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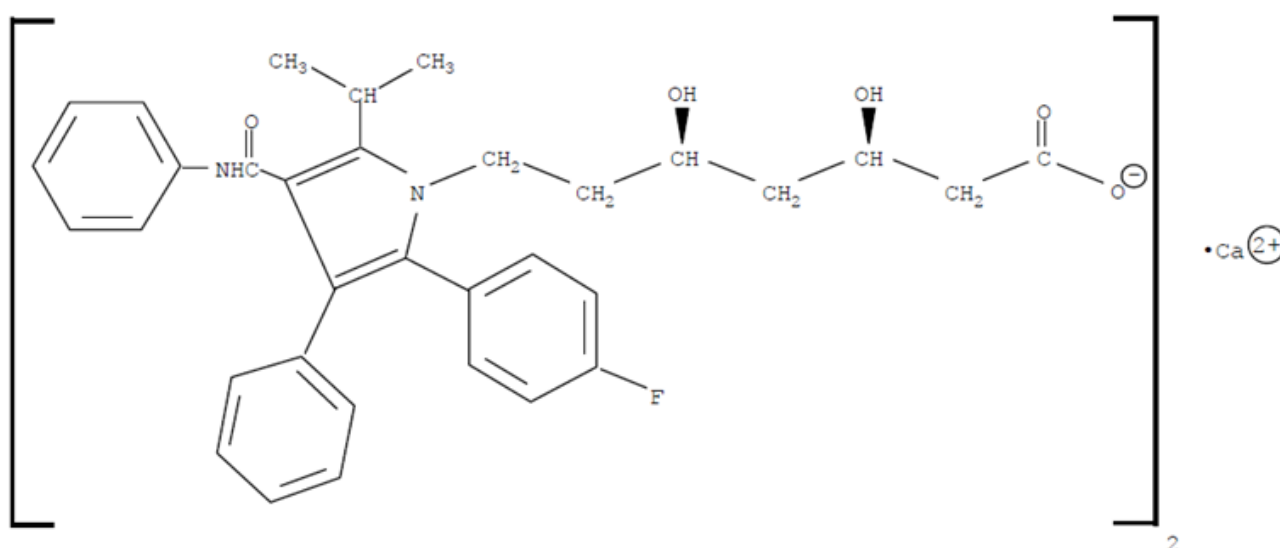
NEW ZEALAND DATA SHEET

LORSTAT
Atorvastatin



Description

Atorvastatin calcium (CAS 134523-03-8) is [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1). The empirical formula of atorvastatin calcium is (C₃₃H₃₄FN₂O₅)₂Ca. and its molecular weight is 1155.36. Its structural formula is:



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.

Pharmacology

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**).

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), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease. Similarly, decreased levels of high density lipoprotein cholesterol (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 very low density lipoprotein cholesterol (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.

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 approximately 381 litres. Atorvastatin is ≥ 98% bound to plasma proteins. A red blood cell/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 (≥ 65 years): 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 **Dosage and Administration, Precautions and Contraindications**).

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	ApoB	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

^aAdjusted 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. 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.

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 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.

Coronary Artery Disease

In the AVERT (Atorvastatin Versus Revascularisation Treatments) randomised, parallel-group, open-label study, the effect of aggressive cholesterol lowering on ischaemic events was assessed in a population referred for angioplasty (based on angiogram showing at least 50% stenosis in 1 or more coronary arteries which had not previously been subjected to interventional treatment). A total of 341 patients (aged 18-80 years) with asymptomatic or mildly to moderately symptomatic coronary artery disease (Canadian Cardiovascular Society class 1 or 2) with a LDL-C level of at least 3.0 mmol/L and a triglyceride level of no more than 5.6 mmol/L, in the absence of left main coronary or triple-vessel disease and congestive heart failure (New York Heart Association classes III or IV), were randomised to either receive atorvastatin 80 mg/day or undergo angioplasty, with or without stents, followed by usual care (UC). Patients were also excluded if they had an episode of unstable angina or a myocardial infarction within the previous 2 weeks or an ejection fraction < 40%. Lipid lowering therapy was included in UC, with 73% of patients in the angioplasty/UC group receiving lipid lowering medication at some time during the trial. In both treatment

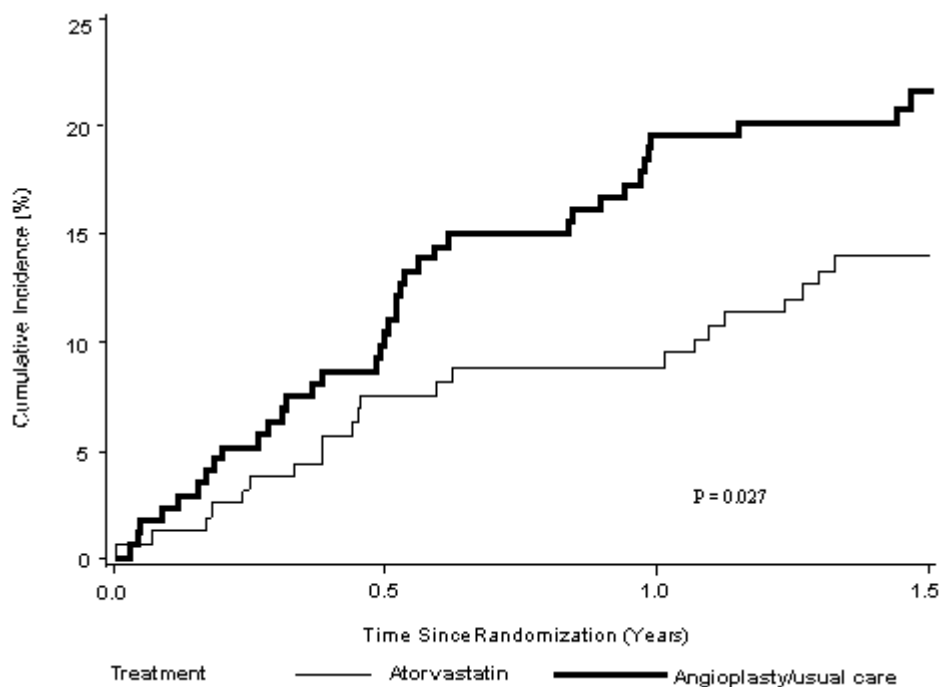
groups, approximately 80% of the patients had a history of hyperlipidaemia. After 18 months, atorvastatin 80 mg/day had a lower mean LDL-C plasma level than angioplasty/usual care (1.98 mmol/L vs 3.07 mmol/L, $p < 0.05$). Patients treated with atorvastatin who achieved reductions in LDL-C values of $> 40\%$ experienced significantly fewer ischaemic events than patients whose LDL-C values decreased by $\leq 40\%$ ($p = 0.014$).

Compared to the angioplasty/UC group, 36% fewer atorvastatin treated patients experienced ischaemic events [22 (13%) vs 37 (21%); $p = 0.048$ versus an adjusted significance level of 0.045] (Table 2) and there was a significant delay in time to first cardiac ischaemic event ($p = 0.027$) (Figure 1). The analysis of the occurrence of an ischaemic event was repeated after excluding coronary artery bypass grafts and angioplasties that were not per protocol ("per-protocol" analysis). The per-protocol analysis revealed that 48% fewer atorvastatin treated patients experienced ischaemic events compared to the angioplasty/UC group (9% vs 18%; $p = 0.022$).

Table 2. Number (%) of Patients who Experienced an Ischaemic Event

Ischaemic Event	Atorvastatin N = 164	Angioplasty/UC N = 177
Cardiac Death	1 (0.6%)	1 (0.6%)
Resuscitated Cardiac Arrest	0 (0.0%)	0 (0.0%)
Nonfatal Myocardial Infarction	4 (2.4%)	5 (2.8%)
Cardiovascular Accident	0 (0.0%)	0 (0.0%)
Coronary Artery Bypass Graft	2 (1.2%)	9 (5.1%)
Angioplasty	18 (11.0%)	21 (11.9%)
Worsening Angina with Objective Evidence Resulting in Hospitalisation	11 (6.7%)	25 (14.1%)
Any Ischaemic Event	22 (13.4%)	37 (20.9%)

Figure 1. Kaplan-Meier Curve of Time to First Ischaemic Event



Prevention of Cardiovascular Disease

In the lipid lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin 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 total-C 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%), type 2 diabetes (25%), history of CHD in a first-degree relative (26%), plasma total-C to HDL-C ratio ≥ 6 (14%), peripheral vascular disease (PVD) (5%), left ventricular

hypertrophy (LVH) 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 10 mg 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; 2,340 patients (45.3%) had total-C 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.

Atorvastatin significantly reduced the rate of coronary events (fatal coronary heart disease and nonfatal MI) by 36% [154 events in the placebo group vs. 100 events in the atorvastatin group, p=0.0005 (see Table 3)]. A reduction in coronary events emerged in the first year of follow up. The risk reduction was consistent across baseline total-C levels, age, smoking status, obesity, presence of LVH, previous PVD, presence of diabetes, renal dysfunction or presence of metabolic syndrome.

Table 3. Summary of risk reductions in primary prevention patients (ASCOT)

Endpoint	Atorvastatin 10mg N (%)	Placebo N (%)	Absolute risk reduction* % (95% CI)	Number needed 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	89 (1.7%)	119 (2.3%)	0.6 (0.05 to 1.14)	555.2	26 (2 to 44)	0.0332
Non-fatal MI (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

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

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 with 3% of placebo-treated patients, a relative risk reduction of 36% (p=0.0005) (Table 3). 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 LVH, PVD 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.

In the **Collaborative Atorvastatin Diabetes Study (CARDS)**, the effect of atorvastatin on fatal and non-fatal coronary and cerebrovascular disease was assessed in 2,838 patients with type 2 diabetes aged 40 - 75 years, without prior history of cardiovascular disease and with LDL < 4.14 mmol/L and TG < 6.78 mmol/L.

Additionally, all patients had at least one of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

In this randomized, double blind, multicentre, placebo-controlled trial, patients were treated with either atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410) for a median follow-up of 3.9 years. CARDS was terminated 2 years earlier than anticipated when the analysis of the primary efficacy parameter reached the pre-specified significance level (p<0.0005, one-sided) in favour of atorvastatin.

The absolute and relative risk reduction effect of atorvastatin is as follows:

Table 4. Summary of risk reductions in primary prevention patients (CARDS)

Endpoint	Number of patients with endpoint (%)		Absolute risk reduction % (95% CI)	Number needed to treat per year	Hazard Ratio % (95% CI)	P value
	Atorvastatin 10 mg	Placebo				
Primary						
Major cardiovascular events (fatal and nonfatal AMI, silent MI, CHD death, unstable angina, CABG, PTCA, revascularisation, stroke)	83 (5.8)	127 (9.0)	3.2 (1.3 to 5.1)	125	0.63 (0.48 to 0.83)	0.0010
MI (fatal and nonfatal AMI infarction, silent MI)	38 (2.7)	64 (4.5)	1.9 (0.5 to 3.2)	213	0.58 (0.39 to 0.86)	0.0070
Stroke (fatal and nonfatal)	21 (1.5)	39 (2.8)	1.3 (0.2 to 2.4)	309	0.52 (0.31 to 0.89)	0.0163
Secondary						
Death due to all causes	61 (4.3)	82 (5.8)	1.5 (0.0, 3.2)	259	0.73 (0.52 to 1.01)	0.0592

There was no evidence of a difference in the primary efficacy treatment effect by patient's gender, age, or baseline LDL-C level.

Type 2 diabetes

A 26 week randomised, double blind, comparator study in type 2 diabetic subjects showed that atorvastatin is effective in dyslipidaemic patients with type 2 diabetes. A 10 mg dose of atorvastatin produced a 34% reduction in LDL-C, 27% reduction in total-C, a 24% reduction in TG and a 12% rise in HDL-C.

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 mg 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 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 \geq 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 randomised, placebo-controlled, double-blind, multicentre study in patients with hypertriglyceridaemia (TG \geq 3.95 mmol/L, LDL-C \leq 4.1 mmol/L), atorvastatin 20 mg/day and 80 mg/day produced significantly greater reductions in triglyceride levels than placebo (Table 5).

Table 5. 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*

^aAdjusted 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, randomised, 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 6).

Table 6. Efficacy in Patients with Dysbetalipoproteinaemia^{a b}

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

^aAdjusted 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 to reduce elevated total-C, LDL-C and TG levels in patients with primary hypercholesterolaemia or mixed dyslipidaemia where the primary abnormality is either elevated cholesterol or triglycerides when response to diet and other non-pharmacological measures is inadequate.

Lorstat is also indicated to reduce total-C and LDL-C in patients with heterozygous and homozygous familial hypercholesterolaemia.

Lorstat is indicated to increase plasma HDL-C and decrease the LDL-C/HDL-C and total cholesterol/HDL-C ratios.

Lorstat is indicated as an adjunct to diet for the treatment of patients with elevated serum triglyceride levels (hypertriglyceridaemia), and for the treatment of patients with dysbetalipoproteinaemia who do not respond adequately to diet.

Lorstat is indicated for the reduction of cardiac ischaemic events in patients with asymptomatic or mildly to moderately symptomatic coronary artery disease with a LDL-cholesterol of at least 3.0 mmol/L and a triglyceride level of no more than 5.6 mmol/L.

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 **Pharmacology** Clinical Trials) to reduce the risk of non-fatal myocardial infarction and non-fatal stroke.

Lorstat is also indicated in patients with type 2 diabetes, with at least one other risk factor for CHD, to reduce the risk of coronary and cerebrovascular events.

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 child-bearing potential, unless on an effective contraceptive and highly unlikely to conceive.

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 atorvastatin is recommended.

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 **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 phosphokinase (CPK) values > 10 x ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness and/or marked elevation of CPK. Patients should be advised to report promptly 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 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, or azole antifungals. Physicians considering combined therapy with atorvastatin 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. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy (see **Precautions**, Drug Interactions). Periodic creatine phosphokinase (CPK) 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. Atorvastatin 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 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 a haemorrhagic 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 or 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.

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.

Carcinogenicity, mutagenesis, impairment of fertility

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.

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.

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. 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. 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 effects in nursing infants, women taking atorvastatin 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 \geq 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.

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-C in some patients may be blunted by raised Lp(a) levels.

Interactions

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. Based on experience with other HMG-CoA reductase inhibitors caution should be exercised when atorvastatin 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 cyclosporine, fibric acid derivatives, erythromycin, azole antifungals or niacin (see **Precautions**).

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 on atorvastatin plasma concentrations.

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

Effects of other Medicines on Atorvastatin

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

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 a 7.7 fold increase in exposure to atorvastatin (see **Dosage and Administration**).

Erythromycin/clarithromycin: In healthy individuals, co-administration of atorvastatin (10 mg QD) and erythromycin (500 mg QID), or clarithromycin (500 mg BID), known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin (see **Precautions**).

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).

Effect of Atorvastatin on other Medicines

The following drugs have been shown to have their pharmacokinetics or pharmacodynamics affected by atorvastatin.

Digoxin: When multiple doses of digoxin (0.25 mg QD) 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: 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 QD) did not alter the plasma concentrations of atorvastatin.

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

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 specific agents have not been conducted.

Effects on laboratory tests

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

Adverse Effects

Atorvastatin is generally well-tolerated. Adverse effects have usually been mild and transient. Less than 2% of patients were discontinued from clinical trials due to side effects attributed to atorvastatin. The most frequent ($\geq 1\%$) adverse effects associated with atorvastatin therapy, in patients participating in controlled clinical studies were:

Body as a Whole: headache, asthenia, abdominal pain

Digestive System: dyspepsia, nausea, flatulence, constipation, diarrhoea

Nervous System: insomnia

Musculoskeletal System: myalgia.

Clinical Adverse Experiences

Adverse experiences reported in $\geq 2\%$ of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in the table below.

Table 7. Adverse Events in Placebo-Controlled Studies (% of Patients)

BODY SYSTEM\ Adverse Event	Placebo N=270	Atorvastatin 10 mg N=863	Atorvastatin 20 mg N=36	Atorvastatin 40 mg N=79	Atorvastatin 80 mg N=94
Body as a whole					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.2
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthma	1.9	2.2	0.0	3.8	0.0
Digestive System					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhoea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
Respiratory System					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
Skin & Appendages					
Rash	0.7	3.9	2.8	3.8	1.1
Musculoskeletal System					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

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

Body as a Whole: angioneurotic oedema

Digestive System: vomiting, anorexia, hepatitis, pancreatitis, cholestatic jaundice

Nervous System: paraesthesia, peripheral neuropathy

Musculoskeletal System: muscle cramps, myositis, myopathy

Skin and Appendages: pruritus, alopecia

Urogenital System: impotence

Special Senses: deafness

Metabolic and Nutritional Disorders: hypoglycemia, hyperglycemia

Cerebrovascular System: haemorrhagic stroke.

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

In ASCOT (see **Pharmacology**, Clinical Trials, Prevention of Cardiovascular Disease) involving 10,305 hypertensive participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

CARDS (see **Pharmacology**, Clinical Trials, Prevention of Cardiovascular Disease) included 2,838 patients with type 2 diabetes, and participants received atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410). The overall incidence of adverse events or serious adverse events in the atorvastatin treated group was similar to that of the placebo-group following a median duration of treatment of 3.9 years

Post-marketing Experience

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

Body as a Whole: allergic reactions (including anaphylaxis), chest pain, malaise, fatigue

Musculoskeletal System: rhabdomyolysis

Nervous System: hypoesthesia, dizziness, amnesia, dysgeusia

Ear and Labyrinth Disorders: tinnitus

Skin and Appendages: bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), urticaria

Metabolic and Nutritional Disorders: peripheral oedema, weight gain

Hemic and Lymphatic System: thrombocytopenia

Injury, poisoning and procedural complications: tendon rupture

Reproductive system and breast disorders: gynaecomastia.

The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares
- Memory loss
- Sexual dysfunction
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see **Precautions**).

Dosage and Administration

Hypercholesterolaemia and Mixed Dyslipidaemia

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 atorvastatin, lipid levels should be re-analysed within 4 weeks and dosage adjusted according to the patient's response.

Primary hypercholesterolaemia and Mixed hyperlipidaemia

The majority of patients are controlled with 10 mg atorvastatin once a day. A therapeutic response is evident within two weeks, and the maximum response is usually achieved within four weeks. The response is maintained during chronic therapy.

Intensive cholesterol lowering with atorvastatin 80 mg once a day should be considered in individuals with stable coronary artery disease (see **Pharmacology**; Clinical Trials; Coronary Artery Disease).

Homozygous Familial Hypercholesterolaemia

Adults: In a compassionate-use study of patients with homozygous familial hypercholesterolaemia, most patients responded to 80 mg of atorvastatin with a greater than 15% reduction in LDL-C (18%-45%).

Children: Treatment experience in a paediatric population is limited to doses of atorvastatin up to 80 mg/day for 1 year in patients with homozygous FH (see **Precautions**; Paediatric Use).

Hypertriglyceridaemia and Dysbetalipoproteinaemia

The dosage of atorvastatin in this patient group is 10-80 mg daily as a single dose. Doses should be individualised and adjusted according to the patient's response after 4 weeks.

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** and **Contraindications**).

Use in combination with other medicinal compounds

In cases where co-administration of atorvastatin with cyclosporin is necessary, the dose of atorvastatin should not exceed 10 mg (see **Precautions**, Skeletal Muscle and **Interactions**).

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

Overdosage

There is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically, and supportive measures instituted as required. 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 alkalization 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 for advice on the management of an overdose.

Presentation

Lorstat tablets are conventional release tablets presented as:

Lorstat 10: White, oval shaped, bi-convex, film coated tablet, debossed "ATO 10" on one side and "G" on the other side.

Lorstat 20: White, oval shaped, bi-convex, film coated tablet, debossed "ATO 20" on one side and "G" on the other side.

Lorstat 40: White, oval shaped, bi-convex, film coated tablet, debossed "ATO 40" on one side and "G" on the other side.

Lorstat 80: White, oval shaped, bi-convex, film coated tablet, debossed "ATO 80" on one side and "G" on the other side.

Lorstat tablets contain 10, 20, 40 or 80 mg atorvastatin as atorvastatin calcium.

Each tablet also contains the following inactive ingredients: lactose, sodium lauryl sulphate, crospovidone, magnesium oxide, poloxamer, croscarmellose sodium, magnesium stearate and Opadry II White Y-30-18037.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

Pharmaceutical Precautions

Store below 25°C.

Medicine Classification

Prescription Medicine.

Package Quantities

Lorstat tablets are available in blister packs of 10 tablets and 30 tablets.

Not all pack sizes may be marketed.

Name and Address

Mylan New Zealand Limited
PO Box 11-183
Ellerslie
AUCKLAND
Telephone: 09-579-2792

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