NEW ZEALAND DATA SHEET

LORSTAT®

1. Product Name

Lorstat, 10 mg, 20 mg, 40 mg & 80 mg, film coated tablet.

2. Qualitative and Quantitative Composition

Each Lorstat tablet contains 10 mg, 20 mg, 40 mg or 80 mg of atorvastatin (as calcium trihydrate).

Excipient(s) with known effect: Lactose.

Allergen Declaration: Contains sugars as lactose.

Each Lorstat 10 mg film coated tablet contains 43 mg lactose.

Each Lorstat 20 mg film coated tablet contains 85 mg lactose.

Each Lorstat 40 mg film coated tablet contains 170 mg lactose.

Each Lorstat 80 mg film coated tablet contains 340 mg lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Lorstat 10 mg: White, oval, biconvex, film coated tablet, plain on one side and debossed “10” on the other side.

Lorstat 20 mg: White, oval, biconvex, film coated tablet, with breakline on one side and debossed “20” on the other side.

Lorstat 40 mg: White, oval, biconvex, film coated tablet, with breakline on one side and debossed “40” on the other side.

Lorstat 80 mg: White, oval, biconvex, film coated tablet, with breakline on one side and debossed “80” on the other side.

The 20 mg, 40 mg and 80 mg tablets can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

Lorstat is indicated as an adjunct to diet to reduce elevated total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (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 high density lipoprotein cholesterol (HDL-C) and decrease the LDL-C/HDL-C and total-C/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-C 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 section 5.1) to reduce the risk of non-fatal myocardial infarction (MI) 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.

4.2 Dose and method of 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 section 5.1).

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 familial hypercholesterolaemia (FH) (see section 4.4).

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.

Special populations

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 section 5).

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 section 4.3, section 4.4 and section 5.1).

Use in combination with other medicinal compounds

In cases where co-administration of atorvastatin with ciclosporin, telaprevir or the combination tipranavir/ritonavir is necessary, the dose of atorvastatin should not exceed 10 mg (see section 4.4 and section 4.5).

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

When atorvastatin and letermovir are administered concomitantly, do not exceed 20 mg atorvastatin daily (see section 4.4 and section 4.5). Appropriate clinical assessment is recommended to ensure that the lowest dose of atorvastatin necessary is used.

Caution should be used when co-prescribing atorvastatin with medicinal compounds that result in an increase in systemic concentrations of atorvastatin, such as elbasvir/grazoprevir and simeprevir, and appropriate clinical assessment is recommended to ensure that the lowest dose of atorvastatin necessary is employed (see section 4.4 and 4.5).

Method of administration

Atorvastatin is for oral administration. It can be taken at any time of the day, with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active liver disease or unexplained persistent elevations of serum transaminases (see section 4.4).
- Pregnancy and lactation (see section 4.6). Women of child-bearing potential, unless on an effective contraceptive and highly unlikely to conceive.
- Concomitant use with fusidic acid (see sections 4.4 and 4.5).
- Treatment with Hepatitis C antivirals, glecaprevir/pibrentasvir.

4.4 Special warnings and precautions for use

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 on two or more occasions) 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 doses respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or medicine treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggesting liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of > 3 x ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin can cause an elevation in transaminases (see section 4.8).

Use in hepatic impairment

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

Skeletal muscle

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see section 4.8). 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 is increased with concurrent administration of medicines that increase the systemic concentration of atorvastatin (see sections 4.5 and 5.2). Many of these medicines inhibit cytochrome P450 3A4 (CYP 3A4) metabolism and/or drug transport. CYP 3A4 is the primary hepatic isozyme known to be involved in the biotransformation of atorvastatin. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive medicines, azole antifungals, human immunodeficiency virus (HIV) / hepatitis C (HCV) protease inhibitors, HCV non-structural protein 5A (NS5A)/5B (NS5B) inhibitors, letermovir, 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 medicine. When atorvastatin and letermovir are administered concomitantly, do not exceed 20 mg atorvastatin daily (see sections 4.2 and 4.5). Appropriate clinical assessment is recommended to ensure that the lowest dose of atorvastatin necessary is used. Lower starting and maintenance doses of atorvastatin should also be considered when taken concomitantly with the aforementioned medicines (see section 4.2).

There have been reports of rhabdomyolysis (including some fatalities) in patients receiving concomitant fusidic acid and statins (see section 4.3 and section 4.5). 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 reintroduced seven days after the last dose of fusidic acid.

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 section 4.4).

As with other medicines in this class, rhabdomyolysis with acute renal failure secondary to myoglobinuria, 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).

Immune mediated necrotising myopathy

There have been reports of an immune-mediated myopathy (IMNM) during or after treatment with some statins (see section 4.8). IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatinine kinase, which persists despite discontinuation of statin treatment, positive anti-HMG CoA reductase antibody and improvement with immunosuppressive agents.

Myasthenia Gravis / Ocular Myasthenia

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). Atorvastatin should be discontinued in case these conditions occur. Recurrences when the same or a different statin was (re-) administered have been reported.

Haemorrhagic stroke

A post-hoc analysis of a clinical study in patients without known coronary heart disease who had a recent stroke or transient ischaemic attack (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, hazard ratio (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

3-hydroxy-3-methylglutaryl-coenzyme A (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 medicines that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone and cimetidine.

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may product a level of hyperglycaemia where formal diabetes care is appropriate. Risk factors for the development of diabetes include raised fasting blood glucose, history of hypertension, raised triglycerides and raised body mass. Patients at risk should be monitored both clinically and biochemically according to national guidelines.

There is insufficient evidence to confirm or exclude an increased risk for an individual statin or a dose-response relationship. The cardiovascular benefits of statin therapy continued to outweigh the risk or diabetes.

Effect on ubiquinone levels (COQ_{10})

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.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). 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 laboratory tests

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

Excipient(s) with known effect

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

Special populations

Paediatrics

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.

Elderly

Treatment experience in adults aged ≥ 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.

4.5 Interaction with other medicines and other forms of interaction

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 medicine interactions that result in increased systemic concentration of atorvastatin have also been noted with other HIV protease inhibitors (fosamprenavir and combinations of lopinavir/ritonavir, saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir), HCV protease inhibitors (boceprevir, elbasvir/grazoprevir, simeprevir), HCV NS5A/NS5B inhibitors, clarithromycin, itraconazole, and letermovir. Caution should be used when co-prescribing atorvastatin with medicinal compounds that result in an increase in systemic concentrations of atorvastatin and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. 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. ciclosporin, 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 ciclosporin, fibric acid derivatives, erythromycin, azole antifungals or niacin (see section 4.2 and section 4.4).

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 section 4.3 and section 4.4). Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

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 section 4.4).

Effects of other medicines on atorvastatin

The following medicines 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 medicine was given alone.

Transporter inhibitors

Atorvastatin is a substrate of the hepatic transporters (see section 5.2)

Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in an increase in exposure to atorvastatin (ratio of AUC: 8.7; see section 5.2). Ciclosporin is an inhibitor of organic anion-transporting polypeptide 1B1 (OATP1B1), OATP1B3, multi-drug resistance protein 1 (MDR1), and breast cancer resistance protein (BCRP) as well as CYP3A4, thus it increases exposure to atorvastatin. Do not exceed 10 mg atorvastatin daily (see section 4.2).

Glecaprevir and pibrentasvir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Co-administration of atorvastatin with products containing glecaprevir or pibrentasvir is contraindicated (see section 4.3).

Concomitant administration of atorvastatin (20 mg single dose) and letermovir (480 mg once daily) for 10 days resulted in an increase in exposure to atorvastatin (ratio of AUC: 3.29; ratio of C_{max}: 2.17; see section 5.2). The ratio of AUC or C_{max} is calculated by dividing the AUC or C_{max} of co-administered letermovir plus atorvastatin alone, respectively. Letermovir inhibits efflux transporters P-gp, BCRP, MRP2, OAT2 and hepatic transporter OATP1B1/1B3, thus it increases exposure to atorvastatin. Do not exceed 20 mg atorvastatin daily (see section 4.2).

The magnitude of CYP3A- and OATP1B1/1B3-mediated medicine interactions on co-administered medicines may be different when letermovir is co-administered with ciclosporin. Use of atorvastatin is not recommended in patients taking letermovir co-administered with ciclosporin.

Elbasvir and grazoprevir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Use with caution and lowest dose necessary (see section 4.2).

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 section 4.4).

Protease inhibitors

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin (see section 4.4).

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 (see section 5.2).

Ticagrelor

Co-administration of atorvastatin (80 mg) and ticagrelor (90 mg twice a day) increased atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

Grapefruit juice

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

Effect of atorvastatin on other medicines

The following medicines 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 of atorvastatin with an oral contraceptive containing norethisterone and ethinyl oestradiol increased AUC values for norethisterone 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 (see section 5.2).

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 with 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 QD) did not alter the plasma concentrations of atorvastatin.

Antipyrine

Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other medicines 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 all specific agents have not been conducted.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category D)

The definition of Pregnancy Category D are medicines 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 medicines may also have adverse pharmacological effects.

Atorvastatin is contraindicated in pregnancy. Women of childbearing potential should use adequate contraceptive measures. Atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus.

Atherosclerosis is a chronic process and discontinuation of lipid-lowering medicines 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 medicine, therapy should be discontinued and the patient apprised of the potential hazard to the foetus (see section 4.3).

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.

Breastfeeding

Atorvastatin is contraindicated while breastfeeding. It is not known whether this medicine 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 breastfeed (see section 4.3 and section 4.4).

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).

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

Atorvastatin is generally well-tolerated. Adverse effects 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 events that may be associated with atorvastatin therapy, reported in patients participating in placebo-controlled clinical studies include:

Gastrointestinal disorders: dyspepsia, nausea, flatulence, diarrhoea.

Infections and infestations: nasopharyngitis.

Investigations: liver function test abnormal[1], 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.

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[1] Refers to the following preferred terms: hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, liver function test abnormal and transaminases increased.

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: myositis, myopathy, muscle fatigue.

Nervous system disorders: peripheral neuropathy.

Skin and subcutaneous tissue disorders: angioedema and alopecia.

A post-hoc analysis of a clinical study 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 section 4.4).

In a study (see section 5.1) 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.

In another study (see section 5.1), it 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.

Paediatric Patients

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

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

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: lupus-like syndrome, muscle rupture, immune mediated necrotising myopathy, rhabdomyolysis which may be fatal[2] (see section 4.3, section 4.4 and section 4.5).

There have been very rare reports of immune-mediated necrotising myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterised by: proximal muscle weakness and elevated serum creatine kinase, which persists despite discontinuation of statin treatment; muscle biopsy showing necrotising myopathy without significant inflammation; improvement with immunosuppressive agents (see section 4.4).

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

Eye disorders: ocular myasthenia.

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 section 4.4).
- Depression

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

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

[2] 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.

output. Urinary alkalinization is not routinely recommended. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA reductase inhibitor. ATC code: C10AA05.

Pharmacodynamic effects

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. Medicine dose rather than systemic medicine concentration correlates better with LDL-C reduction. Individualisation of medicine dose should be based on therapeutic response (see section 4.2).

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 (CVD). 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 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.

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

[a]Adjusted mean % change from baseline

In three further trials, 1,148 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 a 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 medicine 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 ≤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 vs. 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 %)

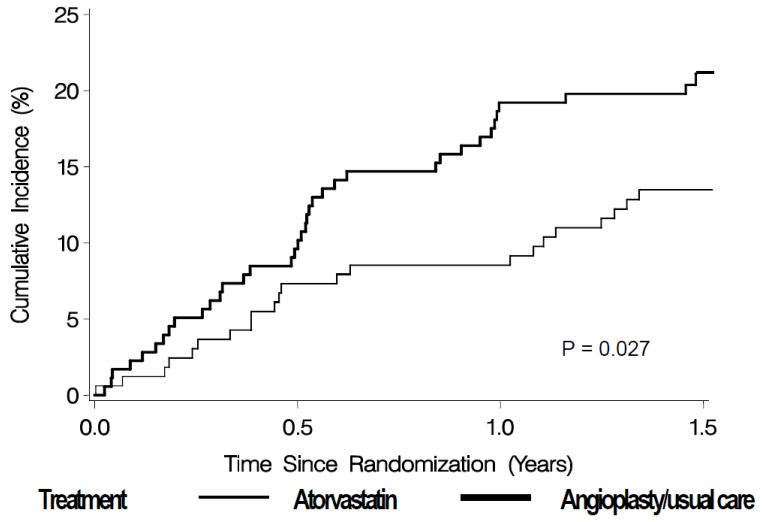

Figure 1. Kaplan-Meier Curve of Time to First Ischaemic Event

Prevention of cardiovascular disease

In the lipid lowering arm of a cardiac outcomes trial, the effect of atorvastatin on the composite endpoint of fatal coronary heart disease and non-fatal MI 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 MI 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 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 (25^{th} & 75^{th} 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 CHD 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

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[b]	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. [b]Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favourable trend was observed with a 26% relative risk reduction.

The primary endpoint examined in this study was the rate of fatal coronary heart disease or non-fatal MI 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 a diabetes study, 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 to 75 years, without prior history of CVD 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 randomised, 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. The study 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 are as follows:

Table 4. Summary of Risk Reductions in Primary Prevention Patients

Endpoint	Number of Patients with Endpoint (%)		Absolute Risk Reduction[a] % (95% CI)	Number Needed to Treat Per Year	Hazard Ratio % (95 CI)	P Value
	Atorvastatin 10 mg	Placebo				
Primary						
Major Cardiovascular Events (Fatal and Non-fatal 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 Non-fatal 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 Non-Fatal)	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

[a]Based on difference in crude event rates occurring over a median follow-up of 4.0 years.

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 FH, a population that has not usually responded to other lipid-lowering medicine. 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%. 25 patients with a reduction in LDL-C had a mean response of 20% (range 7%-53%, median 24%). 5 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 randomised, 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 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*

[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, 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*

[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

5.2 Pharmacokinetic properties

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 medicine 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 medicine administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of medicine administration (see section 4.2).

Distribution

The mean volume of distribution of atorvastatin is approximately 400 litres. Atorvastatin is ≥ 98% bound to plasma proteins. A red blood cell/plasma ratio of approximately 0.25 indicates poor medicine penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk (see section 4.4).

Biotransformation

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 section 4.4). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Elimination

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

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

Special populations

Elderly (≥ 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 section 4.2 and section 4.4).

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 medicine 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 section 4.2, section 4.3 and section 4.4).

5.3 Preclinical safety data

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* hypoxanthine-guanine phosphoribosyltransferase (HGPRT) forward mutation assay in Chinese hamster lung cells. Atorvastatin did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay and was negative in the *in vivo* mouse micronucleus test.

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 ($_{0\text{-}24}$) values. Other HMG-CoA reductase inhibitors have been reported to induce hepatocellular tumours in mice and rats.

6. Pharmaceutical Particulars

6.1 List of excipients

- colloidal anhydrous silica
- sodium carbonate
- microcrystalline cellulose

- L-arginine
- lactose
- croscarmellose sodium
- hydroxypropyl cellulose
- magnesium stearate
- opadry AMB White OY-B-28920 (containing titanium dioxide, talc, xanthan gum, polyvinyl alcohol and soya lecithin).
- opadry II white 85F18378 (containing polyvinyl alcohol – part hydrolysed, titanium dioxide, macrogol and talc)

Lorstat tablets may be coated with either Opadry AMB White OY-B-28920 or Opadry II white 85F18378.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years for HDPE bottle and OPA/Al/PVC/Al cold form blister packs.

2 years for Aclar/Al/PVC blister pack.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

HDPE bottle with a child-resistant closure. Pack-sizes of 90 or 500 film-coated tablets.

HDPE bottle with a screw closure. Pack-sizes of 90 or 500 film-coated tablets.

OPA/Al/PVC/Al cold form blister strip in cardboard outer carton. Pack size of 10 or 30 film-coated tablets.

Aclar/Al/PVC blister strip in cardboard carton. Pack size of 10 or 30 film-coated tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
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AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

16 July 2015

10. Date of Revision of the Text

24 March 2026

Summary table of changes

Section	Summary of new information
2	Updated Excipient(s) with known effect section
4.4	Addition of Excipient(s) with known effect section
4.8	Addition of ‘depression’ as a post-marketing experience Minor editorial changes

LORSTAT® is a Viatris company trade mark.