LORSTAT®

Atorvastatin (as calcium)

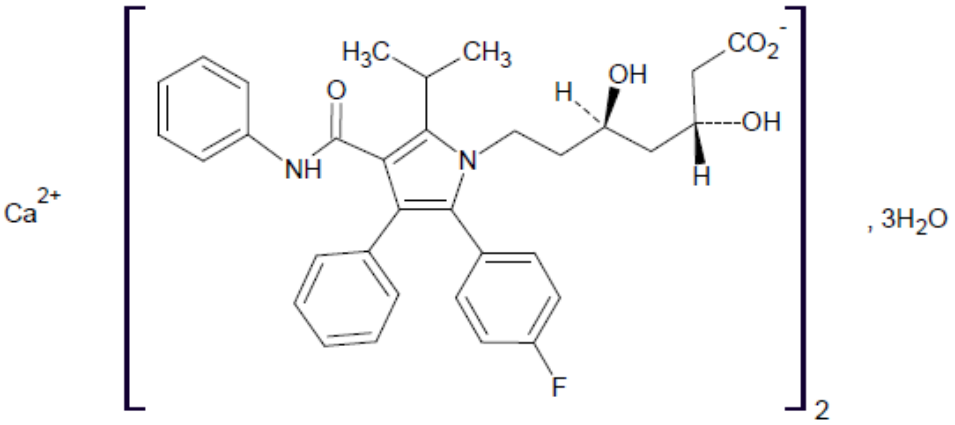
PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient of LORSTAT® tablets is atorvastatin calcium.

The chemical name for atorvastatin calcium is Calcium (3*R*,5*R*)-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4- (phenylcarbamoyl) -1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate trihydrate.

Structural formula:



Molecular formula: $C_{66}H_{68}CaF_2N_4O_{10},3H_2O$

Molecular weight: 1209

CAS Registry no.: 344423-98-9

DESCRIPTION

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

LORSTAT tablets contain atorvastatin calcium equivalent to 10 mg, 20 mg, 40 mg, and 80 mg atorvastatin. The tablets also contain the following inactive ingredients: colloidal anhydrous silica, sodium carbonate anhydrous, microcrystalline cellulose, arginine, lactose anhydrous, croscarmellose sodium, hydroxypropylcellulose, magnesium stearate and Opadry AMB white OY-B-28920 (Proprietary Ingredient ARTG no. 10274).

PHARMACOLOGY

Mechanism of Action

Atorvastatin is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. Low density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the high affinity LDL receptor.

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a marked and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles.

A variety of clinical and pathologic studies have demonstrated that elevated cholesterol and lipoprotein levels of total cholesterol (total-C), LDL-C and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease. Similarly, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

Atorvastatin reduces total-C, LDL-C, and apo B in both normal volunteers and in patients with homozygous and heterozygous familial hypercholesterolaemia (FH), non-familial forms of hypercholesterolaemia, and mixed dyslipidaemia. Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B and TG, and increases HDL-C in patients with isolated hypertriglyceridaemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinaemia. In animal models, atorvastatin limits the development of lipid-enriched atherosclerotic lesions and promotes the regression of pre-established atheroma.

Pharmacodynamics

Atorvastatin and its metabolites are responsible for pharmacological activity in humans. The liver is its primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dose rather than systemic drug concentration correlates better with LDL-C reduction. Individualisation of drug dose should be based on therapeutic response (see **DOSAGE AND ADMINISTRATION**).

Pharmacokinetics

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. A constant proportion of atorvastatin is absorbed intact. The absolute bioavailability is 14%. The low systemic availability is attributed to pre-systemic 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 with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see **DOSAGE AND ADMINISTRATION**).

Distribution

The mean volume of distribution of atorvastatin is about 400 litres. Atorvastatin is ≥98% bound to plasma proteins. A RBC/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 **PRECAUTIONS**).

Metabolism

In humans, atorvastatin is extensively metabolised to ortho- and para-hydroxylated derivatives. *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 cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme (see **PRECAUTIONS**). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Elimination

Atorvastatin is 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.

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. Lipid effects are comparable to that seen in younger patient populations given equal doses of atorvastatin.

Children and Adolescents: Pharmacokinetic studies have not been conducted in the paediatric 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 is no clinically significant difference in lipid effects with atorvastatin between men and women.

Renal impairment: 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 **PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

Haemodialysis: While studies have not been conducted in patients with end-stage renal disease, haemodialysis 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 C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B) (see **CONTRAINDICATIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS

In a multicentre, placebo-controlled, double blind dose-response study in patients with hypercholesterolaemia, atorvastatin was given as a single daily dose over 6 weeks. Atorvastatin (10-80 mg) reduced total-C (30%-46%), LDL-C (41%-61%), apolipoprotein B (34%-50%) and triglycerides (14%-33%) while producing variable increases in HDL-C and apolipoprotein A (TABLE 1). A therapeutic response was seen within 2 weeks, and maximum response achieved within 4 weeks.

Table 1. Dose-response in patients with primary hypercholesterolaemia[a]

Atorvastatin dose (mg)	N	Total-C	LDL-C	Apo B	TG	HDL-C
Placebo	12	4.8	7.6	5.8	-0.7	-2.5
10	11	-30.3	-41.0	-34.4	-14.2	4.5
20	10	-34.5	-44.3	-36.3	-33.2	12.1
40	11	-37.8	-49.7	-40.9	-24.9	-2.6
80	11	-45.7	-61.0	-50.3	-27.2	3.4

[a]Adjusted mean % change from baseline

In three further trials, 1148 patients with either heterozygous familial hypercholesterolaemia, non-familial forms of hypercholesterolaemia, or mixed dyslipidaemia were treated with atorvastatin for one year. The results were consistent with those of the dose response study and were maintained for the duration of therapy.

In patients with primary hypercholesterolaemia and mixed dyslipidaemia (Fredrickson Types IIa and IIb), data pooled from 24 controlled trials demonstrated that the adjusted mean percent increases from baseline in HDL-C for atorvastatin (10–80 mg) were 5.0 to 7.8% in a non-dose-related manner.

Clinical studies demonstrate that the starting dose of 10 mg atorvastatin is more effective than simvastatin 10 mg, and pravastatin 20 mg in reducing LDL-C, total-C, TG triglycerides and apo B. In several multicentre, double-

blind studies in patients with hypercholesterolaemia, atorvastatin was compared to other HMG-CoA reductase inhibitors. After randomisation, patients were treated with atorvastatin 10 mg per day or the recommended starting dose of the comparative agent. At week 16 a greater proportion of atorvastatin treated patients than those treated with simvastatin (46% vs 27%) or pravastatin (65% vs 19%) reached their target LDL-C levels. Increasing the dosage of atorvastatin resulted in more patients reaching target LDL-C goals.

Prevention of cardiovascular disease

In the lipid lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of the atorvastatin calcium tablets on the composite endpoint of fatal coronary heart disease and non-fatal myocardial infarction was assessed in 10,305 hypertensive patients, 40-79 years of age, without a history of symptomatic coronary heart disease and with TC levels ≤6.5 mmol/L. Additionally patients were at moderate risk of coronary heart disease, having at least 3 of the predefined cardiovascular risk factors [male gender (81%), age ≥55 years (84%), smoking (33%), non insulin dependent diabetes mellitus (25%), history of CHD in a first-degree relative (26%), plasma TC to HDL cholesterol ratio ≥6 (14%), peripheral vascular disease (5%), left ventricular hypertrophy on echocardiography (14%), past history of cerebrovascular event (10%), specific ECG abnormality (14%), proteinuria/albuminuria (62%)]. Patients with a history of previous myocardial infarction or angina were excluded.

In this randomised, double blind, placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/90 mmHg for non-diabetic patients, <130/80 mmHg for diabetic patients) and either atorvastatin calcium 10 mg tablets daily (n=5,168) or placebo (n=5,137) and followed for a median duration of 3.3 years. At baseline, in the atorvastatin group, 38 patients (0.7%) had total-C levels less than 3.5 mmol/L; 2340 patients (45.3%) had total-C levels greater than or equal to 3.5 mmol/L and less than 5.5 mmol/L; 2,304 patients (44.6%) had total -C levels greater than or equal to 5.5 mmol/L and less than 6.5 mmol/L; and 486 patients (9.4%) had total -C levels greater than or equal to 6.5 mmol/L. At baseline, 457 patients (9.8%) in the atorvastatin group had LDL-C levels less than or equal to 2.5 mmol/L; 1,731 patients (37%) had LDL-C greater than 2.5 mmol/L and less than 3.4 mmol/L; and 2,495 patients (53.3%) had LDL-C levels greater than or equal to 3.4 mmol/L. Median (25th & 75th percentile) changes from baseline after 1-year of atorvastatin treatment in total -C, LDL-C, TG and HDL-C were -1.40 mmol/L (-1.80, -0.90), -1.27 mmol/L (-1.66, -0.84), -0.20 mmol/L (-0.60, 0.10) and 0.00 mmol/L (-0.10, 0.10). Blood pressure control throughout the trial was similar in patients assigned to atorvastatin and placebo.

Table 2: Summary of risk reductions in primary prevention patients

Endpoint	Atorvastatin 10mg N (%)	Placebo N (%)	Absolute risk reduction[a] % (95% CI)	Number reeded to treat per year	Relative risk reduction % (95% CI)	P value
Primary Fatal CHD and nonfatal MI	100 (1.9)	154 (3.0)	1.07 (0.47 to 1.67)	310.5	36 (17 to 50)	0.0005
Secondary						
Total cardiovascular events including revascularisation procedures	389 (7.6)	483 (9.5)	1.9 (0.80 to 2.96)	176.0	20 (9 to 30)	0.0008
Total coronary events	178 (3.5)	247 (4.8)	1.4 (0.60 to 2.14)	241.9	29 (14 to 41)	0.0006
Fatal and nonfatal stroke[b]	89 (1.7)	119 (2.3)	0.6 (0.05 to 1.14)	555.2	26 (2 to 44)	0.0332
Non-fatal MO (excludes silent MI) and fatal CHD	86 (1.7)	137 (2.7)	1.0 (0.42 to 1.56)	329.1	38 (19 to 53)	0.0005

[a] Based on difference in crude events rates occurring over a median follow-up of 3.3 years.

[b] 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 primary endpoint examined in ASCOT was the rate of fatal coronary heart disease or non-fatal myocardial infarction over 3.3 years. These coronary events occurred in 1.9% of atorvastatin treated patients compared to 3% of placebo treated patients, a relative risk reduction of 36% (p = 0.0005) (Table 2). Although this difference was statistically significant for the whole trial population, this difference was not statistically significant in specified subgroups such as diabetes, patients with left ventricular hypertrophy (LVH), previous vascular disease or metabolic syndrome.

There was no statistically significant reduction in the rate of total mortality, cardiovascular mortality or heart failure in the atorvastatin treated group compared to placebo.

Non insulin dependent diabetes mellitus (NIDDM)

A 26 week randomised, double blind, comparator study in NIDDM subjects showed that atorvastatin is effective in dyslipidaemic patients with NIDDM. A 10 mg dose of atorvastatin produced a 34% reduction in LDL-cholesterol, 27% reduction in total cholesterol, a 24% reduction in triglycerides and a 12% rise in HDL cholesterol.

Homozygous familial hypercholesterolaemia

Atorvastatin has also been shown to reduce LDL-C in patients with homozygous familial hypercholesterolaemia (FH), a population that has not usually responded to other lipid-lowering medication. In an uncontrolled compassionate-use study, 29 patients aged 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of atorvastatin. The mean LDL reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range 7%-53%, median 24%). Five of the 29 patients had absent LDL-receptor function, three of whom responded to atorvastatin with a mean LDL-C reduction of 22%. Experience in paediatric patients has been limited to patients with homozygous FH.

Hypertriglyceridaemia

In patients with hypertriglyceridaemia (baseline TG ≥2.26 mmol/L and LDL-C <4.14 mmol/L) atorvastatin (10 to 80 mg) reduced serum triglycerides by 31% to 40%.

In patients with severe hypertriglyceridaemia (baseline TG >5.7 mmol/L), atorvastatin (10 to 80 mg) reduced serum triglycerides by 30% to 56%.

In a randomized, placebo-controlled, double blind, multicentre study in patients with hypertriglyceridaemia (TG ≥3.95 mmol/L, LDL-C ≤4.1 mmol/L), atorvastatin 20 mg/day and 80 mg/day produced significantly greater reductions in triglyceride levels than placebo (Table 3).

Table 3. Efficacy in patients with hypertriglyceridaemia[a]

Atorvastatin dose (mg)	N	TG	Total-C	LDL-C	VLDL-C	ApoB	HDL-C
Placebo	12	-5.3	+0.3	+1.4	-2.0	+2.7	+2.4
20	13	-33.6*	-33.1*	-31.1*	-46.0*	-32.7*	+10.6
80	11	-42.4-	-41.3*	-36.1*	-54.2*	-38.7*	+11.8*

[a] Adjusted mean % change from baseline
* significantly different from placebo, p<0.05

Dysbetalipoproteinaemia

In patients with dysbetalipoproteinaemia, atorvastatin (10 to 80 mg) reduced intermediate density lipoprotein (IDL-C) (range 28% to 52%) and IDL-C + VLDL-C (range 34% to 58%).

In an open-label, randomized, cross-over study in patients with dysbetalipoproteinaemia, treatment with atorvastatin 80 mg/day resulted in significantly greater mean percent decreases in IDL-C + VLDL-C, IDL-C,

total-C, VLDL-C and Apo B than either simvastatin 40 mg/day or gemfibrozil 1200 mg/day and significantly greater mean percent decreases in triglycerides than simvastatin 40 mg/day (**Table 4**).

Table 4. Efficacy in patients with dysbetalipoproteinaemia [a b]

Treatment	N	IDL-C + VLDL-C	IDL-C	Total-C	TG	VLDL-C	Apo B	HDL-C
Atorvastatin 10mg/day	15	-34	-28	-40	-40	-32	-47	+3
Atorvastatin 80mg/day	16	-58	-50	-57	-56	-59	-66	+13
Gemfibrozil 1200mg/day	15	-33*	-13*^	-34*	-52+	-35*	-53*	+11
Simvastatin 40mg/day	16	-28*	-27*	-41*	-36*	-26*	-52*	+1*

[a] Adjusted mean % change from baseline
[b] Comparisons other than atorvastatin 80 mg/day versus simvastatin 40 mg/day were ad hoc
* Significantly different from atorvastatin 80 mg/day, $p<0.05$
*^ Significantly different from atorvastatin 10 mg/day, $p<0.05$

INDICATIONS

LORSTAT is indicated as an adjunct to diet for the treatment of patients with hypercholesterolaemia.

Prior to initiating therapy with atorvastatin, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, and alcoholism) should be identified and treated.

LORSTAT is indicated in hypertensive patients with multiple risk factors for coronary heart disease (CHD) which may include diabetes, history of stroke or other cerebrovascular disease, peripheral vascular disease or existing asymptomatic CHD (see **CLINICAL TRIALS - Prevention of cardiovascular disease**) to reduce the risk of non-fatal myocardial infarction and non-fatal stroke.

These effects do not replace the need to independently control known causes of cardiovascular mortality and morbidity such as hypertension, diabetes and smoking.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see **PRECAUTIONS**).

Pregnancy and lactation (see **PRECAUTIONS**). Women of childbearing potential, unless on an effective contraceptive and highly unlikely to conceive.

Concomitant use with fusidic acid (see **PRECAUTIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Liver Dysfunction

As with other lipid-lowering agents of the same class, moderate (>3 x upper limit of normal [ULN]) elevations of serum transaminases have been reported following therapy with atorvastatin.

Persistent increases in serum transaminases >3 x ULN occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2, 0.2, 0.6, and 2.3% for 10, 20, 40, and 80 mg 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 increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 x ULN persist, reduction of dose or withdrawal of LORSTAT is recommended.

LORSTAT 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 **CONTRAINDICATIONS**).

Skeletal Muscle

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see **ADVERSE EFFECTS**). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine kinase (CK) values >10 x ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness and/or marked elevation of CK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LORSTAT therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, niacin, azole antifungals, colchicine, hepatitis C protease inhibitors (e.g. telaprevir, boceprevir) or the combination of tipranavir/ritonavir (see **INTERACTIONS WITH OTHER MEDICINES**). Physicians considering combined therapy with LORSTAT and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs 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 **DOSAGE AND ADMINISTRATION, Use in Combination with Other Medicinal Compounds**)

Atorvastatin must not be co-administered with fusidic acid. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving concomitant fusidic acid and statins (see **CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES**). In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of the fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

Periodic creatine kinase (CK) determinations may be considered in such situations, although there is no assurance that such monitoring will prevent the occurrence of severe myopathy (see **PRECAUTIONS**).

As with other drugs in this class, rhabdomyolysis with acute renal failure has 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. LORSTAT therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, (e.g. severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Haemorrhagic Stroke

A post-hoc analysis of a clinical study (SPARCL) in patients without known coronary heart disease who had a recent stroke or TIA, showed a higher incidence of haemorrhagic stroke in patients on atorvastatin 80 mg (55/2365, 2.3%) compared to placebo (33/2366, 1.4%), (p=0.02). Throughout the study, all cause mortality was

numerically higher in the atorvastatin arm than the placebo arm. At study end all cause mortality was 9.1% on atorvastatin vs. 8.9 % on placebo.

The increased risk of haemorrhagic stroke was observed in patients who entered the study with prior haemorrhagic stroke (15.6% for atorvastatin vs. 4.2 % for placebo, HR 4.06; 95% CI 0.84-19.57) or prior lacunar infarct (2.8% for atorvastatin vs. 0.6% for placebo, HR 4.99; 95%CI 1.71-14.61). All cause mortality was also increased in these patients with prior haemorrhagic stroke (15.6% for atorvastatin vs. 10.4% for placebo) or prior lacunar infarct (10.9% for atorvastatin vs. 9.1% for placebo). The potential risk of hemorrhagic stroke should be carefully considered before initiating treatment with atorvastatin in patients with recent (1-6 months) stroke or TIA.

In 68% of patients who entered the study with neither a haemorrhagic stroke nor lacunar infarct, the risk of haemorrhagic stroke on atorvastatin vs. placebo was 2% vs. 1.8 % (large vessel), 1.7% vs. 1.6 % (TIA), 1.6% vs. 1.7 % (unknown cause).

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically may blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration nor 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 pre-menopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with other drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone and cimetidine.

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

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see **ADVERSE EFFECTS**). 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.

Effects on Fertility

The effects of atorvastatin on spermatogenesis and human fertility have not been investigated in clinical studies. Dietary administration of 100 mg atorvastatin/kg/day to rats caused a decrease in spermatid concentration in the testes, a decrease in sperm motility and an increase in sperm abnormalities. Similar effects, however, were not observed in male rats dosed by gavage to 175 mg/kg/day (plasma AUC for HMG-CoA reductase inhibitory activity 14 times higher than in humans dosed at 80 mg/day) and male fertility was not affected in either study. No adverse effects on fertility or reproduction were observed in female rats given doses up to 225 mg/kg/day (plasma AUC for enzyme inhibitory activity 56 times higher than in humans dosed at 80 mg/day). Atorvastatin caused no adverse effects on sperm or semen parameters, or on reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for 2 years (Plasma AUC for enzyme inhibitory activity 13 times higher than in humans).

Use in Pregnancy (Category D)

The definition of Pregnancy Category D is drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Atorvastatin is contraindicated in pregnancy. 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 hypercholesterolaemia. Cholesterol and other products of cholesterol biosynthesis are essential components for foetal 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 foetal harm when administered to pregnant women. LORSTAT should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the foetus (see **CONTRAINDICATIONS**). Atorvastatin crosses the rat placenta and reaches a level in foetal liver equivalent to that in maternal plasma. Animal reproduction studies showed no evidence of teratogenic activity in rats or rabbits at oral doses up to 300 mg/kg/day and 100 mg/kg/day, respectively. Increased post-implantation loss, decreased foetal weight and increased skeletal variations were observed in rats dosed at 100–300 mg/kg/day and rabbits dosed at 50–100 mg/kg/day. In a peri/post natal study, rats dosed at 225 mg/kg/day showed an increased incidence of stillbirths, decreases in birthweight, an increased incidence of dilated renal pelvis, increased postnatal mortality, suppression of pup growth, retardation of physical development and abnormal behavioural development; some of these effects were also observed at the non-maternotoxic dose of 100 mg/kg/day; the plasma AUC for HMG-CoA reductase inhibitory activity at the no effect dose level of 20 mg/kg/day was similar to that in humans dosed at 80 mg/day.

HMG-CoA reductase inhibitors are contraindicated in pregnancy. The risk of foetal injury outweighs the benefits of HMG-CoA reductase inhibitor therapy during pregnancy.

In two series of 178 and 143 cases where pregnant women took a HMG-CoA reductase inhibitor (statin) during the first trimester of pregnancy, serious foetal abnormalities occurred in several cases. These included limb and neurological defects, spontaneous abortions and foetal deaths. The exact risk of injury to the foetus occurring after a pregnant woman is exposed to HMG-CoA reductase inhibitor has not been determined. The current data do not indicate that the risk of foetal injury in women exposed to HMG-CoA reductase inhibitors is high. If a pregnant woman is exposed to a HMG-CoA reductase inhibitor she should be informed of the possibility of foetal injury and discuss the implications with her pregnancy specialist.

Use in Lactation

It is not known whether this drug is excreted in human milk. In rats, plasma concentrations of atorvastatin are similar to those in milk. Because of the potential for adverse reactions in nursing infants, women taking LORSTAT should not breast-feed (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Paediatric Use

Treatment experience in a paediatric population is limited to doses of atorvastatin up to 80 mg/day for 1-year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients.

Use in the Elderly

Treatment experience in adults age ≥70 years with doses of atorvastatin up to 80 mg/day has been evaluated in 221 patients. The safety and efficacy of atorvastatin in this population were similar to those of patients <70 years of age.

Carcinogenicity

In a 2-year study in rats given 10, 30 or 100 mg/kg/day, the incidence of hepatocellular adenoma was marginally, although not significantly, increased in females at 100 mg/kg/day. The maximum dose used was 11 times higher than the highest human dose (80 mg/kg) based on AUC (0–24) values. In a 2-year study in mice given 100, 200 or 400 mg/kg, incidences of hepatocellular adenoma in males and hepatocellular carcinoma in females were increased at 400 mg/kg. The maximum dose used was 14 times higher than the highest human dose (80 mg/kg) based on AUC (0-24) values. Other HMG-CoA reductase inhibitors have been reported to induce hepatocellular tumours in mice and rats.

Genotoxicity

Atorvastatin did not demonstrate mutagenic or clastogenic potential in an appropriate battery of assays. It was negative in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, and in the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells. Atorvastatin did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay and was negative in the *in vivo* mouse micronucleus test.

Effect on Ubiquinone Levels (COQ10)

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term, statin-induced deficiency of ubiquinone has not been established.

Effect on Lipoprotein (a)

Like other HMG-CoA reductase inhibitors, atorvastatin has variable effects on lipoprotein(a) (Lp(a)). It is unclear whether the beneficial effects of lowering LDL-C and total cholesterol in some patients may be blunted by raised Lp(a) levels.

Effect on Laboratory Tests

Atorvastatin can cause elevations in ALT/AST, alkaline phosphatase, GGT, bilirubin and creatine kinase.

Effects on Ability to Drive and Operate Machines

Effects of ability to drive and operate machines on atorvastatin tablets have not been established.

INTERACTIONS WITH OTHER MEDICINES

Atorvastatin is metabolised by cytochrome P450 3A4.

Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4. Pharmacokinetic drug interactions that result in increased systematic concentration of atorvastatin have been noted with HIV protease inhibitors (fosamprenavir and combinations of lopinavir/ritonavir, saquinavir/ritonavir, darunavir/rotinavir, fosamprenavir/ritonavir), hepatitis C protease inhibitors (boceprevir), clarithromycin and intraconazole. Based on experience with other HMG-CoA reductase inhibitors, caution should be exercised when LORSTAT is administered with inhibitors of cytochrome P450 3A4 (e.g. cyclosporin, macrolide antibiotics including erythromycin and azole antifungals including itraconazole). The risk of myopathy during treatment with other HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, azole antifungals or niacin (see **PRECAUTIONS, Skeletal Muscle** and **DOSAGE AND ADMINISTRATION, Use in Combination with Other Medicinal Compounds)**.

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampicin, phenytoin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampicin (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter (OATP1B1), simultaneous co-administration of atorvastatin with rifampicin is recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations.

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown.

Although interaction studies with atorvastatin and fusidic acid have not been conducted, there have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, statin treatment should be discontinued throughout the duration of the fusidic acid treatment (see **CONTRAINDICATIONS** and **PRECAUTIONS, Skeletal Muscle)**.

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. (see **PRECAUTIONS, Skeletal Muscle**)

Effects of Other Medicines on atorvastatin

The following medicines have been shown to have an effect on the pharmacokinetics or pharmacodynamics of atorvastatin tablets:

Antacid: Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides with atorvastatin decreased atorvastatin plasma concentrations approximately 35%, however, LDL-C reduction was not altered.

Colestipol: Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol and atorvastatin were co-administered. However, LDL-C reduction was greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

Transporter Inhibitors: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporin) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporin 5.2 mg/kg/day resulted in an increase in exposure to atorvastatin (see **DOSAGE AND ADMINISTRATION**).

Erythromycin/clarithromycin: In healthy individuals, co-administration of atorvastatin (10 mg once daily) and erythromycin (500 mg four times daily), or clarithromycin (500 mg twice daily), known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin (see **PRECAUTIONS, Skeletal Muscle)**.

Protease inhibitors: Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

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

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

Grapefruit juice: Contains one or more components that inhibit cytochrome P450 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 L per day).

Effects of atorvastatin on Other Medicines

The following medicines have been shown to have their pharmacokinetics or pharmacodynamics affected by atorvastatin tablets:

Digoxin: When multiple doses of digoxin (0.25 mg once daily) and 10 mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, steady-state plasma digoxin concentrations increased by approximately 20% following administration of digoxin with 80 mg atorvastatin daily. Patients taking digoxin should be monitored appropriately.

Oral contraceptives: Co-administration with an oral contraceptive containing norethindrone and ethinyl oestradiol increased AUC values for norethindrone and ethinyl oestradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Medicines shown not to interact with atorvastatin

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Amlodipine: Atorvastatin pharmacokinetics were not altered by the co-administration of atorvastatin 80 mg daily and amlodipine 10 mg daily at steady-state. In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin, which was not clinically meaningful.

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

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

ADVERSE EFFECTS

LORSTAT is generally well tolerated. Adverse events have usually been mild and transient.

Clinical Adverse Events

In the atorvastatin placebo-controlled clinical trial database of 16,066 patients (8,755 atorvastatin; 7,311 placebo), treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

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

Gastrointestinal disorders: dyspepsia, nausea, flatulence, diarrhoea.

Infections and infestations: nasopharyngitis.

Investigations: liver function test abnormal (hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, liver function test abnormal and transaminases increased), blood creatine phosphokinase increased.

Metabolism and nutrition disorders: hyperglycaemia.

Musculoskeletal and connective tissue disorders: myalgia, arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, joint swelling.

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

Additional Adverse Events

The following have been reported in clinical trials of atorvastatin, however, not all the events listed have been causally associated with atorvastatin therapy.

Common (≥1% and <10%)

Gastrointestinal disorders: constipation.

Infections and infestations: urinary tract infection.

Nervous system disorders: headache.

Uncommon (≥0.1% and <1%)

Ear and labyrinth disorders: deafness.

Eye disorders: vision blurred.

Gastrointestinal disorders: abdominal discomfort, abdominal pain, vomiting.

General disorders and administration site conditions: asthenia, malaise.

Infections and infestations: infection, influenza.

Metabolism and nutrition disorders: anorexia.

Musculoskeletal and connective tissue disorders: back pain, neck pain.

Nervous system disorders: paraesthesia.

Psychiatric disorders: insomnia, nightmare.

Reproductive system and breast disorders: erectile dysfunction.

Respiratory, thoracic and mediastinal disorders: asthma.

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

Rare (≥0.01% and <0.1%)

Ear and labyrinth disorders: tinnitus.

Gastrointestinal disorders: pancreatitis, eructation.

General disorders and administration site conditions: pyrexia.

Hepatobiliary disorders: hepatitis, cholestasis.

Immune system disorders: hypersensitivity (including anaphylaxis).

Infections and infestations: sinusitis, pharyngitis.

Injury, poisoning and procedural complications: injury.

Investigations: white blood cells urine positive.

Metabolism and nutrition disorders: hypoglycaemia.

Musculoskeletal and connective tissue disorders: immune mediated necrotising myopathy, myositis, myopathy, muscle fatigue.

Nervous system disorders: peripheral neuropathy.

Skin and subcutaneous tissue disorders: angioedema, alopecia.

A post-hoc analysis of a clinical study (SPARCL) in patients without known coronary heart disease who had a recent stroke or TIA, showed an increased risk of haemorrhagic stroke in patients with prior haemorrhagic stroke or prior lacunar infarct (see **PRECAUTIONS**).

In ASCOT (see **CLINICAL TRIALS - Prevention of Cardiovascular Disease**) involving 10,305 participants treated with atorvastatin 10 mg tablets daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of

the group treated with atorvastatin tablets was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Post-marketing experience

Rare adverse events that have been reported post-marketing which are not listed above, regardless of causality, include the following:

Blood and lymphatic system disorders: thrombocytopenia.

General disorders and administration site conditions: chest pain, fatigue, peripheral oedema.

Hepatobiliary disorders: hepatic failure.

Injury, poisoning and procedural complications: tendon rupture.

Investigations: weight increased.

Musculoskeletal and connective tissue disorders: rhabdomyolysis which may be fatal[1] (see **CONTRAINDICATIONS**, **PRECAUTIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

Nervous system disorders: hypoaesthesia, dizziness, amnesia, dysgeusia.

Reproductive system and breast disorders: gynaecomastia.

Skin and subcutaneous tissue disorders: bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).

The following adverse events have been reported with some statins: Exceptional cases of interstitial lung disease, especially with long term therapy (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

LORSTAT can be administered within the dosage range of 10–80 mg/day as a single daily dose. LORSTAT can be taken at any time of the day, with or without food. Therapy should be individualised according to the target lipid levels, the recommended goal of therapy, and the patient's response. After initiation and/or upon titration of LORSTAT, lipid levels should be re-analysed within 4 weeks and dosage adjusted according to the patient's response.

Primary hypercholesterolaemia and mixed dyslipidaemia

The majority of patients are controlled with 10 mg LORSTAT 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 hypercholesterolaemia

Adults: In the compassionate-use study of patients with homozygous familial hypercholesterolaemia, most patients responded to 80 mg of atorvastatin tablets with a greater than 15% reduction in LDL-C (18%-42%).

Children: Treatment experience in a paediatric population (with doses of atorvastatin up to 80 mg/day) is limited.

[1] examples of signs and symptoms are muscle weakness, muscle swelling, muscle pain, dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure and cardiac arrhythmia

Use in renal impairment

Renal disease has no influence on the plasma concentrations or on the LDL-C reduction of atorvastatin; thus, no adjustment of the dose is required (see **PHARMACOLOGY**).

Use in hepatic impairment

Plasma concentrations of atorvastatin are markedly increased in patients with chronic alcoholic liver disease (Childs-Pugh B). The benefits of therapy should be weighed against the risks when atorvastatin is to be given to patients with hepatic insufficiency (see **PHARMACOLOGY, CONTRAINDICATIONS** and **PRECAUTIONS**).

Use in Combination with Other Medicines

In cases where co-administration of atorvastatin with cyclosporine, telaprevir, or the combination tipranavir/ritonavir is necessary, the dose of atorvastatin should not exceed 10mg. Caution should be used when co-prescribing atorvastatin with medicinal compounds that result in an increase in systematic concentrations of atorvastatin and appropriate clinical assessment is recommended to ensure that the lowest necessary dose of atorvastatin is employed (see **PRECAUTIONS, Skeletal Muscle** and **INTERACTIONS WITH OTHER MEDICINES**) .

OVERDOSAGE

There is no specific treatment for LORSTAT overdosage. Should an overdose occur, the patient should be treated symptomatically, and supportive measures instituted as required. In symptomatic patients, monitor serum creatinine, BUN, creatinine phosphokinase, and urine myoglobin for indications of renal impairment secondary to rhabdomyolysis. Liver function tests should be performed in symptomatic patients.

If there has been significant ingestion, consider administration of activated charcoal. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. For rhabdomyolysis, administer sufficient 0.9% saline to maintain urine output of 2 to 3 mL/kg/hr. Diuretics may be necessary to maintain urine output. Urinary alkalinization is not routinely recommended. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

Contact the Poisons Information Centre on 131126 (Australia) for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

LORSTAT 10 – White, oval, biconvex, film coated tablet plain on one side and debossed '**10**' on the other side.

LORSTAT 20 – White, oval, biconvex, film coated tablet with break line on one side and debossed '**20**' on the other side.

LORSTAT 40 – White, oval, biconvex, film coated tablet with break line on one side and debossed '**40**' on the other side.

LORSTAT 80 - White, oval, biconvex, film coated tablet with break line on one side and debossed '**80**' on the other side.

LORSTAT tablets are available in blister packs (OPA/AL/PVC or PVC/Aclar) of 10 or 30 tablets or bottle (HDPE) of 10, 30 or 90 tablets. Bottle (HDPE) of 500 tablets is for dispensing only.

Store below 25°C. Protect from light and moisture.

Discard blister pack 30 days after the first tablet is taken and discard bottle 90 days after opening.

Not all presentations may be marketed.

NAME AND ADDRESS OF THE SPONSOR

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ABN 93 002 359 739

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

11/07/2012

DATE OF MOST RECENT AMENDMENT

24/02/2015

LORSTAT_pi\Feb15/00