AUSTRALIAN PRODUCT INFORMATION

CHOLSTAT

pravastatin sodium tablet

1 NAME OF THE MEDICINE

Pravastatin sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pravastatin belongs to 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 catalysing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate

Each tablet contains 10 mg, 20 mg or 40 mg of pravastatin sodium as the active ingredient.

Excipients with known effect: soya bean products and sugars as lactose.

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS. .

3 PHARMACEUTICAL FORM

CHOLSTAT 10	:	Pravastatin 10 mg tablets, white to off-white, capsule shaped, biconvex tablets with "G | G" on one side and "PR | 10" on the other side
CHOLSTAT 20	:	Pravastatin 20 mg tablets; white to off-white, capsule shaped, biconvex tablets with "G | G" on one side and "PR | 20" on the other side
CHOLSTAT 40	:	Pravastatin 40 mg tablets; white to off-white, capsules shaped, biconvex tablets with "G" on one side and "PR 40" on the other side

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

1. As an adjunct to diet for the treatment of hypercholesterolemia. Prior to initiating therapy with pravastatin, secondary causes of hypercholesterolaemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

2. Pravastatin is indicated in patients with previous myocardial infarction including those who have normal (4.0 to 5.5 mmol/L) serum cholesterol levels.

3. Pravastatin is indicated in patients with unstable angina pectoris (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials).

4. Pravastatin is indicated as an adjunct to diet and lifestyle modification for the treatment of Heterozygous Familial Hypercholesterolaemia in children and adolescent patients aged 8 years and older (See Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

Prior to initiating Cholstat (pravastatin sodium), the patient should be placed on a standard cholesterol-lowering diet (AHA Phase 1 or NCEP Step 1) for a maximum of 3 to 6 months, depending upon the severity of the lipid elevation. Dietary therapy should be continued during treatment.

Adult Patients

The recommended starting dose is 10 to 20 mg once daily at bedtime. In primary hypercholesterolemic patients with significant renal or hepatic dysfunction, and in the elderly, a starting dose of 10 mg daily at bedtime is recommended. For maximum effect, pravastatin should be taken at bedtime on an empty stomach.

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 to 80 mg administered once a day at bedtime.

Pravastatin may be given in divided doses.

For the prevention of coronary heart disease in patients with Hypercholesterolaemia the dose is 40 mg per day as a single dose. The same dose is recommended for secondary prevention of MI in patients with average (normal) serum cholesterol.

Paediatric Patients

Children (Ages 8 to 13 Years, Inclusive)

The recommended dose is 20 mg once daily in children 8-13 years of age. Doses greater than 20mg have not been studied in this patient population.

Adolescents (Ages 14 to 18 Years)

The recommended dose is 40 mg once daily in adolescents 14 to 18 years of age. Doses greater than 40 mg have not been studied in this patient population.

Children and adolescents treated with pravastatin should be re-evaluated in adulthood and appropriate changes made to their cholesterol-lowering regimen to achieve adult goals for LDL-C.

Ciclosporin

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.

Concomitant Therapy

Pravastatin has been administered concurrently with colestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See section 4.4 SPECIAL AND WARNINGS AND PRECAUTIONS FOR USE: Skeletal Muscle and Drug Interactions.)

The efficacy and safety of pravastatin 80 mg in combination with other lipid-lowering agents have not been investigated.

Pravastatin tablets should not be broken in half.

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations in liver function tests.

Use in Pregnancy (Category D)

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 1,000 mg/kg daily nor in rabbits at doses of up to 50 mg/kg daily, pravastatin should be administered to women of child-bearing 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 as to the potential hazards to the foetus.

Women of Childbearing Potential

Pravastatin should not be administered to women of childbearing age unless on an effective contraception and are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient again advised of the potential hazard to the foetus.

Concomitant use of fusidic acid (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

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.

Hypertrigylceridemia

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).

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. 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. Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also very rarely 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. Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is suspected or diagnosed. (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.) CPK levels should be checked at 6 to 12 month intervals in paediatric patients.

The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either fibrates, ciclosporin, erythromycin or nicotinic acid. 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. The combined use of pravastatin and fibrates should generally be avoided.

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 mg 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 nicotinic 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. 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 $\geq 50\%$ rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. 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. 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.

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

In a placebo-controlled study of 214 paediatric patients with HeFH, of which 106 were treated with pravastatin (20mg in the children aged 8-13 years and 40mg in the adolescents aged 14-18 years) for two years, there were no detectable differences seen in any of the endocrine parameters □ACTH, cortisol, DHEAS, FSH, LH, TSH, estradiol (girls) or testosterone (boys)□ relative to placebo. There were no detectable differences seen in height and weight changes, testicular volume changes, or Tanner score relative to placebo.

CNS Toxicity

CNS vascular lesions, characterized by perivascular haemorrhage, 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 angiodema, urticaria, photosensitivity, polyarthralgia, fever, malaise.

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 creatinine kinase, which persists despite discontinuation of statin treatment.

Use in Hepatic Impairment

HMG-CoA reductase inhibitors have been associated with biochemical abnormalities of liver function. As with other lipid-lowering agents, marked persistent increases (greater than three times the upper limit of normal) in serum transaminases were seen in 1.3% of 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 pretreatment 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 pretreatment 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.

As with other lipid-lowering agents, liver function tests should be performed periodically. Special attention should be given to patients who develop increased transaminase levels and those on higher doses of pravastatin. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in alanine aminotransferase (ALT) and asparate 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 the 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 3 α-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.

Use in the 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. As a precautionary measure, the lowest dose should be administered initially.

Paediatric Use

The safety and effectiveness of pravastatin in children and adolescents with heterozygous familial hypercholesterolaemia from 8-18 years of age have been evaluated in a placebo-controlled study of 2 years duration. Patients treated with pravastatin had an adverse experience profile generally similar to that observed in adults with influenza and headache commonly reported in both treatment groups. (See section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS): Paediatric Patients). Doses greater than 40 mg have not been studied in this population. For dosing information see section 4.2 DOSE AND METHOD OF ADMINISTRATION: Adult Patients and Paediatric Patients.

Double-blind, placebo-controlled pravastatin studies in children less than 8 years of age have not been conducted.

Effects on Laboratory Tests

See section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS): Laboratory test Abnormalities.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Gemfibrozil

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 Tmax for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

Colestyramine/Colestipol

When pravastatin was administered one hour before or four hours after colestyramine or one hour before colestipol and a standard meal, there was no clinically significant decrease in bio-availability 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).

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 cytochrome P450 3A4.

Warfarin

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

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 drugs (e.g., phenytoin, quinidine) metabolised by the cytochrome P450 system will occur.

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 bio-availability were seen when pravastatin was administered. In other interaction studies antacids (one hour prior to pravastatin) reduce and cimetidine increase the bio-availability 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 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.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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

The clinical significance of these findings is not clear.

Use in Pregnancy

Pregnancy Category: D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. 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 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 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 a 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.

Use in Lactation

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

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 ADVERSE EFFECTS (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 randomised 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 4.8-5.9 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 table below:

Table 1

		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
	edema	0.6	0.6
	myocardial infarction	0.5	0.7
Dermatologic			
	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

		Pravastatin N=10,784 (%)	Placebo N=10,719 (%)
	diarrhoea	0.9	1.1
	abdominal pain	0.9	1.0
	distention 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
	paresthesia	0.9	0.9
	numbness	0.5	0.4
Renal/Genitourinary			
	abnormality urination (includes dysuria and nocturia)	1.0	0.8
Respiratory			
	dyspnea	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
Special Senses			
	vision disturbance (includes blurred vision)	1.5	1.3
	disturbance eye (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:

Table 2

	Pravastatin Number of Patients (%)	**Placebo/Control Number of Patients (%)**
Improved No change Worsened	29 (14%) 142 (70%) 31 (15%)	13 (14%) 63 (68%) 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], Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID] (see section 5.1 PHARMACODYNAMIC PROPERTIES) involving a total of 19,786 patients treated with pravastatin (N=9895) or placebo (N=9873), the safety and tolerability profile in the pravastatin group was comparable to that of the placebo group over the median 4.8 to 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, arthralgia.

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 (refer to see section 4.3 CONTRAINDICATIONS, section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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, insomnia, depression.

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.

Eye

Progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory abnormalities

Elevated transaminases, alkaline phosphatise and bilirubin, and thyroid function abnormalities.

Sleep disturbances

Including insomnia and nightmares

Depression

Sexual dysfunction

Exceptional cases of interstitial lung disease, especially with long term therapy.

Laboratory test abnormalities

Increase in serum transaminase (ALT, AST) values and CPK have been observed (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

Paediatric Use

In a two (2) year double-blind placebo-controlled study involving 100 boys and 114 girls with HeFH, there were no serious adverse events or discontinuations for adverse events attributable to pravastatin. Pravastatin was generally well tolerated in paediatric patients and the adverse reaction profile was similar to that observed in adults. The incidence of headache was 23.6% vs 15.7%; musculoskeletal pain, 16.0% vs 7.4%; CPK elevations greater than four times the pre-treatment level 3.8% vs 2.8% and dizziness 5.7% vs 0%, in pravastatin treated patients vs placebo treated patients, respectively (see section 5.1 PHARMACODYNAMIC PROPERTIES: Paediatric Clinical Study and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE; Paediatric Use).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 overdose occur, treat symptomatically and institute supportive measures as required.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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 low density lipoprotein (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 very low density lipoprotein (VLDL), the LDL precursor.

Clinical and pathologic studies have shown that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B, (a membrane transport complex for LDL) promote human atherosclerosis. Similarly decreased levels of high density lipoprotein (HDL) - cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic 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 pharmacologic and/or non-pharmacologic interventions that lowered Total-C and LDL-C and increased HDL-C reduced the rate of cardiovascular events (both fatal and nonfatal myocardial infarctions) 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 high density lipoprotein cholesterol (HDL-C) and apolipoprotein A.

The effects of HMG-CoA reductase inhibitors on lipoprotein A (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 Trials

Hypercholesterolaemia

In controlled trials in patients with moderate Hypercholesterolaemia with or without atherosclerotic cardiovascular disease, pravastatin mono-therapy 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 1 week, and the maximum response usually is achieved within 4 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, and 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.

Table 3

Primary Hypercholesterolaemia Study Dose Response of Pravastatin* Once Daily Administration At Bedtime				
DOSE	**Total-C**	**LDL-C**	**HDL-C**	**TG**
10mg	- 16%	- 22%	+ 7%	- 15%
20mg	- 24%	- 32%	+ 2%	- 11%
40mg	- 25%	- 34%	+ 12%	- 24%
* Percent change from baseline after 8 weeks				

In a pooled analysis of two multicentre, double-blind, placebo-controlled studies in patients with primary hypercholesterolaemia, treatment with pravastatin at a daily dose of 80 mg increased HDL-C and significantly decreased Total-C, LDL-C and TG from baseline after 6 weeks. The efficacy results of the individual studies were consistent with the pooled data. Mean percent changes from baseline after 6 weeks of treatment were: Total-C (-27%), LDL-C (-37%), HDL-C (+3%) and TG (-19%), with placebo-subtracted changes for LDL-C and TG of -36% and -20% respectively.

Pravastatin, in combination with diet has been shown to reduce the incidence of cardiovascular events (e.g., fatal and non-fatal myocardial infarction). The mechanism responsible for the beneficial effects of pravastatin in hypercholesterolaemic patients is not known.

Atherosclerosis

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 Hypercholesterolaemia (baseline LDL-C range = 3.4 to 4.9 mmol/L). In this double-blind, multi-centre, controlled clinical trial, in which 408 patients were randomised, 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, randomised trial in patients with mild to moderate hyperlipidaemia, 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 Hypercholesterolaemia.

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 hypercholesterolemic male 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=4-6.6 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 4.

Table 4

WEST OF SCOTLAND STUDY RESULTS		
Endpoint	**Events Prevented Per 1,000 Patients Treated with Pravastatin For 5 Years[1]**	**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%
[1] 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.

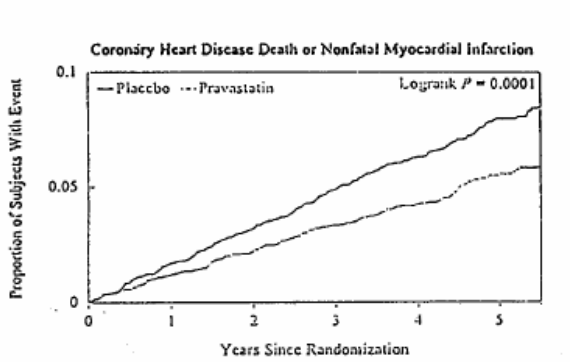
There was no statistically significant difference between treatment groups in non-cardiovascular mortality, including cancer death.

Table 5

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 [1] 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
[1] All changes statistically significant (p<0.001)			

Figure 1 : Myocardial Infarction and Unstable Angina Pectoris



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

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 4159 men and women with average (normal) serum cholesterol levels (baseline mean Total-C=209 mg/dL) (5.4 mmol/L), and who had experienced a myocardial infarction in the preceding 3 to 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 nonfatal MI) by 24% (p=0.003). This risk reduction was statistically significant in those patients aged 65 years of age or older and in those who demonstrated a serum LDL-cholesterol of >3.36 mmol/L. 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 summarised in the following table.

Table 6

CARE STUDY RESULTS

	Number (%*) of Subjects				
Event	**Pravastatin (N=2081)**	**Placebo (N=2078)**	**Number of Events Avoided per 1000 Subjects over 5 Years of Treatment with Pravastatin**	**Risk Reduction†95% CI**	**Logrank P-value‡**
Fatal CHD or definite § non-fatal	212 (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

* Kaplan-Meier estimate of 5-year event rate.
† Due to treatment with pravastatin by Cox proportional hazards model.
‡ Mantel-Haenszel logrank P-value for between group difference of cumulative event curves.
§ The terms 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 40mg daily was assessed in 9014 men and women with normal to elevated serum cholesterol levels (baseline Total-C = 4.0 to 7.0 mmol/L; mean Total-C = 5.66 mmol/L; mean Total-C/HDL-C ratio = 5.9), 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 baseline levels of HDL cholesterol did not restrict enrolment. At baseline, 82% of patients were receiving aspirin, 76% were receiving antihypertensive medication, and 41% had undergone myocardial revascularisation. Patients in this multi-centre, double-blind, placebo-controlled study participated for a mean of 5.6 years (median= 5.9 years). Treatment with pravastatin significantly reduced the risk for CHD death by 24% (p=0.0004). The risk for coronary events (either CHD death or nonfatal MI) was significantly reduced by 24% (p<0.0001) in the pravastatin treated patients. The risk for fatal or nonfatal myocardial infarction 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 prespecified subgroup (age, sex, hypertensives, diabetics, smokers, lipid subgroups) analyses were conducted using the combined end point of CHD and non-fatal MI. The study was not powered to examine results within each subgroup but formal testing for heterogeneity of treatment effect was undertaken across each of the subgroups and no significant heterogeneity was found (p≥0.08) i.e., a consistent treatment effect was seen with pravastatin therapy across all patient subgroups and event parameters. Among patients who qualified with a history of myocardial infarction, pravastatin significantly reduced the risk for total mortality by 25% (p=0.0016); for CHD mortality by 23% (p=0.004); for CHD events by 22% (p=0.002) and for fatal or non-fatal MI by 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 by 26% (p=0.0035; for CHD mortality by 26% (p=0.0358); for CHD events by 29% (p=0.0001) and for fatal or non-fatal MI by 37% (p=0.0003).

Table 7

LIPID STUDY RESULTS

Comparison of event rates by treatment group (primary, secondary and tertiary efficacy measures)

Event	Number (%[a]) Pravastatin (N=4.512)	Placebo (N=4.502)	Number of Events Avoided per 1000 Subjects Over 5 Years of Treatment with Pravastatin	Risk Reduction [b](95% CI)	Logrank P-value[c]
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	169 (3.0)	204 (3.9)	9	19% (0.34)	0.0477
Non-haemorrhagic	154 (2.7)	196 (3.8)	11	23% (5.38)	0.0154
Cardiovascular mortality	331 (6.0)	433 (7.5)	15	25% (13.35)	<0.0001
Myocardial revascularization procedures (CABG or PTCA)	584 (11.4)	706 (14.1)	27	20% (10.28)	<0.0001
Atherosclerotic events	1.116 (21.2)	1.352 (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 unadjusted Cox proportional hazards model
c Stratified Mantel-Haenszel logrank P-value for between group difference of cumulative curves, stratified by qualifying event (MI or UAP at randomisation).

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 immunosuppresive regimen of ciclosporin and prednisone. Cardiac transplant patients also received azathioprine as part of their immunosuppresive 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 creatinine 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 hyperlipidaemia in transplant patients.

Paediatric Study

A double-blind placebo-controlled study in 214 patients (100 boys and 114 girls) with heterozygous familial hypercholesterolaemia (HeFH), aged 8-18 years was conducted for two (2) years. The children (aged 8-13 years) were randomised to placebo (n=63) or 20mg of pravastatin daily (n=65) and the adolescents (aged 14-

18 years) were randomised to placebo (n=45) or 40mg of pravastatin daily (n=41). Inclusion in the study required an LDL-C level > 95th percentile for age and sex and one parent with either a clinical or molecular diagnosis of familial hypercholesterolaemia. The mean baseline LDL-C value was 239 mg/dL (6.2mmol/L) and 237 mg/dL (6.1 mmol/L) in the pravastatin (range: 151-405 mg/dL, 3.9-10.5 mmol/L) and placebo (range: 154-375 mg/dL, 4.0-9.7 mmol/L) groups, respectively. The mean baseline total cholesterol and apolipoprotein B levels in the pravastatin group were: 302 mg/dL (7.8 mmol/L) and 141 mg/dL (1.4 g/L), respectively; mean baseline total cholesterol and apolipoprotein B levels in the placebo group were: 299 mg/dL (7.7 mmol/L) and 140 mg/dL (1.4 g/L), respectively.

The treatment criteria for Heterozygous Familial Hypercholesterolaemia in children and adolescent patients aged 8 years and older are:

- LDLc consistently greater than 95th percentile for age and gender and;
- An adequate trial of a lipid lowering diet and
- One parent with a clinical or molecular diagnosis of familial hypercholesterolaemia.

Pravastatin significantly decreased plasma levels of LDL-C, Total-C, and apolipoprotein B in both children and adolescents (See Table). The effect of pravastatin treatment in the two age groups was similar.

Table 8

Lipid-Lowering Effects of Pravastatin in Paediatric Patients with Heterozygous Familial hypercholesterolaemia: Least-Squares Mean Percent Change from Baseline at Month 24 (Last Observation Carried Forward: Intent-to-Treat)*

	Pravastatin 20mg (Aged 8-13 years) N=65	**Pravastatin 40mg (Aged 14-18 years) N=41**	**Combined Pravastatin (Aged 8-18 years) N=106**	**Combined Placebo (Aged 8-18 years) N=108**	**95% CI of the difference between combined pravastatin and placebo**
LDL-C	-26.04**	-21.07**	-24.07**	-1.52	(-26.74, -18.86)
TC	-20.75**	-13.08**	-17.72**	-0.65	(-20.40, -13.83)
HDL-C	1.04	13.71	5.97	3.13	(-1.71, 7.43)
TG	-9.58	-0.30	-5.88	-3.27	(-13.95, 10.01)
ApoB (N)	-23.16** (61)	-18.08** (39)	-21.11** (100)	-0.97 (106)	(-24.29, -16.18)

* The above least-squares mean values were calculated based on log-transformed lipid values.
** Significant at p ≤0.0001 when compared with placebo.

The safety and efficacy of pravastatin doses above 40 mg daily have not been studied in children. The long-term efficacy of pravastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 PHARMACOKINETIC PROPERTIES

Pravastatin is administered orally in the active form. It is 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 bio-availability is 17%.

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

The plasma elimination half-life (t½) of pravastatin (oral) is between 1.5 and 3.5 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. The major metabolite of pravastatin is the 3 α- hydroxy isomer. This metabolite has one-tenth to one-fortieth the HMG-Co-A reductase inhibitory activity of the parent compound.

After 2 weeks of once-daily 20mg oral pravastatin administration, the geometric means AUC were 80.7 (CV 44%) and 44.8 (CV 89%) ng.hr/mL for children (8-11 years, n=14) and adolescents (12-16 years, n=10), respectively. The corresponding values for C_{max} were 42.4 (CV 54%) and 18.6ng/mL (CV 100%) for children and adolescents, respectively. No conclusion can be made based on these findings due to small number of samples and large variability.

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

Cholstat tablets contain the following inactive ingredients: aluminium magnesium silicate, lactose monohydrate, povidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and purified talc.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Al/Al

Pack sizes: 10's, 30's, 100's.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 98486 – CHOLSTAT 10 pravastatin sodium 10mg tablet blister pack

AUST R 98488 – CHOLSTAT 20 pravastatin sodium 20mg tablet blister pack

AUST R 98489 – CHOLSTAT 40 pravastatin sodium 40mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

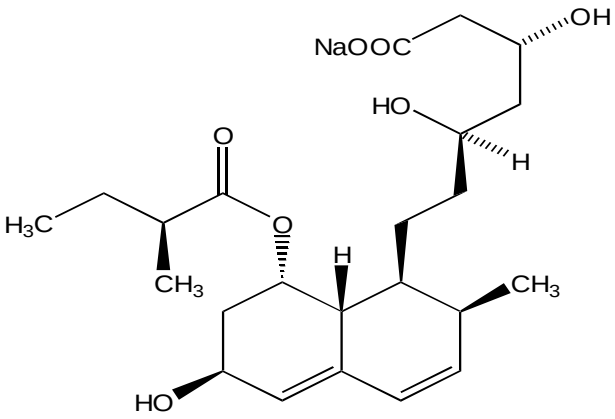
6.7 PHYSICOCHEMICAL PROPERTIES

Pravastatin sodium is an odourless, white to off-white, fine or crystalline powder. It is a relatively polar hydrophilic compound with a partition coefficient (octanol/water) of 0.59 at a pH of 7.0. It is freely soluble in methanol and water (>300 mg/mL), slightly soluble in isopropanol, and practically insoluble in acetone, acetonitrile, chloroform and ether.

Chemical Structure

(3R,5R)-7-[(1S,2S,6S,8S,8aR)-1,2,6,7,8,8a-Hexahydro-6-hydroxy-2-methyl-8-[(S)-2-methylbutyryloxy-1-naphthyl]]-3,5-dihydroxyheptanoic acid, sodium salt

Structural formula



Molecular Formula

$C_{23}H_{35}NaO_7$

Molecular Weight

446.52

CAS Number

81131–70-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

02/12/2003

10 DATE OF REVISION

12/01/2022

Summary Table of Changes

Section Changed	Summary of New Information
All	New internal template and format updates
1	Trade name removed
6.7 and 9	Editorial changes
8	Sponsor’s detail updated

CHOLSTAT® is a Viatris company trade mark.

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