NEW ZEALAND DATA SHEET

1 PRAVASTATIN TABLETS

PRAVASTATIN 10mg tablet

PRAVASTATIN 20mg tablet

PRAVASTATIN 40mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pravastatin sodium 10mg

Pravastatin sodium 20mg

Pravastatin sodium 40mg

Excipient with known effect:
Gluten: PRAVASTATIN 10mg, 20mg and 40mg tablets are gluten free.

Lactose: PRAVASTATIN 10mg, 20mg and 40mg tablets contain Lactose. If you have been told by your doctor that you may have intolerance to some sugars, please contact your doctor before taking this medicinal product.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

PRAVASTATIN 10 mg tablets are light pink, round, unscored tablets, imprinted “APO” on one side and “PRA” over “10” on the other side.

PRAVASTATIN 20 mg tablets are off-white to light yellow, round, unscored tablets, imprinted “APO” on one side and “PRA” over “20” on the other side.

PRAVASTATIN 40 mg tablets are light green, round, unscored tablets, imprinted “APO” on one side and “PRA” over “40” on the other side.

4 CLINICAL PARTICULARS

4.1 **Therapeutic indications**

PRAVASTATIN is indicated for:

1. In hypercholesterolaemic patients without clinically evident coronary heart disease, pravastatin is indicated as an adjunct to diet to reduce the risk of fatal and non-fatal myocardial infarction, need for myocardial revascularisation procedures and to improve survival by reducing cardiovascular deaths.

2. the reduction of elevated Total and LDL cholesterol levels in patients with primary hypercholesterolaemia when the response to diet and other non-pharmacological measures alone have been inadequate.

3. as an adjunct to diet to slow the progressive course of atherosclerosis and reduce the incidence of clinical cardiovascular events in hypercholesterolaemic men under the age of 75 with coronary artery disease.

4. Coronary Artery Disease: In patients with a history of either a myocardial infarction or unstable angina pectoris, pravastatin is indicated to reduce the risk for total mortality, coronary heart disease death, recurrent coronary event (including myocardial infarction), need for myocardial revascularisation procedures and need for hospitalisation.

5. Cerebrovascular Disease: In patients with a history of coronary artery disease (*i.e.* either a myocardial infarction or unstable angina pectoris), pravastatin is indicated to reduce the risk of stroke or transient ischemic attacks.

6. Cardiac and Renal Transplantation: In patients receiving immunosuppressive therapy, pravastatin is indicated to improve survival in cardiac transplant patients and to reduce the risk of acute rejection in kidney transplant patients.

4.2 Dose and method of administration

Prior to initiating PRAVASTATIN, the patient should be placed on a standard cholesterol-lowering diet which should be continued during treatment.

Prior to initiating therapy with PRAVASTATIN, secondary causes for hypercholesterolaemia (e.g. obesity, poorly-controlled diabetes, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other medicine therapy, alcoholism) should be excluded and a lipid profile performed to measure Total-C, HDL-C and TG. For patients with TG < 4.52 mmol/L, LDL-C can be estimated using the following equation:

LDL-C = Total-C – HDL-C – 1/5 TG

For TG levels > 4.52 mmol/L, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

Since the goal of treatment is to lower LDL-C, the National (United States) Cholesterol Education Programme recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available should the Total-C be used to monitor therapy.

Dose

The recommended starting dose is 10–20 mg once daily at bedtime. If serum cholesterol is markedly elevated (e.g. Total-C greater than 7.76 mmol/L), dosage may be initiated at 40 mg per day. Pravastatin may be taken without regard to meals. Since the maximal effect of a given dose is seen within four weeks, periodic lipid determinations should be performed at this time and dosage adjusted according to the patient's response to therapy and established treatment guidelines. The recommended dosage range is 10–40 mg administered once a day at bedtime. Pravastatin may be given in divided doses.

For the prevention of coronary heart disease in hypercholesterolaemic patients the dose is 40 mg per day as a single dose.

For cardiac and renal transplantation patients the recommended dose is 10–20 mg as a single dose.

Special Populations

Paediatric

Safety and effectiveness in individuals less than 18 years old have not been established. Hence treatment in patients less than 18 years old is not recommended.

Concomitant Therapy

Some patients may require combination therapy with one or more lipid-lowering agents. Pharmacokinetic interaction studies with pravastatin administered concurrently with nicotinic acid, probucol and gemfibrozil (see **section 4.4 Special Warnings and Precautions for use, Skeletal Muscle**) did not demonstrate any alterations in the bioavailability of pravastatin.

The lipid-lowering effects of pravastatin on Total and LDL cholesterol are enhanced when combined with a bile acid-binding resin. When administering pravastatin and a bile acid-binding resin (e.g. cholestyramine, colestipol), pravastatin should be given either one hour or more before or at least four hours following the resin.

In patients taking ciclosporin, with or without other immunosuppressive drugs, concomitantly with pravastatin, therapy should be initiated with 10 mg per day and titration to higher doses should be performed with caution. The maximum pravastatin dose for patients treated with this combination should not exceed 20 mg/day.

Method of administration
PRAVASTATIN maybe taken without regards to meals.

4.3 **Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (List of Excipients).

Active liver disease or unexplained persistent elevations of serum transaminase elevation exceeding 3 times the upper limit of normal (ULN) in liver function tests (see section 4.4 Special Warnings and Precautions for Use).

Concomitant use of fusidic acid (see sections 4.4 Special Warnings and Precautions for Use and 4.5 Interations with other medicines and other forms of interactions)

Pregnancy and lactation (see section 4.6 Fertility, pregnancy and lactation).
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 a pregnant woman. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy.

Safety in pregnant women has not been established.

Although pravastatin was not teratogenic in rats at doses as high as 1000 mg/kg daily, nor in rabbits at doses of up to 50 mg/kg daily, PRAVASTATIN should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVASTATIN, it should be discontinued, and the patient advised again of the potential hazards to the foetus.

Women of childbearing potential (see section 4.6 Fertility, pregnancy and lactation).
PRAVASTATIN 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. If the patient becomes pregnant while taking this class of medicine, therapy should be discontinued, and the patient again advised of the potential hazard to the foetus.

4.4 Special warnings and precautions for use

General

Pravastatin may elevate creatine phosphokinase and transaminase levels (see section 4.8 Undesirable effects). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Use in hepatic impairment

HMG-CoA reductase inhibitors have been associated with biochemical abnormalities of liver function. As with other lipid-lowering agents, including non-absorbable bile acid-binding resins, marked persistent increases (greater than three times the upper limit of normal) in serum transaminases were seen in 1.3% of the patients treated with pravastatin in the U.S. for an average period of 18 months. In clinical trials these elevations were not associated with clinical signs and symptoms of liver disease and usually declined to pre-treatment levels upon discontinuation of therapy. Only two patients had marked persistent abnormalities possibly attributable to therapy.

The significance of these changes, which usually appear during the first few months of treatment initiation, is not known. In the majority of patients treated with pravastatin in clinical trials, these increased values declined to pre-treatment levels despite continuation of therapy at the same dose.

These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

There have been rare post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including pravastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with pravastatin sodium, promptly interrupt therapy. If an alternate etiology is not found, do not restart pravastatin.

As with other lipid-lowering agents, liver function tests should be performed before treatment begins and periodically thereafter in all patients. Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm any elevation and subsequently monitored at more frequent intervals. If increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) equal or exceed three times the upper limit of normal and persist, therapy should be discontinued.

Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion. Such patients should be closely monitored, started at lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Use in renal impairment

A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3x-hydroxy isomeric metabolite (SQ 31,908). A small increase was seen in mean AUC values and half-life (1.5) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored and as a precautionary measure, the lowest dose should be used in these patients.

Use in elderly

Pharmacokinetic evaluation of pravastatin in patients over the age of 65 years indicates an increased AUC. There were no reported increases in the incidence of adverse effects in these or other studies involving patients in that age group. However elderly patients may be more susceptible to myopathy. As a precautionary measure, the lowest dose should be administered initially.

Hypertriglyceridemia

PRAVASTATIN has only a moderate triglyceride lowering effect and it is not indicated where hypertriglyceridemia is the abnormality of most concern (i.e.: hypertriglyceridemia types I, IV and V).

Severe Hypercholesterolemia

Higher doses (>40 mg/day) required for some patients with severe hypercholesterolemia are associated with increase plasma levels of pravastatin. **Caution should be exercised in such patients who are also significantly renally impaired or elderly.**

Thyroid function

Serum thyroxine was studied in 661 patients who were administered pravastatin in five controlled clinical trials. From observations of up to two years in duration, no clear association was found between pravastatin use and changes in thyroxine levels.

Skeletal muscle

Myalgia, myopathy, and rhabdomyolysis have been reported with the use of HMG-CoA reductase inhibitors.

Although there is no muscular contraindication to the prescription of statin, certain predisposing factors may increase the risk of muscular toxicity and therefore justify a careful evaluation of the benefit/risk and special clinical monitoring (see below)

Uncomplicated myalgia has been reported in pravastatin-treated patients. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal, was reported to be possibly due to pravastatin in < 0.1% of patients in clinical trials. During therapy with lovastatin, another HMG-CoA reductase inhibitor, either alone or in combination with gemfibrozil, markedly elevated CPK values have been seen in conjunction with a myositis syndrome. Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also been rarely reported with pravastatin. Very rarely (in about 1 case over 100,000 patient-years), rhabdomyolysis occurs, with or without secondary renal insufficiency. Rhabdomyolysis is an acute potentially fatal condition if skeletal muscle, which may develop at any time during treatment and is characterised by massive muscle destruction associated with major increase in CK (usually > 30 or 40 x ULN) leading to myoglobinuria. Rhabdomyolysis resulting in renal failure has also been observed during concomitant therapy with lovastatin and the immunosuppressive agent, ciclosporin. Although myalgia has been associated with pravastatin therapy, the myositis syndrome, as seen with lovastatin, has not so far been reported with pravastatin. However, myopathy should be considered in any patients with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness. In such cases CK levels should be measured (see below). Statin therapy should be temporarily interrupted when CK levels are > 5 x ULN or when there are severe clinical symptoms. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g.:sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine, or electrolyte disorders, or uncontrolled epilepsy).

The risk of myopathy with statins appears to be exposure- dependent and therefore may vary with individual drugs (due to lipophilicity and pharmacokinetic differences), including their dosage and potential for drug interactions. An increase in the incidence of myopathy has been described in patients receiving other statins in combination with inhibitors of cytochrome P450 metabolism. This may result from pharmacokinetic interactions that have not been documented for PRAVASTATIN.

The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either fibrates, ciclosporin, erythromycin or niacin. The use of fibrates alone is occasionally associated with myopathy. In a limited size clinical trial of combined therapy with pravastatin (40 mg/day) and gemfibrozil (1200 mg/day) myopathy was not reported, although a trend towards CPK elevations and musculoskeletal symptoms was seen. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving pravastatin and fusidic acid in combination. As for other HMG-CoA reductase inhibitors, combination of pravastatin with fibrates is not recommended and should generally be avoided. PRAVASTATIN must not be co-administered with fusidic acid.

Myopathy has not been observed in 3 post-transplant clinical trials which had involved a total of 100 patients (76 cardiac and 24 renal). Some patients have been treated for up to 2 years with pravastatin (10 to 40 mg) and ciclosporin and either with or without other immunosuppressants. In a separate lipid lowering trial involving 158 patients, no myopathy has been reported with pravastatin in combination with niacin.
In adults, asymptomatic adult patients on statin therapy, routing monitoring of CK or other muscle enzyme levels is not recommended. However, measurement of CK is recommended before starting statin therapy in patients with special predisposing factors and in patients developing muscular symptoms during satin therapy, as described below. If CK levels are significantly elevated at baseline (> 5 x ULN), CK levels should be measured about 5 to 7 days later to confirm the results. When measured, CK levels should be interpreted in the context of other potential factors that can cause transient muscle damage, such as strenuous exercise or muscle trauma.

Before treatment initiation: Caution should be used in patients with predisposing factors such as renal impairment, hypothyroidism, previous history of muscular toxicity with statin or fibrate, personal or familial history of hereditary muscular disorders, or alcohol abuse.

In these cases, CK levels should be measured prior to initiation of therapy. CK measurement should also be considered before starting treatment in persons over 70 years of age especially in the presence of other predisposing factors in this population. If CK levels are significantly elevated (>5 Page 6 of 22 x ULN) at baseline, treatment should not be started, and the results should be re-measured after 5- 7 days. The baseline CK levels may also be useful as a reference in the event of a later increase during statin therapy.

During treatment: patients should be advised to report promptly unexplained muscle pain, tenderness, weakness or cramps. In these cases, CK levels should be measured. If a markedly elevated (>5 x ULN) CK level is detected, statin therapy must be interrupted. Treatments discontinuation should also be considered if the muscular symptoms are severe and cause daily discomfort, even if the CK increase remains ≤5 x ULN. If symptoms resolve and CK levels return to normal, then reintroduction of statin therapy may be considered at the lowest dose and with close monitoring. If a hereditary muscular disease is suspected in such patients, restarting statin therapy is not recommended.

Fusidic acid

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

Endocrine function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels, and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown.

In one long-term study investigating the endocrine function in hypercholesterolemic patients, pravastatin treatment had no effect upon basal and stimulated cortisol levels as well as on aldosterone secretion. Although no change was reported in the testicular function, conflicting results were observed in the analysis of sperm motility after administration of pravastatin. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥ 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g.: ketoconazole, spironolactone, cimetidine) that may diminish the levels of activity of steroid hormones.

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including pravastatin (see below under Type 2 Diabetes Mellitus).

CNS toxicity

CNS vascular lesions, characterized by perivascular haemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibres) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Hypersensitivity

With lovastatin an apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, thrombocytopenia, leukopenia, haemolytic anaemia, positive antinuclear antibody (ANA), erythrocytes sedimentation rate (ESR) increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever and malaise. Although to date hypersensitivity syndrome has not been described as such, in few instances eosinophilia and skin eruptions appear to be associated with pravastatin treatment. If hypersensitivity is suspected pravastatin should be discontinued. Patients should be advised to report promptly any signs of hypersensitivity such as angioedema, urticaria, photosensitivity, polyarthralgia, fever, malaise.

Homozygous familial hypercholesterolaemia

Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolaemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Type 2 Diabetes Mellitus

There is sufficient evidence to support an association between statin use and new-onset type 2 diabetes mellitus; however the risk appears to be mainly in patients already at risk of developing diabetes. 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 of exclude an increased risk for any individual statin or a dose-response relationship. The cardiovascular benefits of statin therapy continue to outweigh the risk of diabetes.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Immune mediated necrotizing myopathy

There have been rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persists despite discontinuation of statin treatment.

Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

Effects on laboratory tests

See section 4.8 Undesirable effects.

4.5 Interaction with other medicines and other forms of interaction

Gemfibrozil, fenofibrates and fibric acid derivatives

In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

The use of fibrates alone is occasionally associated with myopathy. An increased risk of muscle related adverse events, including rhabdomyolysis, have been reported when fibrates are coadministered with other statins, particularly in subjects with pre-existing renal insufficiency. Although e.g. gemfibrozil does not statistically affect the bioavailability of pravastatin, an association with concomitant use of pravastatin cannot be excluded. Therefore, the combined use of pravastatin and fibrates (e.g. gemfibrozil, fenofibrate) should generally be avoided. If this combination is considered necessary, careful clinical and CK monitoring of patients on such regimen is required.

Based on post-marketing surveillance, gemfibrozil, fenofibrate, other fibrates and lipid lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone (see section 4.4 Special Warnings and Precautions for Use). Therefore, combined drug therapy should be approached with caution.

Antipyrine

Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolising enzymes, it is not expected that any significant interaction of pravastatin with other medicines (e.g. phenytoin, quinidine) metabolised by the cytochrome P450 system will occur.

Antacids

On average, antacids reduce the bioavailability of pravastatin. This change is not statistically significant, and the clinical significance is not known.

Cimetidine

Cimetidine increases the bioavailability of pravastatin. The change is not statistically significant, and the clinical significance is not known.

Macrolides

Macrolides have the potential to increase statin exposure while used in combination. Pravastatin should be used cautiously with macrolide antibiotics due to the potential increased risk of myopathies. In one of the two interaction studies with pravastatin and erythromycin a statistically significant increase in pravastatin AUC and C_{max} was observed. In a similar study with clarithromycin a statistically significant increase in AUC and C_{max} was observed. Although these changes were minor, caution should be exercised when associating pravastatin with erythromycin or clarithromycin.

Propranolol

Co-administration of propranolol and pravastatin reduced the AUC values.

Vitamin K antagonists

As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of pravastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or other coumarin anticoagulant) may result in an increased International Normalised Ration (INR). Discontinuation or down-titration of pravastatin may result in a decrease of INR. In such situations, appropriate monitoring of INR is needed.

Bile Acid Sequestrants
Preliminary evidence suggests that the cholesterol-lowering effect of pravastatin sodium and the bile acid sequestrants, cholestyramine/colestipol are additive. When pravastatin was administered one hour before or four hours after cholestyramine or one hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. Concomitant administration resulted in decrease in the mean AUC of pravastatin.

Cholestyramine/colestipol
When pravastatin was administered one hour before or four hours after cholestyramine or one hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin (see section 4.2 Dose and method of administration).

Warfarin
With concomitant administration, pravastatin did not alter the plasma protein-binding of warfarin. Chronic dosing of the two medicines did not produce any changes in the anticoagulant status.

Ciclosporin
In a single-dose study, pravastatin levels were found to be increased in cardiac patients receiving ciclosporin. In a second multi-dose study, in renal transplant patients receiving ciclosporin, pravastatin levels were higher than those seen in healthy volunteer studies. This does not appear to be a metabolic interaction involving P450 3A4.

Digoxin
Co-administration of digoxin with HMG-CoA reductase inhibitors has been shown to increase the steady state digoxin concentrations. The potential effects of coadministration of digoxin should be closely monitored.

Fusidic acid
The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of pravastatin with systemic fusidic acid. 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. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, pravastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. (Also see section 4.4 Special Warnings and Precautions for use).

Other drugs
Unlike simvastatin and atorvastatin, pravastatin is not significantly metabolised in vivo by cytochrome P450 3A4. Therefore, plasma concentrations of pravastatin are not significantly elevated when cytochrome P450 3A4 is inhibited by agents such as diltiazem and itraconazole.

In interaction studies with aspirin, gemfibrozil, nicotinic acid or probucol, no statistically significant differences in bioavailability were seen when pravastatin was administered. In other interaction studies antacids (one hour prior to pravastatin) reduce and cimetidine increase the bioavailability of pravastatin; these changes were not statistically significant.
The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of pravastatin with systemic fusidic acid. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, pravastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4 Special Warnings and Precautions for Use.

During clinical trials, no noticeable medicine interactions were reported when pravastatin sodium tablets were added to: diuretics, antihypertensives, digitalis, angiotensin converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerins.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category D - Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformation or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

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 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 a 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 HMG- CoA reductase inhibitor she should be informed of the possibility of foetal injury and discuss the implications with her pregnancy specialist (see section 4.3 Contraindications)

Breast-feeding

A negligible amount of pravastatin is excreted in human breast milk. Because of the potential for adverse reactions in nursing infants, if the mother is being treated with pravastatin, nursing should be discontinued.

Fertility

In a study in rats, with daily doses as high as 500 mg/kg pravastatin did not produce any adverse effects on fertility or general reproductive performance.

The clinical significance of these findings it not clear.

4.7 Effects on ability to drive and use machines

Pravastatin has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness and visual disturbances may occur during treatment.

4.8 Undesirable effects

Pravastatin is generally well tolerated. Adverse events, both clinical and laboratory, are usually mild and transient. In all clinical studies (controlled and uncontrolled), approximately 2% of patients were discontinued from treatment due to adverse experiences attributable to pravastatin.
The safety and tolerability of pravastatin at a dose of 80 mg in two controlled trials, with a mean exposure of 8.6 months were similar to that of pravastatin at lower doses. However, musculoskeletal adverse events, gastrointestinal adverse events and CK elevations are slightly more common with an 80 mg dose

In seven randomized double-blind placebo-controlled trials involving over 21,500 patients treated with pravastatin 40 mg (N = 10,784) or placebo (N = 10,719), the safety and tolerability in the pravastatin group was comparable to that of the placebo group. Over 19,000 patients were followed for a median of 4.8 to 5.9 years, while the remaining patients were followed for two years or more.

Clinical adverse events probably or possibly related, or of uncertain relationship to therapy, occurring in at least 0.5% of patients treated with pravastatin or placebo in these long-term morbidity/mortality trials are shown in the following table:

	PRAVASTATIN (n = 10,784) (%)	PLACEBO (n = 10,719) (%)
Cardiovascular		
Angina pectoris	3.1	3.4
Disturbance rhythm (subjective)	0.8	0.7
Hypertension	0.7	0.9
Oedema	0.6	0.6
Myocardial infarction	0.5	0.7
Dermatological		
Rash	2.1	2.2
Pruritus	0.9	1.0
Endocrine / Metabolic		
Sexual dysfunction	0.7	0.7
Gastrointestinal		
Dyspepsia / heartburn	3.5	3.7
Nausea / vomiting	1.4	1.6
Flatulence	1.2	1.1
Constipation	1.2	1.3
Diarrhoea	0.9	1.1
Abdominal pain	0.9	1.0
distension abdomen	0.5	0.5
General		
Fatigue	3.4	3.3
Chest pain	2.6	2.6
Weight gain	0.6	0.7
Influenza	0.6	0.5
Weight loss	0.6	0.5
Weakness	0.5	0.6
Musculoskeletal		
Musculoskeletal pain (includes arthralgia)	5.9	5.7
Muscle cramp	2.0	1.8
Myalgia	1.4	1.4
Musculoskeletal trauma	0.5	0.3
Nervous		
Dizziness	2.2	2.1
Headache	1.9	1.8
Sleep disturbance	1.0	0.9
Depression	1.0	1.0
Anxiety / nervousness	1.0	1.2
Paraesthesia	0.9	0.9
Numbness	0.5	0.4
Renal / Genitourinary		
Abnormal urination (includes dysuria and nocturia)	1.0	0.8
Respiratory		
Dyspnoea	1.6	1.6
Upper respiratory infection	1.3	1.3
Cough	1.0	1.0
Sinus abnormality (includes sinusitis)	0.8	0.8
Pharyngitis	0.5	0.6

	PRAVASTATIN (n = 10,784) (%)	PLACEBO (n = 10,719) (%)
Special Senses		
Vision disturbance (includes blurred vision)	1.5	1.3
Eye disturbance (includes eye inflammation)	0.8	0.9
Hearing abnormality (includes tinnitus and hearing loss)	0.6	0.5
Lens opacity	0.5	0.4

Lens

In 820 patients treated with pravastatin for periods up to a year or more, there was no evidence that pravastatin was associated with cataract formation. In placebo-controlled studies, 294 patients (92 on placebo/control, 202 on pravastatin) were evaluated using the Lens Opacity Classification System (a sophisticated method of lens assessment) at six months and one year following the initiation of treatment. When compared with the baseline evaluation, the final examination revealed the following:

	PRAVASTATIN (Number of Patients (%)	Placebo/Control Number of Patients (%)
Improved	29 (14%)	13 (14%)
No change	142 (70%)	63 (68%)
Worsened	31 (15%)	16 (17%)
Total	202	92

There was no statistically significant difference in the change in lens opacity between the control and pravastatin treatment groups during this time interval.

Comparative data indicate that pravastatin is 100-fold less potent than both lovastatin and simvastatin (other HMG-CoA reductase inhibitors) in inhibiting cholesterol biosynthesis in rat lens and 40-fold less potent than lovastatin in inhibiting cholesterol biosynthesis in rabbit lens. Furthermore, unlike lovastatin and simvastatin, cataracts have not been observed in animal studies (beagle dogs) when chronic oral doses of pravastatin were administered for two years.

In three large placebo-controlled trials [West of Scotland Study (WOS), Cholesterol and Recurrent Events Study (CARE) and Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)] involving a total of 19,768 patients treated with pravastatin (N = 9,895) or placebo (N = 9,873), the safety and tolerability profile in the pravastatin group was comparable to that of the placebo group over the median 4.8–5.9 years of follow-up.

The following effects have been reported with drugs in this class; not all the effects listed below have necessarily been associated with pravastatin therapy:

Skeletal
myopathy
rhabdomyolysis (examples of signs and symptoms are muscle weakness, muscle swelling, muscle pain, dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure, cardiac arrhythmia.) Rhabdomyolysis may be fatal. (see sections 4.3, 4.4 and 4.5)
arthralgia
Neurological
dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis)
tremor
vertigo
memory loss
paraesthesia
peripheral neuropathy
peripheral nerve palsy
anxiety
depression
sleep disturbances including insomnia and nightmares
Hypersensitivity reactions
an apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, haemolytic anaemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
Gastrointestinal
pancreatitis
hepatitis, including chronic active hepatitis
cholestatic jaundice
fatty change in liver, and, rarely, cirrhosis
fulminant hepatic necrosis, and hepatoma
anorexia
vomiting
Skin
alopecia
pruritus
a variety of skin changes (e.g. nodules, discolouration, dryness of skin/mucous membranes, changes to hair/nails) have been reported
Reproductive
gynecomastia
loss of libido
erectile dysfunction
sexual dysfunction
Eye
progression of cataracts (lens opacities)
ophthalmoplegia

Laboratory abnormalities elevated transaminases, alkaline phosphatase, and bilirubin thyroid function abnormalities increases in serum transaminase (ALT, AST) values and CPK have been observed (see section 4.4) transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy anaemia, thrombocytopenia, and leukopenia have been reported with HMG- CoA reductase inhibitors
Respiratory exceptional cases of interstitial lung disease, especially with long term therapy

Post marketing

In addition to the above the following adverse events have been reported during post marketing experience of pravastatin:

Nervous system disorders
Very rare: peripheral polyneuropathy, in particular if used for long period of time, paresthaesia
Immune system disorders
Very rare: Hypersensitivity reactions, anaphylaxis, angioedema, lupus erythematlous-like syndrome
Gastrointestinal disorders
Very rare: pancreatitis
Hepatobiliary diorders
Very rare: jaundice, hepatitis, fulminant hepatic necrosis
Musculoskeletal and connective tissue disorders
Very rare: rhabdomyolysis, which can be associated with acute renal failure secondary to thyroid function abnormalities (see section 4.4 Special Warnings and Precautions for Use), myositis, polymyositis
Frequency not known: Immune-mediated necrotizing myopathy (see section 4.4 Special Warnings and Precautions for Use. Isolated cases of tendon disorders, sometimes complicated by rupture
Class Effects
Nightmares
Memory Loss
Depression
Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4 Special Warnings and Precautions for Use)
Endocrine disorders
Diabetes mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose $\geq$ 5.6 mmol/L, BMI > 30kg/m^2 of hypertension)

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://nzphvc.otago.ac.nz/reporting/

4.9 **Overdose**

Symptoms

There has been limited experience with overdosage of pravastatin. To date, there are two reported cases, both of which were asymptomatic and not associated with clinical laboratory test abnormalities. Of these two

cases, one occurred in a clinical trial patient who ingested 3 g pravastatin; the other ingested 280 mg pravastatin, as marketed tablets. Both cases also involved overdose of concomitant medications.

Treatment
Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

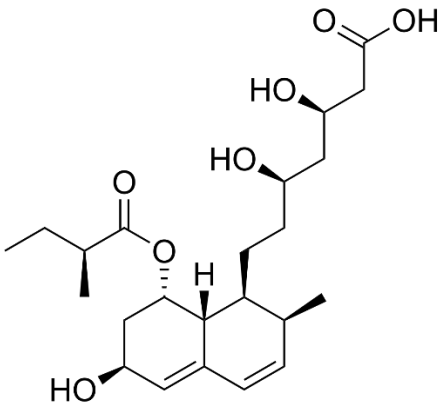
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Serum lipid reducing agents/cholesterol and triglyceride reducers/HMG-CoA reductase inhibitors

ATC code: C10AA03

Chemical Structure:



Molecular Formula: $C_{23}H_{36}O_7$

CAS number: 81093-37-0

Molecular weight: 424.53

General

Pravastatin sodium, is one of a class of lipid-lowering compounds, the HMG-CoA reductase inhibitors, that reduce cholesterol biosynthesis. These agents are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate.

Pravastatin produces its lipid-lowering effect in two ways. First, as a consequence of its reversible inhibition of HMG-CoA reductase activity, it affects modest reductions in intracellular pools of cholesterol. This results in an increase in the number of LDL- receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL. Second, pravastatin inhibits LDL production by inhibiting hepatic synthesis of VLDL, the LDL precursor.

Clinical and pathological studies have shown that elevated levels of Total-C, LDL-cholesterol (LDL-C) and apolipoprotein B (a membrane transport complex for LDL) promote human atherosclerosis. Similarly,

decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, 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. In multi-centre clinical trials those pharmacological and/or non-pharmacological interventions that lowered Total-C and LDL-C and increased HDL-C reduced the rate of cardiovascular events [both fatal and non-fatal myocardial infarctions (MI)] and improved survival. In both normal volunteers and patients with hypercholesterolaemia, treatment with pravastatin reduced Total-C, LDL-C, apolipoprotein B, VLDL-C and triglycerides (TG) while increasing HDL-C and apolipoprotein A.

The effects of HMG-CoA reductase inhibitors on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

Pravastatin is a hydrophilic HMG CoA reductase inhibitor.

Clinical Efficacy and Safety

Hypercholesterolaemia

In controlled trials in patients with moderate hypercholesterolemia with or without atherosclerotic cardiovascular disease, pravastatin monotherapy reduced the progression of atherosclerosis, and cardiovascular events (e.g. fatal and non-fatal MI) or death.

Pravastatin is highly effective in reducing Total-C and LDL-C in patients with heterozygous familial, familial combined, and non-familial (non-FH) forms of hypercholesterolaemia. A therapeutic response is seen within one week and the maximum response usually is achieved within four weeks. This response is maintained during extended periods of therapy.

A single daily dose administered in the evening is as effective as the same total daily dose given twice a day. Once daily administration in the evening appears to be marginally more effective than once daily administration in the morning, perhaps because hepatic cholesterol is synthesized mainly at night.

In multi-centre, double-blind, placebo-controlled studies of patients with primary hypercholesterolaemia, treatment with pravastatin significantly decreased Total-C, LDL-C, Total-C/HDL-C and LDL-C/HDL-C ratios, decreased VLDL-C and plasma TG levels, and increased HDL-C. Whether administered once or twice daily, a clear dose-response relationship (i.e. lipid-lowering) was seen by 1 to 2 weeks following the initiation of treatment.

Primary Hypercholesterolaemia Study
Dose Response of Pravastatin*
Once Daily Administration at Bedtime

Dose	Total C	LDL-C	HDL-C	TG
5 mg	-14%	-19%	+ 5%	-14%
10 mg	-16%	-22%	+ 7%	-15%
20 mg	-24%	-32%	+ 2%	-11%
40 mg	-25%	-34%	+12%	-24%

* Percent change from baseline after 8 weeks

Atherosclerosis

The Pravastatin Limitation of Atherosclerosis in the Coronary Arteries trial (PLAC I) study, the effect of pravastatin therapy on coronary atherosclerosis was assessed by coronary angiography in patients with coronary disease and moderate hypercholesterolemia (baseline LDL-C range = 3.4 to 4.9 mmol/L). In

this double-blind, placebo-controlled, multi-centre controlled trial in which 408 patients with moderate hypercholesterolaemia (baseline mean LDL-C = 163 mg/dL, Total-C = 231 mg/dL) and coronary artery disease; 206 of these patients received pravastatin. In a prospectively planned analysis of clinical events occurring 90 days after initiating therapy to allow for maximum lipid lowering effect, treatment with pravastatin resulted in a 74% reduction in the rate of myocardial infarction (fatal and non-fatal) [p = 0.006], and a 62% reduction for the combined endpoint of non-fatal MI or all cause death [p = 0.02]. For the entire study duration, myocardial infarction (fatal and non-fatal) rate was reduced by 60% [p = 0.0498].

In the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I) study, the effect of pravastatin therapy on coronary atherosclerosis was assessed by coronary angiography in patients with coronary disease and moderate hypercholesterolemia (baseline LDL-C range = 3.4 to 4.9 mmol/L). In this double-blind, , multicentre, controlled clinical trial, in which 408 patients were randomized, angiograms were evaluated at baseline and at three years in 264 patients. No statistically significant difference between pravastatin and placebo was seen for the primary endpoint (per-patient change in mean coronary artery diameter), or for one of two secondary endpoints (change in percent lumen diameter stenosis). For the other secondary endpoint (change in minimum lumen diameter), statistically significant slowing of disease was seen in the pravastatin treatment group (p = 0.02). Although the trial was not designed to assess clinical coronary events, for myocardial infarction (fatal and non-fatal), the event rate was reduced in the pravastatin group by a statistically significant margin (10.5% for placebo versus 4.2% for pravastatin, p = 0.0498). In another 3-year, double-blind, placebo-controlled, randomized trial in patients with mild to moderate hyperlipidemia, the Pravastatin, Lipids, and Atherosclerosis in the Carotids (PLAC II) study, the effect of pravastatin therapy on carotid atherosclerosis was assessed by B-mode ultrasound. No statistically significant differences were seen in the carotid bifurcation, internal carotid artery, or all segments combined (the primary endpoint); pravastatin did reduce the increase in wall thickness in the common carotid artery (p = 0.02). Although the study was not designed to assess cardiovascular events or mortality, the event rates were reduced in the pravastatin treatment group by statistically significant margins for two combined endpoints: non-fatal or fatal myocardial infarction (13.3% placebo versus 2.7% for pravastatin, p = 0.018): and non-fatal myocardial infarction or all deaths (17.1% for placebo versus 6.7% for pravastatin, p = 0.049). Analysis of pooled events from PLAC I and PLAC II showed that treatment with pravastatin was associated with a 67% reduction in the event rate of fatal and non-fatal myocardial infarction (11.4% for placebo versus 3.8% for pravastatin, p = 0.003), and 55% for the combined endpoint of non-fatal myocardial infarction or death from any cause (13.8% placebo versus 6.2% pravastatin, p = 0.009). Divergence in the cumulative event rate curves began at one year and was statistically significant at 2 years.

In consideration of the results of Pravastatin Limitation of Atherosclerosis in Coronary and Carotid Arteries Trials (PLAC I and PLAC II), it is important to be aware of the limitations of angiography in defining the extent and site of atherosclerosis plaque. Acute coronary events tend to occur not at the site of severe stenosis, but at lesser stenoses which are lipid rich and more prone to rupture. In addition, angiographic changes are not properly validated end points to measure morbidity and/or mortality in patients with atherosclerotic coronary artery disease associated with hypercholesterolemia.

Prevention of coronary heart disease

Pravastatin is effective in reducing the risk of coronary heart disease (CHD) death (fatal MI and sudden death) plus non-fatal MI and improving survival in hypercholesterolaemic patients without previous myocardial infarction.

The West of Scotland Study (WOS) was a randomised, double-blind, placebo-controlled trial among 6595 male patients (45 to 64 years) with moderate to severe hypercholesterolaemia (LDL-C = 4 to 6.6 mmol/L), a total fasting cholesterol > 6.5 mmol/L, and without a previous MI. Patients were treated with standard care, including dietary advice, and either pravastatin 40 mg (N = 3302) or placebo (N = 3293) each evening for a median duration of 4.8 years. The study was designed to assess the effect of pravastatin on fatal and non-fatal coronary heart disease (CHD). Significant results (p > 0.05) are given in table below.

West of Scotland results		
Endpoint	Events prevented per 1000 patients treated with pravastatin for 3 years	Relative risk reduction
Non-fatal myocardial infarction	19	31%
Cardiovascular death	7	28%
Death any cause	9	22%
Coronary heart disease death or non-fatal myocardial infarction	24	31%
Coronary angiography	14	31%
Coronary angioplasty or coronary artery bypass graft	8	37%

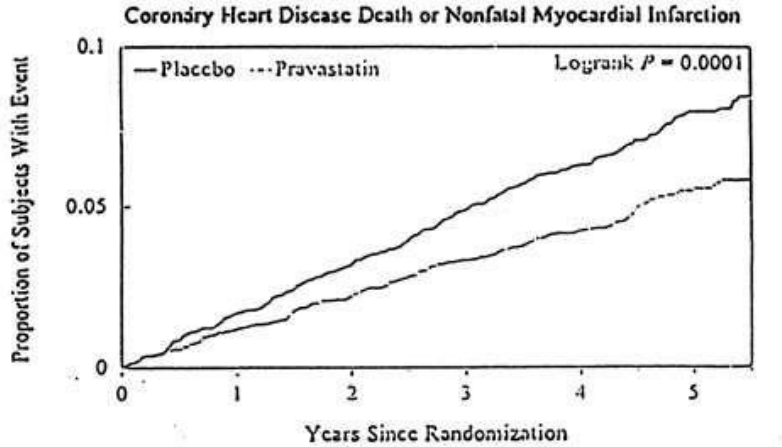
* Based on the Kaplan-Meier estimates of 5 year event rates

The effect on the combined endpoint of coronary heart disease death or non-fatal myocardial infarction was evident as early as six months after beginning pravastatin therapy.

There was no statistically significant difference between treatment groups in non-cardiovascular mortality, including cancer death.

West of Scotland Study – effect of pravastatin on plasma lipids (mmol/L) (intention to treat analysis)			
	Baseline mean (n = 3302)	Year 5 mean (n = 1335)	% change * mean
LDL-Cholesterol	5.0	3.8	-24.9
HDL-Cholesterol	1.1	1.3	10.1
Total Cholesterol	7.0	5.8	-18.6
Triglycerides	1.9	1.8	-4.4

* All changes statistically significant ($p < 0.001$)



Kaplan-Meier estimates for the effect of pravastatin and placebo on the occurrence of definite CHD death or nonfatal MI.

Myocardial infarction or unstable angina pectoris

Pravastatin is effective in reducing the risk of a fatal coronary event and non-fatal MI in patients with a previous myocardial infarction and average (normal) serum cholesterol, who are > 65 years of age and whose serum LDL-cholesterol is > 3.36 mmol/L. Pravastatin is effective in reducing the frequency of stroke in patients with a previous myocardial infarction and average (normal) serum cholesterol. Pravastatin is also effective in reducing the risk of total mortality, CHD death, and recurrent coronary events (including myocardial infarction) in patients with unstable angina pectoris

In the Cholesterol and Recurrent Events (CARE) study the effect of pravastatin on coronary heart disease death and non-fatal MI was assessed in 4,159 men and women with average (normal) serum cholesterol levels (baseline mean Total-C = 209mg/dL) and who had experienced a MI in the preceding 3–20 months. Patients in this double-blind, placebo-controlled study participated for an average of 4.9 years. Treatment with pravastatin significantly reduced the rate of a recurrent coronary event (either CHD death or non-fatal MI) by 24% (p = 0.003). The reduction in risk for this combined endpoint was significant for both men and women. The risk of undergoing revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) was significantly reduced by 27% (p < 0.001) in the pravastatin treated patients. Pravastatin also significantly reduced the risk for stroke by 32% (p = 0.032), and stroke or transient ischemic attack (TIA) combined by 26% (p = 0.025). At baseline, 84% of the patients were receiving aspirin and 82% were taking antihypertensive medications. The comparison of the primary, secondary and tertiary endpoints for the study are summarized in the following table.

CARE Study results					
Event	**Number (%[a]) of subjects**		**Number of events avoided per 1000 subjects over 5 years of treatment with pravastatin**	**Risk reduction[b] 95% CI**	**Logrank p-value[c]**
	Pravastatin (n = 2081)	**Placebo (n = 2078)**			
Fatal CHD or definite* non-fatal	202 (10.4)	274 (13.3)	29	24 (9.36)	0.003
Fatal CHD	96 (4.9)	119 (5.6)	7	20 (-5.39)	0.104
Total mortality	180 (8.6)	196 (9.4)	8	9 (-12.26)	0.366

a Kaplan-Meier estimate of 5-year event rate

b Due to treatment with pravastatin by Cox proportional hazards model

c Mantel-Haenszel logrank p-value for between group difference of cumulative event curves

* The term "definite" refers to a report of a clinical MI by a clinical centre that meets the criteria for MI described in the Manual of Operations as determined by review by the MI Confirmation Centre

In the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study, the effect of pravastatin was assessed in 9,014 men and women with normal to elevated serum cholesterol levels (baseline Total-C = 4.0–7.0 mmol/L); mean Total-C = 5.66 mmol/L) and who had experienced either a myocardial infarction or had been hospitalised for unstable angina pectoris in the preceding 3–36 months. Patients with a wide range of baseline levels of triglycerides were included (≤ 5.0 mmol/L) and enrolment was not restricted by baseline levels of HDL cholesterol. At baseline, 82% of patients were receiving aspirin and 76% were receiving antihypertensive medication. Patients in this multi-centre, double-blind, placebo-controlled study participated for a mean of 5.6 years (median = 5.9years). Treatment with pravastatin significantly reduced the risk for CHD death by 24% (p = 0.0004). The risk for coronary events (either CHD death or non-fatal MI) was significantly reduced by 24% (p < 0.0001) in the pravastatin treated patients. The risk for fatal or non-fatal MI was reduced by 29% (p < 0.0001). Pravastatin reduced both the risk for total mortality by 23% (p < 0.0001) and cardiovascular mortality by 25% (p < 0.0001). The risk for undergoing myocardial revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) was significantly reduced by 20% (p < 0.0001) in the pravastatin treated patients. Pravastatin also significantly reduced the risk for stroke by 19% (p = 0.0477). Treatment with pravastatin significantly reduced the number of days of hospitalisation per 100 person-years of follow-up by 15% (p < 0.001). The effect of pravastatin on reducing CHD events was consistent regardless of age, gender or diabetic status. Among patients who qualified with a history of myocardial infarction, pravastatin significantly reduced the risk for total mortality and for fatal or non-fatal MI (risk reduction for total mortality = 21% ,p = 0.0016; risk reduction for fatal or non-fatal MI = 25%,p = 0.0008). Among patients who qualified with a history of hospitalisation for unstable angina pectoris,

pravastatin significantly reduced the risk for total mortality and for fatal or non-fatal MI (risk reduction for total mortality = 26%, p = 0.0035; risk reduction for fatal or non-fatal MI = 37%, p = 0.0003).

Lipid Study results Comparison of event rates by treatment group (primary, secondary and tertiary efficacy measures)					
Event	**Number (%[a]) of subjects**		**Number of events avoided per 1000 subjects over 5 years of treatment with pravastatin**	**Risk reduction[b] 95% CI**	**Logrank p-value[c]**
	Pravastatin (n = 5412)	**Placebo (n = 4502)**			
CHD mortality	287 (5.3)	373 (6.4)	11	24 (12.35)	0.0004
Total mortality	498 (8.9)	633 (10.5)	16	23 (13.31)	<0.0001
CHD mortality or non-fatal MI	557 (10.5)	715 (13.2)	27	24 (15.32)	<0.0001
Stroke • All-cause • Non-haemorrhagic	169 (3.0) 154 (2.7)	204 (3.9) 196 (3.8)	9 11	19 (0.34) 23 (5.38)	0.0477 0.0154
Cardiovascular mortality	331 (6.0)	433 (7.5)	15	25 (13.35)	<0.0001
Myocardial revascularisation procedures (CABG or PTCA)	584 (11.4)	706 (14.1)	27	20 (10.28)	<0.0001
Atherosclerotic events	1116 (21.1)	1352 (25.6)	44	21 (14.27)	<0.0001
Fatal or non-fatal MI	336 (6.5)	463 (9.0)	25	29 (18.38)	<0.0001

a Kaplan-Meier estimate of 5-year event rate

b Due to treatment with pravastatin by an unadjsuted Cox proportional hazards model

c Stratified Mantel-Haenszel logrank p-value for between group difference of cumulative event curves stratified by qualifying event (MI or UAP at randomization)

* The term "definite" refers to a report of a clinical MI by a clinical centre that meets the criteria for MI described in the Manual of Operations as determined by review by the MI Confirmation Centre

Solid organ transplantation

The safety and efficacy of pravastatin treatment in patients receiving immunosuppressive therapy following kidney and cardiac transplantation were assessed in two prospective randomised controlled trials. Patients were treated concurrently with either 20 mg or 40 mg pravastatin and a standard immunosuppressive regimen of ciclosporin and prednisone. Cardiac transplant patients also received azathioprine as part of the immunosuppressive regimen. Plasma lipid levels were reduced in patients who received pravastatin. In the patients who received pravastatin in these trials (n = 71) no significant increases in creatine phosphokinase or hepatic transaminases were observed and there were no cases of myositis and rhabdomyolysis. However, there is limited data available on the incidence of these adverse events in transplant patients and physicians should consider the risk of myositis and rhabdomyolysis when prescribing pravastatin therapy for hyperlipidemia in transplant patients.

5.2 Pharmacokinetic properties

Absorption

Pravastatin tablets are administered orally in the active form. They are rapidly absorbed, with peak plasma levels attained 1 to 1.5 hours following ingestion. Based on urinary recovery of radio labelled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%.

Distribution

Steady-state AUCs, C_{max} and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily administration of pravastatin sodium tablets. Approximately 50% of the circulating drug is bound to plasma proteins.

Biotransformation

Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance. Since it is excreted in the bile, plasma levels are of limited value in predicting therapeutic effectiveness.

The major metabolite of pravastatin is the 3a-hydroxy isomer. This metabolite has one-tenth to one- fortieth the HMG-CoA reductase inhibitory activity of the parent compound.

Elimination

The plasma elimination half-life ($T_{1/2}$) of pravastatin (oral) is between 1.5 and 2 hours. Approximately 20% of a radio labelled oral dose is excreted in urine and 70% in the faeces. After intravenous administration of radio labelled pravastatin to normal volunteers, approximately 47% of total body clearance was via renal excretion and 53% by non-renal routes (i.e. biliary excretion and biotransformation).

Accumulation of drug and/or metabolites may occur in patients with renal or hepatic insufficiency, although, as there are dual routes of elimination, the potential exists for compensatory excretion by the alternate route.

Linearity/non-linearity

Pravastatin plasma concentrations [including: area under the concentration-time curve (AUC), peak (C_{max}), and steady-state minimum (C_{min})] are directly proportional to administered dose.

5.3 Preclinical safety data

Genotoxicity

In six genetic toxicology studies performed with pravastatin, there was no evidence of mutagenic potential at the chromosomal or gene level.

Carcinogenicity

In a 2-year oral study of rats, a statistically significant increase in the incidence of hepatocellular carcinomas was observed in male rats given 100 mg/kg daily of pravastatin. This change was not seen in male rats given 40 mg/kg or less, or in female rats at doses up to 100 mg/kg daily. Increased incidences of hepatocellular carcinomas were also observed in male and female mice dosed with pravastatin at 250 and 500 mg/kg daily, but not at 100 mg/kg/day or less. An increased incidence of pulmonary adenomas was seen in female mice dosed at 250 mg/kg/day. The AUC value for the serum concentration of pravastatin at the no effect dose level of 100 mg/kg/day in mice was 2 times higher than that in humans receiving 80 mg pravastatin per day.

The hepatocarcinogenic effect of pravastatin in rats is associated with proliferation of hepatic peroxisomes. Other HMG-CoA reductase inhibitors (simvastatin and lovastatin) also induce hepatic peroxisome proliferation and hepatocellular carcinomas in rats and mice. The clinical significance of these findings is unclear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PRAVASTATIN tablets contain the following excipients:

- Lactose monohydrate
- Microcrystalline Cellulose
- Magnesium Stearate
- Croscarmellose Sodium
- Iron oxide red (in 10 mg tablets)
- Iron oxide yellow (in 20 mg and 40 mg tablets)
- Brilliant blue FCF (in 40 mg tablets)

PRAVASTATIN tablets are gluten free.

PRAVASTATIN tablets contain lactose.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months from date of manufacture

6.4 Special Precautions

Store at or below 25°C

Protect from light and moisture.

Keep the container tightly closed.

6.5 Nature and contents of container

Blister packs of 30 tablets.

Bottles packs of 30, 100 and 500 tablets.

Not all pack types pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Clinect NZ Pty Limited
C/- Ebos Group Limited
108 Wrights Road
Christchurch 8024
New Zealand
Telephone: 0800 138 803

9 DATE OF FIRST APPROVAL

09 October 2008

10 DATE OF REVISION OF THE TEXT

25 September 2023

Summary Table of Changes

Section changed	Summary of new information
4.3	Inclusion of serum transaminase elevation information
4.4	Updated information for hepatic impairment, renal impairment, use in elderly, skeletal muscle, endocrine function. Addition of information on sever hypercholesterolemia
4.5	Updated information on gemfibrozil and inclusion of fenofibrates and fibric acid derivatives with this information. Updated percentage decrease results in the mean AUC of pravastatin when concomitantly administered with Cholestyramine/colestipol Updated information of statins with fusidic acid Inclusion of information on Antacids, Cimetidine, Macrolides, Propranolol, Bile Acid Sequestrants, Digoxin Inclusion of information on risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of pravastatin with systemic fusidic acid.
4.8	Additional controlled trial results and post marketing adverse event data