDL-C, apo B, and TG in patients with primary hypercholesterolemia, combined (mixed) hyperlipidemia, and heterozygous and homozygous familial hypercholesterolemia when response to diet and other non pharmacological measures are inadequate.

Prevention of Cardiovascular Complications
In patients with hypertension (40 years or older) and dyslipidemia with at least 3 risk factors for future cardiovascular events such as LVH, ECG abnormalities, NIDDM, peripheral vascular disease, post history of cerebrovascular events including transient ischemic attack (TIA) ≥3 months previously, microalbuminuria/proteinuria, smoking (regular smoker within the last year of 20 cigarettes or cigars/week), TC/HDL – C ratio ≥6, and history of coronary artery disease event in a first degree relative before age 55 (males) or 60 (women), atorvastatin is indicated to:
- Reduce the risk of fatal CHD and non-fatal MI
- Reduce the risk of stroke
- Reduce the risk of revascularization procedures and angina pectoris.

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.

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.

Special Warnings and Precautions for Use

Hepatic Effects - As with other lipid-lowering agents of the same class, moderate (>3 × 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 × 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 mg, 20 mg, 40 mg, and 80 mg doses, respectively. One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were 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. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of LIPITOR.

Liver function tests should be performed before the initiation of treatment and at 12 weeks following both the initiation therapy and any evaluation of dose, and periodically (semiannually) 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 × ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

Atorvastatin can cause an elevation in transaminases (see section **Undesirable Effects**).

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. (see section **Contraindications**.)

Skeletal Muscle Effects - Myalgia has been reported in atorvastatin-treated patients (see section **Undesirable Effects**). Myopathy, defined as muscle ache or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 × 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 is increased with concurrent administration of drugs that increase the systemic concentration of atorvastatin (see section **Interaction with Other Medicinal Products and Other Forms of Interaction** and section **Pharmacokinetic Properties**). 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 fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, HIV/HCV protease inhibitors, letermovir, HCV NS5A/NS5B inhibitors or lipid-lowering doses of niacin 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 (see section **Posology and Method of Administration**). The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin is advised during fusidic acid therapy (see section **Interaction with Other Medicinal Products and Other Forms of Interaction**).

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 section **Undesirable Effects**).

There have been rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins (see section **Undesirable Effects**). IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment, positive anti-HMG CoA reductase antibody and 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 post-hoc analysis of a clinical study in 4731 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 **Pharmacodynamic Properties**: **Recurrent Stroke**)

Information for the patient – Patient should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Adolescent females and women of childbearing potential should be counseled on appropriate contraceptive methods while on atorvastatin therapy (see section **Fertility**, **Pregnancy and Lactation**).

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.

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 cyclosporine, fibric acid derivatives, lipid-modifying doses of niacin or CYP 3A4/transporter inhibitors (e.g., erythromycin (see below), and azole antifungals) (see also section – **Special Warnings and Precautions for Use: Skeletal Muscle Effect**).

Inhibitors of CYP 3A4:

Atorvastatin is metabolized by CYP 3A4.

Concomitant administration of atorvastatin with inhibitors of CYP 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 CYP 3A4.

Erythromycin/Clarithromycin: Co-administration of atorvastatin with erythromycin (500 mg four times daily) or clarithromycin (500 mg twice daily), known inhibitors of CYP 3A4, was associated with higher plasma concentrations of atorvastatin (see section **Special Warnings and Precautions for Use: Skeletal Muscle Effects** and section **Pharmacokinetic Properties**).

Protease Inhibitors: Co-administration of atorvastatin with protease inhibitors, known inhibitors of CYP 3A4, was associated with increased plasma concentrations of atorvastatin. (see section **Pharmacokinetic Properties**).

Diltiazem Hydrochloride: Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin (see section **Pharmacokinetic Properties)**.

Cimetidine: An atorvastatin interaction study with cimetidine was conducted, and no clinically significant interactions were seen (see section **Pharmacokinetic Properties**).

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

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 L/day) (see section **Pharmacokinetic Properties**).

Transporter Inhibitors:

Atorvastatin is a substrate of the hepatic transporters (see section **Pharmacokinetic Properties**).

Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an increase in exposure to atorvastatin (ratio of AUC: 8.7; see section **Pharmacokinetic Properties**). 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. Do not exceed 10 mg atorvastatin daily (see section **Posology and Method of Administration: Use in Combination with Other Medicinal Compounds**).

Glecaprevir and pibrentasvir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Co-administration of glecaprevir/pibrentasvir is not recommended. (see section **Posology and Method of Administration: Use in Combination with Other Medicinal Compounds**).

Concomitant administration of atorvastatin 20 mg and letermovir 480 mg daily resulted in an increase in exposure to atorvastatin (ratio of AUC: 3.29; see section **Pharmacokinetic Properties**). 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 (see section **Posology and Method of Administration: Use in Combination with Other Medicinal Compounds**).

The magnitude of CYP 3A4 and OATP1B1/1B3-mediated drug interactions on co-administered drugs may be different when letermovir is co-administered with cyclosporine. Use of atorvastatin is not recommended 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 (see section **Posology and Method of Administration: Use in Combination with Other Medicinal Compounds**).

Inducers of CYP 3A4:

Concomitant administration of atorvastatin with inducers of CYP 3A4 (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 (see section **Pharmacokinetic Properties**).

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 co-administered 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: An atorvastatin interaction studies with warfarin was conducted, and no clinically significant interactions were seen.

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.

Amlodipine: In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg with amlodipine 10 mg resulted in an increase in exposure to atorvastatin (ratio of AUC: 1.18) which was not clinically meaningful.

Fusidic Acid: Although interaction studies with atorvastatin and fusidic acid have not been conducted, 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.

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 specific agents have not been conducted.

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

Fertility, Pregnancy and Lactation

Atorvastatin is contraindicated in pregnancy. Women of childbearing potential should use 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. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient appraised of the potential hazard to the fetus.

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women, therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers.

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

Effects on Ability to Drive and Use Machine

None known

Undesirable Effects

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. Less than 2% of patients were discontinued from clinical trials due to side effects attributed to atorvastatin. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of patients on placebo.

The most frequent (≥1%) adverse effects associated with atorvastatin therapy, reported in patients participating in placebo-controlled clinical studies were:

Infections and Infestations: nasopharyngitis

Respiratory, Thoracic and Mediastinal Disorders: pharyngolaryngeal pain, epistaxis

Psychiatric Disorders: insomnia, nightmare

Nervous System Disorders: headache

Gastrointestinal Disorders: nausea, diarrhea, abdominal pain, dyspepsia, constipation, flatulence

Musculoskeletal and Connective Tissue Disorders: myalgia, arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, joint swelling

Investigations: liver function test abnormal, blood creatine phosphokinase increased

General Disorders and Administration Site Conditions: asthenia

The following additional adverse effects have been reported in atorvastatin clinical trials:

Eye Disorders: vision blurred

Metabolism and Nutrition Disorders: hypoglycaemia, hyperglycemia, anorexia

Nervous System Disorders: peripheral neuropathy, paresthesia

Ear and Labyrinth Disorders: tinnitus

Gastrointestinal Disorders: pancreatitis, vomiting, abdominal discomfort, eructation

Hepatobiliary Disorders: hepatitis, cholestatic jaundice

Skin and Subcutaneous Tissue Disorders: alopecia, pruritus, rash, urticaria

Musculoskeletal and Connective Tissue Disorders: myopathy, myositis, muscle cramps, muscle fatigue, neck pain

Reproductive System and Breast Disorders: impotence

General Disorders and Administration Site Conditions: angioneurotic edema, malaise, pyrexia

Cardiovascular: angina

Investigations: white blood cells urine positive

Not all effects listed above have been causally associated with atorvastatin therapy.

Pediatric Patients (aged 10-17 years)
Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections.

Post-marketing Experience

In post-marketing experience, the following additional undesirable effects have been reported:

Blood and Lymphatic System Disorders: thrombocytopenia;

Immune System Disorders: allergic reactions (including anaphylaxis);

Injury, Poisoning, and Procedural Complications: tendon rupture;

Metabolism and Nutrition Disorders: weight gain;

Nervous System Disorders: hypoesthesia, amnesia, dizziness, dysgeusia;

Gastrointestinal Disorders: pancreatitis;

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, erythema multiforme, bullous rashes;

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, immune mediated necrotizing myopathy, myositis, back pain;

General Disorders and Administration Site Conditions: chest pain, peripheral edema, fatigue.

Reporting of Suspected Adverse Events
Reporting suspected adverse events after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacovigilance Center/National MESO at e-meso.pom.go.id, and/or to pv@dexagroup.com and pharmacovigilance.id@aurobindo.com.

Overdose

There is no specific treatment for atorvastatin overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

Posology and Method of 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 the underlying medical problems. The patient should continue

on a standard cholesterol-lowering diet during treatment with atorvastatin. The usual starting dose is 10 mg once a day. The dosage range is 10 mg 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 goal 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 daily. A therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 4 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 atorvastatin.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age) - The recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see section **Therapeutic Indications**, and section **Pharmacodynamic Properties**). Adjustments should be made at intervals of 4 weeks or more.

Use in Patients with Hepatic Insufficiency – (see section **Contraindications** and section **Special Warnings and Precautions for Use**).

Use in Patients with Renal Insufficiency – Renal disease has no influence on plasma concentrations or on the LDL-C reduction of atorvastatin. Thus, no dose adjustment is required (see section **Special Warnings and Precautions for Use**).

Use in Children – 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.

Use in Elderly – No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population (see section – **Pharmacokinetic Properties: Special Populations**).

Use in Combination with Other Medicinal Compounds – In cases where co-administration of atorvastatin with cyclosporine, telaprevir, or the combination tipranavir/ritonavir is necessary, the dose of atorvastatin should not exceed 10 mg.

Use of atorvastatin is not recommended in patients taking letermovir co-administered with cyclosporine.

Pharmacokinetic drug interactions that result in increased systemic concentration of atorvastatin have also been noted with other human immunodeficiency virus (HIV) protease inhibitors (lopinavir/ritonavir, saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir, fosamprenavir/ritonavir and nelfinavir), hepatitis C (HCV) protease inhibitors (boceprevir, elbasvir/grazoprevir, simeprevir), clarithromycin, itraconazole, and letermovir. Caution should be used when co-prescribing atorvastatin, and appropriate clinical assessment is recommended to ensure that the lowest dose of atorvastatin necessary is employed (see section **Special Warnings and Precautions for Use – Skeletal Muscle Effects** and section **Interaction with Other Medicinal Products and Other Forms of Interaction - Transporter Inhibitors**).

PHARMACEUTICAL PARTICULARS

How Supplied

Lipitor 10 mg Film-Coated Tablets are white round shape. They are marked with “10” on one side and “ATV” on the other side; Box of 3 blisters @ 10 tablets; Reg. No. DKIxxxxxxxxxxx
Lipitor 10 mg Film-Coated Tablets are white round shape. They are marked with “10” on one side and “ATV” on the other side; Box of 9 blisters @ 10 tablets; Reg. No. DKIxxxxxxxxxxx
Lipitor 20 mg Film-Coated Tablets are white round shape. They are marked with “20” on one side and “ATV” on the other side; Box of 3 blisters @ 10 tablets; Reg. No. DKIxxxxxxxxxxx
Lipitor 20 mg Film-Coated Tablets are white round shape. They are marked with “20” on one side and “ATV” on the other side; Box of 9 blisters @ 10 tablets; Reg. No. DKIxxxxxxxxxxx
Lipitor 40 mg Film-Coated Tablets are white round shape. They are marked with “40” on one side and “ATV” on the other side; Box of 3 blisters @ 10 tablets; Reg. No. DKIxxxxxxxxxxx
Lipitor 40 mg Film-Coated Tablets are white round shape. They are marked with “40” on one side and “ATV” on the other side; Box of 9 blisters @ 10 tablets; Reg. No. DKIxxxxxxxxxxx
Lipitor 80 mg Film-Coated Tablets are white round shape. They are marked with “80” on one side and “ATV” on the other side; Box of 3 blisters @ 10 tablets; Reg. No. DKIxxxxxxxxxxx
Lipitor 80 mg Film-Coated Tablets are white round shape. They are marked with “80” on one side and “ATV” on the other side; Box of 9 blisters @ 10 tablets; Reg. No. DKIxxxxxxxxxxx

Storage

Store below 30°C.

Lipitor 10 mg; 20 mg; 40 mg; 80 mg Tablet:

Manufactured by:
Viatris Pharmaceuticals LLC, Vega Baja, Puerto Rico, AS

Packed and Released by:
Pfizer Manufacturing Deutschland GmbH, Freiburg, Germany

Secondary packed by:
PT Pfizer Indonesia, Jakarta-Indonesia

Registered by:
PT Fonko International Pharmaceuticals, Bekasi, Indonesia

Marketed by:
PT Aurogen Pharma Indonesia, Jakarta, Indonesia

HARUS DENGAN RESEP DOKTER
On Medical Prescription Only

DISETUJUI OLEH BPOM: 14/07/2025

ID REG: EREG100241VR12400119; EREG100241VR12400121;
EREG100241VR12400124; EREG100241VR12400125;
EREG100241VR12400127; EREG100241VR12400128;
EREG100241VR12400196; EREG100241VR12400197

Brosur kemasan: Informasi bagi pengguna

LIPITOR® 10 mg tablet salut selaput
LIPITOR® 20 mg tablet salut selaput
LIPITOR® 40 mg tablet salut selaput
LIPITOR® 80 mg tablet salut selaput

Atorvastatin

Baca seluruh bagian brosur ini dengan saksama sebelum Anda mulai meminum obat ini karena brosur ini berisi informasi penting untuk Anda.

- Simpanlah brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, bertanyalah kepada dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan berikan kepada orang lain. Obat ini dapat membahayakan mereka, sekali pun gejala-gejala penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Ini termasuk segala bentuk efek samping yang tidak tercantum pada brosur ini. Lihat bagian 4.

Isi brosur ini

1. Apa itu Lipitor dan apa kegunaannya

Lipitor tergolong dalam kelompok obat yang dikenal sebagai statin, yang merupakan obat pengontrol lipid (lemak).

Lipitor digunakan untuk menurunkan kadar lipid yang dikenal dengan istilah kolesterol dan trigliserida dalam darah jika diet rendah lemak serta perubahan gaya hidup gagal menurunkannya. Jika Anda berisiko tinggi terkena penyakit jantung, maka Lipitor juga dapat digunakan untuk menurunkan risiko tersebut sekali pun kadar kolesterol Anda normal. Anda harus mempertahankan diet standar untuk menurunkan kolesterol selama pengobatan berlangsung.

2. Apa yang perlu Anda ketahui sebelum meminum Lipitor

Jangan meminum Lipitor:
- jika Anda alergi terhadap atorvastatin atau bahan lainnya dalam obat ini (tercantum di bagian 6)
- jika Anda mengidap atau pernah mengidap penyakit yang memengaruhi hati
- jika Anda pernah memperoleh hasil tes darah abnormal untuk fungsi hati yang tidak dapat dijelaskan
- jika Anda adalah perempuan yang dapat hamil dan tidak menggunakan alat kontrasepsi yang andal
- jika Anda sedang hamil atau berusaha untuk hamil
- jika Anda sedang menyusui

Peringatan dan langkah-langkah pencegahan

Konsultasikan dengan dokter, apoteker, atau perawat Anda sebelum meminum Lipitor:
- jika Anda mengalami gagal napas parah
- jika Anda sedang meminum atau dalam 7 hari terakhir telah meminum obat bernama asam fusidat (obat untuk infeksi bakteri) baik secara oral atau melalui injeksi. Kombinasi asam fusidat dan Lipitor dapat menyebabkan gangguan otot serius (rabdomiolisis)
- jika sebelumnya Anda pernah mengalami stroke dengan perdarahan di otak, atau memiliki kantong kecil berisi cairan di otak akibat serangan stroke sebelumnya
- jika Anda memiliki gangguan ginjal
- jika kelenjar tiroid Anda kurang aktif (hipotiroidisme)
- jika Anda mengalami nyeri atau rasa sakit pada otot yang berulang atau tidak dapat dijelaskan, serta memiliki masalah otot dalam riwayat diri atau riwayat keluarga
- jika sebelumnya Anda pernah mengalami masalah otot selama pengobatan dengan obat penurun lipid lainnya (misalnya obat '-statin' atau '-fibrat' lain)
- jika Anda meminum alkohol dalam jumlah besar secara rutin
- jika Anda memiliki riwayat penyakit hati
- jika Anda berusia lebih dari 65 tahun

Jika salah satu hal di atas berlaku bagi Anda, dokter perlu melakukan tes darah sebelum dan mungkin selama Anda menjalani pengobatan dengan Lipitor untuk memprediksi risiko efek samping yang terkait dengan otot. Risiko efek samping yang terkait dengan otot, misalnya rabdomiolisis, diketahui dapat meningkat jika obat-obatan tertentu diminum secara bersamaan (lihat bagian 2 "Obat-obatan lain dan Lipitor").

Beritahukan pula kepada dokter atau apoteker jika Anda mengalami kelemahan otot yang terus menerus. Mungkin diperlukan tes dan obat-obatan tambahan untuk mendiagnosis dan mengobati gangguan ini.
Selama meminum obat ini, dokter akan memantau Anda dengan saksama untuk melihat apakah Anda mengalami hiperglikemia atau berisiko mengalami hiperglikemia.

Obat-obatan lain dan Lipitor
Beritahukan dokter atau apoteker Anda jika Anda sedang menggunakan, baru saja menggunakan atau mungkin akan menggunakan obat lain. Terdapat sejumlah obat yang dapat mengubah efek Lipitor atau sebaliknya efek obat itu dapat diubah oleh Lipitor. Jenis interaksi ini dapat menyebabkan salah satu atau kedua obat menjadi kurang efektif. Kemungkinan lain, interaksi ini juga dapat meningkatkan risiko atau tingkat keparahan efek samping, termasuk kondisi melemahnya otot yang signifikan yang dikenal dengan istilah rabdomiolisis sebagaimana dijelaskan dalam bagian 4:
- Obat-obatan yang digunakan untuk mengubah cara kerja sistem kekebalan tubuh Anda, misalnya siklosporin
- Obat-obatan antibiotik atau antijamur tertentu, misalnya eritromisin, klaritromisin, ketokonazol, itrakonazol, rifampin, asam fusidat
- Obat-obatan lain untuk mengontrol kadar lipid, misalnya kolestipol
- Beberapa pemblokir saluran kalsium yang digunakan untuk angina atau tekanan darah tinggi, misalnya amlodipin, diltiazem, obat-obatan untuk mengatur ritme jantung Anda, misalnya digoksin
- Letermovir
- Obat-obatan lain yang diketahui dapat berinteraksi dengan Lipitor, termasuk warfarin (yang mengurangi pembekuan darah), pil kontrasepsi, simetidin (digunakan untuk nyeri ulu hati dan tukak lambung), antasida (produk gangguan pencernaan yang mengandung aluminium atau magnesium), antipirin, kolestipol, dan efavirenz
- Obat-obatan yang diperoleh tanpa resep: St John's Wort
- Jika Anda perlu meminum asam fusidat untuk mengobati infeksi bakteri, maka Anda perlu menghentikan penggunaan obat ini untuk sementara. Dokter akan memberi tahu Anda saat yang

aman untuk mulai meminum kembali Lipitor. Meminum Lipitor bersama asam fusidat dapat menyebabkan kelemahan otot, nyeri tekan, atau rasa sakit (rabdomiolisis) kendati hal ini langka. Lihat informasi selengkapnya mengenai rabdomiolisis di bagian 4.

– Obat-obatan yang digunakan untuk pengobatan hepatitis C, misalnya boceprevir, simpeprevir dan kombinasi elbasvir/grazoprevir atau glecaprevir/pibrentasvir, inhibitor HCV NS5A/NS5B.
– Obat-obatan yang digunakan untuk pengobatan HIV, misalnya lopinavir/ritonavir, saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir, fosamprenavir/ritonavir dan nelfinavir.

Lipitor dengan makanan dan minuman
Lihat bagian 3 untuk petunjuk mengenai cara meminum Lipitor. Perhatikan catatan berikut ini:

Jus buah Grapefruit
Jangan meminum lebih dari satu atau dua gelas kecil jus buah *grapefruit* per hari karena jus buah *grapefruit* dalam jumlah banyak dapat mengubah efek dari Lipitor.

Alkohol
Hindari meminum terlalu banyak alkohol selama menggunakan obat ini. Lihat bagian 2 “Peringatan dan tindakan pencegahan” untuk informasi selengkapnya.

Kehamilan dan menyusui
Jangan meminum Lipitor jika Anda sedang hamil, atau berusaha untuk hamil.
Jangan meminum Lipitor jika Anda berpotensi untuk hamil kecuali Anda menggunakan metode kontrasepsi yang andal.
Jangan meminum Lipitor jika Anda sedang menyusui.
Keamanan penggunaan Lipitor selama kehamilan dan menyusui belum dibuktikan. Mintalah saran dari dokter atau apoteker Anda sebelum meminum obat apa pun.

Mengemudi dan menjalankan mesin
Normalnya obat ini tidak memengaruhi kemampuan Anda untuk mengemudi atau mengoperasikan mesin. Namun, jangan mengemudi jika obat ini memengaruhi kemampuan Anda untuk mengemudi. Jangan gunakan perkakas atau mesin jika kemampuan Anda untuk mengoperasikannya terpengaruh oleh obat ini.

Lipitor mengandung laktosa
Jika Anda telah diberi tahu oleh dokter bahwa Anda memiliki intoleransi terhadap beberapa jenis gula, hubungi dokter sebelum meminum produk obat ini.

3. Cara meminum Lipitor

Sebelum memulai pengobatan, dokter akan meminta Anda menjalani diet rendah kolesterol, yang juga harus Anda pertahankan selama terapi dengan Lipitor.

Dosis awal Lipitor pada umumnya adalah 10 mg satu kali sehari pada orang dewasa dan anak-anak berusia 10 tahun atau lebih. Bila perlu, dosis ini dapat ditingkatkan oleh dokter Anda sampai Anda mendapatkan dosis yang dibutuhkan. Dokter akan menyesuaikan dosis dalam interval 2-4 minggu atau lebih, berdasarkan hasil analisis kadar lemak. Dosis maksimum Lipitor adalah 80 mg satu kali sehari.

Tablet Lipitor harus ditelan utuh bersama air, dan dapat diminum kapan saja, setelah atau sebelum makan. Namun, cobalah untuk meminum tablet Anda pada waktu yang sama setiap hari.

Selalu minum obat ini dengan tepat sesuai anjuran dokter atau apoteker Anda. Tanyakan kepada dokter atau apoteker jika Anda merasa tidak yakin.

Durasi pengobatan dengan Lipitor ditentukan oleh dokter Anda.
Konsultasikan dengan dokter jika Anda merasa efek Lipitor tidak sesuai harapan anda (terlalu kuat atau terlalu lemah).

Jika Anda meminum Lipitor melebihi yang seharusnya
Jika Anda tanpa sengaja meminum terlalu banyak tablet Lipitor (melebihi dosis harian Anda), hubungi dokter atau rumah sakit terdekat untuk meminta saran.

Jika Anda lupa meminum Lipitor
Jika Anda lupa meminum satu dosis Lipitor, cukup minum dosis yang dijadwalkan berikutnya pada waktu yang tepat. Jangan meminum dosis ganda untuk menggantikan dosis yang terlupa.

Jika Anda berhenti meminum Lipitor
Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini atau bermaksud menghentikan pengobatan Anda, berkonsultasilah dengan dokter atau apoteker.

4. Kemungkinan efek samping

Seperti halnya obat-obatan lainnya, obat ini dapat menimbulkan efek samping kendati tidak semua orang mengalaminya.

Jika Anda mengalami efek samping serius mana pun berikut ini, hentikan minum tablet Anda dan berkonsultasilah segera dengan dokter Anda atau kunjungi unit gawat darurat di rumah sakit terdekat.

– Reaksi alergi serius yang menyebabkan pembengkakan wajah, lidah, dan tenggorok sehingga sangat menyulitkan Anda untuk bernapas.
– Penyakit serius dengan pengelupasan dan pembengkakan parah pada kulit, lepuh pada kulit, mulut, mata, alat kelamin, serta demam. Ruam kulit dengan bercak kemerahan khususnya pada telapak tangan atau telapak kaki yang dapat melepuh.
– Kelemahan otot, nyeri tekan, atau rasa sakit dan khususnya, jika pada saat yang sama Anda merasa tidak sehat atau suhu tubuh Anda tinggi, bisa jadi disebabkan oleh kerusakan otot abnormal (rabdomiolisis). Kerusakan otot abnormal tidak selalu langsung hilang sekali pun Anda menghentikan meminum atorvastatin, dan kondisi ini dapat mengancam jiwa serta menyebabkan gangguan ginjal.
– Jika Anda mengalami masalah berupa perdarahan atau memar yang tidak diduga atau tidak biasa, maka hal ini dapat menunjukkan adanya gangguan hati. Anda harus berkonsultasi dengan dokter sesegera mungkin.

Efek samping lainnya yang mungkin terjadi saat menggunakan Lipitor

Efek samping paling sering (≥1%) yang dikaitkan dengan terapi atorvastatin, pada pasien yang berpartisipasi dalam penelitian klinis terkontrol adalah:

- susah tidur
- sakit kepala
- mual, diare, sakit perut, dispepsia, sembelit, kembung
- nyeri sendi, nyeri otot
- astenia
- nasofaringitis
- nyeri pada pharyngolaryngeal (tenggorokan dan pita suara), mimisan (epistaksis)
- kejang otot, pembengkakan sendi
- tes fungsi hati abnormal, kreatinin fosfokinase darah meningkat

Efek samping tambahan berikut ini telah dilaporkan dalam uji klinis atorvastatin:

- penurunan kadar gula darah (jika Anda mengidap diabetes Anda harus terus memantau kadar gula darah Anda dengan cermat), peningkatan kadar gula darah (jika Anda mengidap diabetes Anda harus terus memantau kadar gula darah Anda dengan cermat), anoreksia (kehilangan selera makan)
- neuropati perifer, parestesia
- telinga dan/atau kepala berdenging
- pankreatitis (peradangan pankreas yang menyebabkan sakit perut), muntah, perut terasa tidak nyaman, sering bersendawa
- hepatitis (peradangan hati), kolestasis (menguningnya kulit dan bagian putih pada mata)
- kerontokan rambut, ruam kulit dan gatal-gatal, ruam, kaligata
- miopati, miositis, kram otot, sakit leher
- impotensi
- edema angioneurotik, malaise
- angina
- mimpi buruk
- penglihatan kabur
- demam
- sel darah putih urine positif

Pada kejadian pasca pemasaran, dilaporkan adanya tambahan efek yang tidak diinginkan sebagai berikut:

- trombositopenia
- reaksi alergi - gejala-gejalanya meliputi mengi dan nyeri dada atau rasa sesak yang tiba-tiba, pembengkakan kelopak mata, wajah, bibir, mulut, lidah, atau tenggorok, kesulitan bernapas, pingsan
- cedera tendon
- kenaikan berat badan
- penurunan sensasi terhadap rasa sakit atau sentuhan, menurunnya memori, pening, perubahan indra pengecap
- telinga dan/atau kepala berdenging
- Sindrom Stevens-Johnson, nekrolisis epiderma toksik, eritema multiformis, ruam bulosa
- rabdomiolisis, sakit punggung, miopati nekrosis dengan perantara imun, miositis
- nyeri dada, pembengkakan khususnya di pergelangan kaki (edema), kelelahan
- pankreatitis

Pelaporan efek samping

Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Hal ini meliputi segala bentuk kemungkinan efek samping yang tidak dicantumkan pada brosur ini. Anda dapat melaporkan efek smping tersebut melalui pv@dexagroup.com dan pharmacovogilance.id@aurobindo.com. Dengan melaporkan efek samping, Anda dapat membantu memberikan lebih banyak informasi perihal keamanan obat ini.

5. Cara menyimpan Lipitor

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah melewati tanggal kedaluwarsanya yang tercantum di wadah atau kemasan luar. Tanggal kedaluwarsa mengacu pada hari terakhir dari bulan yang tertera.

Simpan pada suhu di bawah 30 °C.

Jangan membuang obat melalui saluran pembuangan air atau bersama sampah rumah tangga. Tanyakan kepada apoteker Anda mengenai cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Apa kandungan Lipitor

– Zat aktifnya adalah atorvastatin.
Setiap tablet salut selaput mengandung 10 mg atorvastatin (dalam bentuk atorvastatin kalsium trihidrat).
Setiap tablet salut selaput mengandung 20 mg atorvastatin (dalam bentuk atorvastatin kalsium trihidrat).
Setiap tablet salut selaput mengandung 40 mg atorvastatin (dalam bentuk atorvastatin kalsium trihidrat).
Setiap tablet salut selaput mengandung 80 mg atorvastatin (dalam bentuk atorvastatin kalsium trihidrat).

– Bahan lainnya adalah:
kalsium karbonat, mikrokristalin selulosa, laktosa monohidrat, kroskarmelosa natrium, polisorbat 80, hidroksipropil selulosa, dan magnesium stearat.

Lapisan penyalut Lipitor mengandung hipromelosa, makrogol 8000, titanium dioksida (E171), talk, emulsi simetikon yang mengandung simetikon, pengemulsi stearat (polietilen glikol sorbitan tristearat, polietoksilat stearat, gliserida), pengental (metilselulosa, xanthan gum), asam benzoat, dan asam sorbat.

Seperti apa bentuk Lipitor beserta isi kemasannya

Lipitor 10 mg tablet salut selaput berbentuk bulat dengan warna putih. Tablet ditandai dengan 10 pada satu sisinya dan “ATV” di sisi sebaliknya. Reg. No. DKIxxxxxxxxxxx
Lipitor 20 mg tablet salut selaput berbentuk bulat dengan warna putih. Tablet ditandai dengan 20 pada satu sisinya dan “ATV” di sisi sebaliknya. Reg. No. DKIxxxxxxxxxxx
Lipitor 40 mg tablet salut selaput berbentuk bulat dengan warna putih. Tablet ditandai dengan 40 pada satu sisinya dan “ATV” di sisi sebaliknya. Reg. No. DKIxxxxxxxxxxx
Lipitor 80 mg tablet salut selaput berbentuk bulat dengan warna putih. Tablet ditandai dengan 80 pada satu sisinya dan “ATV” di sisi sebaliknya. Reg. No. DKIxxxxxxxxxxx

Kemasan blister terdiri atas cangkang depan yang terbuat dari poliamida/aluminium foil/polivinil klorida, dan bagian belakang yang terbuat dari aluminium foil/lapisan vinil yang disegel oleh panas.

Lipitor tablet salut selaput tersedia dalam kemasan blister yang berisi 30 dan 90 tablet salut selaput.

Tidak semua ukuran kemasan dapat ditemukan di pasaran.

Pemegang Izin Pemasaran dan Produksi

Diproduksi oleh:
Viatris Pharmaceuticals LLC, Vega Baja, Puerto Rico, AS

Diblister dan dirilis oleh:
Pfizer Manufacturing Deutschland GmbH, Freiburg, Jerman

Nama Generik: Atorvastatin
Nama Dagang: Lipitor
Tanggal Efektif DCS: 24 Januari 2020
Menggantikan: 1 Juni 2009
Disetujui oleh BPOM:

Dikemas sekunder oleh:
PT Pfizer Indonesia, Jakarta, Indonesia

Didaftarkan oleh:
PT Fonko International Pharmaceuticals, Bekasi, Indonesia

Dipasarkan oleh:
PT Aurogen Pharma Indonesia, Jakarta, Indonesia

HARUS DENGAN RESEP DOKTER