

Public Assessment Report

Decentralised Procedure

Pravastatin Sodium 10 mg Tablets

Pravastatin Sodium 20 mg Tablets

Pravastatin Sodium 40 mg Tablets

PL 20075/0018-20

UK/H/1095/01-03/DC

Accord Healthcare Limited

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Accord Healthcare Limited marketing authorisations (licences) for the medicinal products Pravastatin Sodium 10 mg, 20 mg and 40 mg Tablets (PL 20075/0018-20).

Pravastatin sodium tablets work by reducing your body's production of 'bad cholesterol' and raising levels of 'good cholesterol'. Cholesterol is a lipid that can cause coronary heart disease by narrowing the vessels that supply the heart with blood. This condition, called hardening of the arteries (atherosclerosis), may lead to angina, a heart attack (myocardial infarction) or stroke.

If you have already had a heart attack or have unstable angina (chest pain), pravastatin sodium reduces the risk of you having another heart attack or stroke in the future, regardless of your cholesterol level.

If you have raised levels of cholesterol but do not have coronary heart disease, pravastatin sodium reduces the risk of this occurring, or of you having a heart attack or stroke in the future.

The data submitted in support of the applications for Pravastatin Sodium 10 mg, 20 mg and 40 mg Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence marketing authorisations have been granted.

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Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	Pravastatin Sodium 10 mg, 20 mg and 40 mg Tablets
Name of the active substance (INN)	Pravastatin sodium
Pharmacotherapeutic classification (ATC code)	HMG CoA reductase inhibitors (C10A A03)
Pharmaceutical form and strength	10 mg, 20 mg & 40 mg Tablets
Reference numbers for the Decentralised Procedure	UK/H/1095/01-03/DC
Reference Member State	United Kingdom
Member States concerned	BE, DE, EE, ES, HU, IE, IT, LV, MT, NL & PT
Date of start of the procedure	15 June 2007
End date of decentralised procedure	9 July 2008
Marketing Authorisation Number	PL 20075/0018-20
Name and address of the authorisation holder	Accord Healthcare Limited Sage House 319, Pinner Road North Harrow Middlesex HA1 4 HF United Kingdom

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pravastatin Sodium 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg pravastatin sodium.

Excipient: Lactose monohydrate 50 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Pravastatin Tablets 10 mg: Yellow colored, rounded rectangular shaped, biconvex, uncoated tablets debossed 'PDT' on one side and '10' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia.

Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (eg. exercise, weight reduction) is inadequate.

Primary prevention

Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolaemia and at high risk of a first cardiovascular event, as an adjunct to diet (see section 5.1)

Secondary prevention

Reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina pectoris and with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors (see section 5.1).

Post transplantation

Reduction of post transplantation hyperlipidaemia in-patient receiving immunosuppressive therapy following solid organ transplantation (see sections 4.2, 4.5 and 5.1).

4.2 Posology and method of administration

Prior to initiating Pravastatin Tablets, secondary causes of hypercholesterolaemia should be excluded and patients should be placed on a standard lipid-lowering diet, which should be continued during treatment.

Pravastatin sodium is administered orally once daily preferably in the evening with or without food.

Hypercholesterolaemia: The recommended dose range is 10 - 40 mg once daily. The therapeutic response is seen within a week and the full effect of a given dose occurs within four weeks, therefore periodic lipid determinations should be performed and the dosage adjusted accordingly. The maximum daily dose is 40 mg.

Cardiovascular prevention: In all preventive morbidity and mortality trials, the only studied starting and maintenance dose was 40 mg daily.

Dosage after transplantation: Following organ transplantation a starting dose of 20 mg per day is recommended in patients receiving immunosuppressive therapy (see section 4.5). Depending on the response of the lipid parameters, the dose may be adjusted upto 40 mg under close medical supervision (see section 4.5).

Children and adolescents (8-18 years of age) with heterozygous familial

hypercholesterolaemia: The recommended dose range is 10 –20 mg once daily between 8 and 13 years of age as doses greater than 20 mg have not been studied in this population and 10- 40 mg daily between 14 and 18 years of age (for children and adolescent females of child –bearing potential see section 4.6; for results of the study see section 5.1).

Elderly patients: There is no dose adjustment necessary in these patients unless there are predisposing risk factors (see section 4.4).

Renal or hepatic impairment: A starting dose of 10 mg a day is recommended in patients with moderate or severe renal impairment or significant hepatic impairment. The dosage should be adjusted according to the response of lipid parameters and under medical supervision.

Concomitant therapy: The lipid lowering effects of pravastatin sodium on total cholesterol and LDL - cholesterol are enhanced when combined with a bile acid – binding resin (eg. colestyramine, colestipol). Pravastatin sodium should be given either one hour before or atleast four hours after the resin (see section 4.5).

For patients taking ciclosporin with or without other immunosuppressive medicinal products, treatment should begin with 20 mg of pravastatin sodium once daily and titration to 40 mg should be preformed with caution (see section 4.5).

4.3 **Contraindications**

Hypersensitivity to the active substance or to any of the excipients. Acute liver disease or unexplained, persistent elevations of serum transaminase elevation exceeding 3 times the upper limit of normal (see section 4.4).

Pregnancy and lactation (see section 4.6).

4.4 **Special warnings and precautions for use**

Pravastatin has not been evaluated in patients with homozygous familial hypercholesterolaemia. Therapy is not suitable when hypercholesterolaemia is due to elevated HDL-cholesterol.

As for other HMG-CoA reductase inhibitors, combination of pravastatin with fibrates is not recommended.

In children before puberty, the benefit /risk of treatment should be carefully evaluated by physicians before treatment initiation.

Hepatic disorders: As with other lipid- lowering agents, moderate increase in liver transaminase levels has been observed. In majority of cases, liver transaminase levels have returned to their baseline value without the need for treatment discontinuation. Special attention should be given to patients who develop increased transaminase levels and therapy should be discontinued if increases in alanine aminotransferase (ALT) and aspartate aminotransferase exceed three times the upper limit of normal and persist.

Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion.

Muscle disorders: As with other HMG-CoA reductase inhibitors (statins), pravastatin has been associated with the onset of myalgia, myopathy and very rarely, rhabdomyolysis. Myopathy must be considered in any patient under statin therapy presenting with unexplained muscle symptoms such as muscle weakness, or muscle cramps. In such cases creatine kinase levels should be measured. Statin therapy should be temporarily interrupted when creatine kinase levels are $> 5 \times \text{ULN}$ or when there are severe clinical symptoms. Very rarely (in about 1 case over 100,000 patients-years) rhabdomyolysis occurs, with or without secondary renal insufficiency. Rhabdomyolysis is an acute potentially fatal condition of skeletal muscle, which may develop at any time during treatment and is characterized by massive muscle destruction associated with major increase in creatine kinase (usually > 30 or $40 \times \text{ULN}$) leading to myoglobinuria.

The risk of myopathy with statins appears to be exposure- dependant and therefore may vary with individual drugs (due to lipophilicity and pharmacokinetic differences), including their dosage and potential for drug interactions.

Although there is no muscular contraindication to the prescription of a statin, certain predisposing factor may increase the risk of muscular toxicity and therefore justify a careful evaluation of benefit/risk and special clinical monitoring. CK measurement is indicated before starting statin therapy in these patients.

The risk and severity of muscular disorders during statin therapy is increased by the co administration of interacting medicines. The use of fibrates alone is occasionally associated with myopathy. The combined use of a statin and fibrates should generally be avoided. The co-administration of statins and nicotinic acid should be used with caution. An increase in the incidence of myopathy has also 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. When associated with statin therapy, muscle symptoms usually resolve following discontinuation of statin therapy.

Creatine kinase measurement and interpretation:

Routine monitoring of creatine kinase (CK) or other muscle enzyme levels is not recommended in asymptomatic patients on statin therapy. However, measurement of CK is recommended before starting statin therapy in patients with special predisposing factors, and in patient developing muscular symptoms during statin therapy as described below. If CK levels are significantly elevated at baseline ($> 5 \times \text{ULN}$), Ck levels should be remeasured 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 a 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 ($> 5 \times \text{ULN}$) 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 ($> 5 \times \text{ULN}$) CK level is detected, statin therapy must be interrupted. Treatment discontinuation should also be considered if the muscular symptoms are severe and cause daily discomfort, even if the CK increase remains $\leq 5 \times \text{ULN}$. 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.

Lactose: This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Fibrates: The use of fibrates alone is occasionally with myopathy. An increased risk of muscle related adverse events, including rhabdomyolysis, have been reported when fibrates are co-administered with other statins. These adverse events with pravastatin cannot be excluded,

therefore the combined use of pravastatin and fibrates (e.g. gemfibrozil, fenofibrate) should generally be avoided (see section 4.4). If this combination is considered necessary, careful clinical and CK monitoring of patients on such regimen is required.

Colestyramine / Colestipol: Concomitant administration resulted in approximately 40 to 50% decrease in the bioavailability of pravastatin. There was no clinically significant decrease in bioavailability or therapeutic effect when pravastatin was administered one hour before or four hours after colestyramine or one hour before colestipol (see section 4.2).

Ciclosporin: Concomittant administration of pravastatin and ciclosporin leads to an approximately 4- fold increase in pravastatin systemic exposure. In some patients, however, the increase in pravastatin exposure may be larger. Clinical and biochemical monitoring of patients receiving this combination is recommended (see section 4.2).

Warfarin and other oral anticoagulants: Bioavailability parameters at steady state for pravastatin were not altered following administration with warfarin. Chronic dosing of the two products did not produce any changes in the anticoagulant action of warfarin.

Products metabolized by cytochrome P450: Pravastatin is not metabolized to a clinically significant extent by the cytochrome P450 system. This is why products that are metabolized by, or inhibitors of, the cytochrome P450 system can be added to a stable regimen of pravastatin without causing significant changes in the plasma levels of pravastatin as have been seen with other statins. The absence of a significant pharmacokinetic interaction with pravastatin has been specifically demonstrated for several products, particularly those that are substrates/inhibitors of CYP3A4 e.g. diltiazem, verapamil, itraconazole, Ketoconazole, protease inhibitors, grapefruit juice and CYP2C9 inhibitors (e.g. fluconazole).

In one of the two interaction studies with pravastatin and erythromycin a statistically significant increase in pravastatin AUC (70%) and C_{max} (121%) was observed. In a similar study with clarithromycin a statistically significant increase in AUC (110%) and C_{max} (127%) was observed. Although these changes were minor, caution should be exercised when associating pravastatin with erythromycin or clarithromycin.

Other products: In interaction studies no statistically significant differences in bioavailability were observed when pravastatin was administered with acetylsalicylic acid, antacids (when given one hour prior to pravastatin), nicotinic acid or probucol.

4.6 **Pregnancy and lactation**

Pregnancy: Pravastatin is contraindicated during pregnancy and should be administered to women of childbearing potential only when such patients are unlikely to conceive and have been informed of the potential risk. Special caution is recommended in adolescent females of childbearing potential to ensure proper understanding of the potential risk associated with pravastatin therapy during pregnancy. If a patient plans to become pregnant or becomes pregnant the doctor has to be informed immediately and pravastatin should be discontinued because of the potential risk to the fetus.

Lactation: A small amount of pravastatin is excreted in human breast milk, therefore pravastatin is contraindicated during breastfeeding.

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 may occur during treatment.

4.8 **Undesirable effects**

The frequencies of adverse events are ranked according to the following: very common ($\geq 1/10$); common ($\geq 1/100, < 1/10$); uncommon ($\geq 1/1000, < 1/100$); rare ($\geq 1/10000, < 1/1000$); very rare ($< 1/10000$); not known (cannot be estimated from the available data).

Clinical trials: Pravastatin has been studied at 40 mg in seven randomised double-blind placebo-controlled trials involving over 21,000 patients treated with pravastatin (n = 10764) or placebo (n = 10719), representing over 47,000 patients years of exposure to pravastatin. Over 19,000 patients were followed for a median of 4.8 – 5.9 years.

The following adverse drug reactions were reported; none of them occurred at a rate in excess of 0.3% in the pravastatin group compared to the placebo group.

Nervous system disorder:

Uncommon: dizziness, headache, sleep disturbance, insomnia.

Eye disorders:

Uncommon: vision disturbance (including blurred vision and diplopia).

Gastrointestinal disorders:

Uncommon: dyspepsia/heartburn, abdominal pain, nausea/ vomiting, constipation, diarrhoea, flatulence.

Skin and subcutaneous tissue disorders:

Uncommon: pruritus, rash, urticaria, scalp/hair abnormality (including alopecia).

Renal and urinary disorders:

Uncommon : abnormal urination (including dysuria, frequency, nocturia)

Reproductive system and breast disorders:

Uncommon : sexual dysfunction.

General disorders:

Uncommon: fatigue.

Events of special clinical interest:

Skeletal muscle: Effects on the skeletal muscle, eg. musculoskeletal pain including arthralgia, muscle cramps, myalgia, muscle weakness and elevated creatine kinase levels have been reported in clinical trials. The rate of myalgia (1.4% pravastatin vs. 1.4% placebo) and muscle weakness (0.1% pravastatin vs. <0.1% placebo) and the incidence of CK level $> 3 \times$ ULN and $>$

10 x ULN in CARE, WOSCOPS and LIPID was similar to placebo (1.6% pravastatin vs. 1.6% placebo and 1.0% pravastatin vs. 1.0% placebo, respectively) (see section 4.4).

Liver effects: Elevations of serum transaminases have been reported. In the three long-term, placebo-controlled clinical trials CARE, WOSCOPS and LIPID, marked abnormalities of ALT and AST (> 3 x ULN) occurred at similar frequency (≤ 1.2%) in both treatment groups.

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, paresthesia.

Immune system disorders:

Very rare: Hypersensitivity reactions: anaphylaxis, angioedema, lupus erythematosus- like syndrome.

Gastrointestinal disorders:

Very rare: pancreatitis.

Hepatobiliary disorders:

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 myoglobinuria, myopathy (see section 4.4) myositis, polymyositis.

Isolated cases of tendon disorders, sometimes complicated by rupture.

4.9 Overdose

The experience with overdose of Pravastatin sodium in humans is very limited. There is no specific treatment in the event of overdose. In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC Code: C10AA03.

Pravastatin is a competitive inhibitor of 3-hydroxy –3- methylglutaryl-coenzyme A reductase, the enzyme catalyzing the early rate limiting step in cholesterol biosynthesis, and produces its

lipid lowering effect in two ways. Firstly with the reversible and specific competitive inhibition of HMG-CoA reductase, it effects modest reduction in the synthesis of intracellular 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-cholesterol.

Secondly, pravastatin inhibits LDL production by inhibiting the hepatic synthesis of VLDL-cholesterol, the LDL- cholesterol precursor.

In both healthy subjects and patients with hypercholesterolaemia, pravastatin sodium lowers the following lipid values: total cholesterol, LDL-cholesterol, apolipoprotein B, VLDL-cholesterol and triglycerides; while HDL-cholesterol and apolipoprotein A are elevated.

Clinical efficacy:

Primary prevention

The "West of Scotland Coronary Prevention Study (WOSCOPS)" was a randomised, double-blind, placebo-controlled trial among 6,595 male patients aged from 45 to 64 years with moderate to severe hypercholesterolaemia (LDL-C: 155 - 232 mg/dl [4.0 - 6.0 mmol/l]) and with no history of myocardial infarction, treated for an average duration of 4.8 years with either a 40 mg daily dose of pravastatin or placebo as an adjunct to diet. In pravastatin-treated patients, results showed:

- A decrease in the risk of mortality from coronary disease and of non-lethal myocardial infarction (relative risk reduction RRR was 31%; $p = 0.0001$ with an absolute risk of 7.9% in the placebo group, and 5.5% in pravastatin treated patients); the effects on these cumulative cardiovascular events rates being evident as early as 6 months of treatment;
- A decrease in the total number of deaths from a cardiovascular event (RRR 32%; $p = 0.03$);
- When risk factors were taken into account, a RRR of 24% ($p = 0.039$) in total mortality was also observed among patients treated with pravastatin;
- A decrease in the relative risk for undergoing myocardial revascularisation procedures (coronary artery bypass graft surgery or coronary angioplasty) by 37% ($p = 0.009$) and coronary angiography by 31% ($p = 0.007$).

The benefit of the treatment on the criteria indicated above is not known in patients over the age of 65 years, who could not be included in the study.

In the absence of data in patients with hypercholesterolaemia associated with a triglyceride level of more than 6 mmol/l (5.3 g/l) after a diet for 8 weeks, in this study, the benefit of pravastatin treatment has not been established in this type of patient.

Secondary prevention

The "Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)" study was a multi-center, randomised, double-blind, placebo-controlled study comparing the effects of pravastatin (40 mg OD) with placebo in 9014 patients aged 31 to 75 years for an average duration of 5.6 years with normal to elevated serum cholesterol levels (baseline total cholesterol = 155 to 271 mg/dl [4.0 - 7.0 mmol/l], mean total cholesterol = 219 mg/dl [5.66 mmol/l]) and with variable

triglyceride levels of up to 443 mg/dl [5.0 mmol/l] and with a history of myocardial infarction or unstable angina pectoris in the preceding 3 to 36 months. Treatment with pravastatin significantly reduced the relative risk of CHD death by 24% ($p = 0.0004$, with an absolute risk of 6.4% in the placebo group, and 5.3% in pravastatin treated patients), the relative risk of coronary events (either CHD death or nonfatal MI) by 24% ($p < 0.0001$) and the relative risk of fatal or nonfatal myocardial infarction by 29% ($p < 0.0001$). In pravastatin-treated patients, results showed:

- A reduction in the relative risk of total mortality by 23% ($p < 0.0001$) and cardiovascular mortality by 25% ($p < 0.0001$);
- A reduction in the relative risk of undergoing myocardial revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 20% ($p < 0.0001$);
- A reduction in the relative risk of stroke by 19% ($p = 0.048$).

The "Cholesterol and Recurrent Events (CARE)" study was a randomised, double-blind, placebo-controlled study comparing the effects of pravastatin (40 mg OD) on coronary heart disease death and nonfatal myocardial infarction for an average of 4.9 years in 4,159 patients aged 21 to 75 years, with normal total cholesterol levels (baseline mean total cholesterol < 240 mg/dl), who had experienced a myocardial infarction in the preceding 3 to 20 months. Treatment with pravastatin significantly reduced:

- The rate of a recurrent coronary event (either coronary heart disease death or nonfatal MI) by 24% ($p = 0.003$, placebo 13.3%, pravastatin 10.4%);
- The relative risk of undergoing revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 27% ($p < 0.001$).

The relative risk of stroke was also reduced by 32% ($p = 0.032$), and stroke or transient ischaemic attack (TIA) combined by 27% ($p = 0.02$).

The benefit of the treatment on the above criteria is not known in patients over the age of 75 years, who could not be included in the CARE and LIPID studies.

In the absence of data in patients with hypercholesterolaemia associated with a triglyceride level of more than 4 mmol/l (3.5 g/l) or more than 5 mmol/l (4.45 g/l) after following a diet for 4 or 8 weeks, in the CARE and LIPID studies, respectively, the benefit of treatment with pravastatin has not been established in this type of patient.

In the CARE and LIPID studies, about 80% of patients had received ASA as part of their regimen.

Heart and kidney transplantation

The efficacy of pravastatin in patients receiving an immunosuppressant treatment following:

Heart transplant was assessed in one prospective, randomised, controlled study ($n = 97$). Patients were treated concurrently with either pravastatin (20 – 40 mg) or not, and a standard immunosuppressive regimen of ciclosporin, prednisone and azathioprine. Treatment with

pravastatin significantly reduced the rate of cardiac rejection with haemodynamic compromise at one year, improved one-year survival ($p = 0.025$), and lowered the risk of coronary vasculopathy in the transplant as determined by angiography and autopsy ($p = 0.049$).

Renal transplant was assessed in one prospective not controlled, not randomised study ($n = 48$) of 4 months duration. Patients were treated concurrently with either pravastatin (20 mg) or not, and a standard immunosuppressive regimen of ciclosporin, and prednisone. In patients following kidney transplantation, pravastatin significantly reduced both the incidence of multiple rejection episodes and the incidence of biopsy-proved acute rejection episodes, and the use of pulse injections of both prednisolone and Muromonab-CD3.

Children and adolescents (8 - 18 years of age):

A double-blind placebo-controlled study in 214 paediatric patients with heterozygous familial hypercholesterolaemia was conducted over 2 years. Children (8 - 13 years) were randomised to placebo ($n = 63$) or 20 mg of pravastatin daily ($n = 65$) and the adolescents (aged 14 - 18 years) were randomised to placebo ($n = 45$) or 40 mg of pravastatin daily ($n = 41$).

Inclusion in this study required one parent with either a clinical or molecular diagnosis of familial hypercholesterolaemia. The mean baseline LDL-C value was 239 mg/dl (6.2 mmol/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]). There was a significant mean percent reduction in LDL-C of -22.9% and also in total cholesterol (-17.2%) from the pooled data analysis in both children and adolescents, similar to demonstrated efficacy in adults on 20 mg of pravastatin.

The effects of pravastatin treatment in the two age groups were similar. The mean achieved LDL-C was 186 mg/dl (4.8 mmol/l) (range: 67 - 363 mg/dl [1.7 - 9.4 mmol/l]) in the pravastatin group compared to 236 mg/dl (6.1 mmol/l) (range: 105 - 438 mg/dl [2.7 - 11.3 mmol/l]) in the placebo group. In subjects receiving pravastatin, there were no differences seen in any of the monitored endocrine parameters [ACTH, cortisol, DHEAS, FSH, LH, TSH, estradiol (girls) or testosterone (boys)] relative to placebo. There were no developmental differences, testicular volume changes or Tanner score differences observed relative to placebo. The power of this study to detect a difference between the two groups of treatment was low.

The long-term efficacy of pravastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic properties

Absorption:

Pravastatin is administered orally in the active form. It is rapidly absorbed; peak serum levels are achieved 1 to 1.5 hours after ingestion. On average, 34% of the orally administered dose is absorbed, with an absolute bioavailability of 17%.

The presence of food in the gastrointestinal tract leads to a reduction in the bioavailability, but the cholesterol-lowering effect of pravastatin is the same whether taken with or without food.

After absorption, 66% of pravastatin undergoes a first pass extraction through the liver, which is the primary site of its action and the primary site of cholesterol synthesis and clearance of LDL-cholesterol. In vitro studies demonstrated that pravastatin is transported into hepatocytes and with substantially less intake in other cells. In view of this substantial first pass through the liver,

plasma concentrations or pravastatin have only a limited value in predicting the lipid-lowering effect.

The plasma concentrations are proportional to the doses administered.

Distribution:

About 50% of circulating pravastatin is bound to plasma proteins. The volume of distribution is about 0.51 l/kg. A small quantity of pravastatin passes into the human breast milk.

Metabolism and elimination:

Pravastatin is not significantly metabolized by cytochrome P450 nor does it appear to be a substrate or an inhibitor of p-glycoprotein but rather a substrate of other transport proteins. Following oral administration, 20% of the initial dose is eliminated in the urine and 70% in the faeces. Plasma elimination half life of oral pravastatin is 1.5 to 2 hours.

After intravenous administration, 47% of the dose is eliminated by renal excretion and 53% by biliary excretion and transformation. The major degraded product of pravastatin is the 3- α -hydroxy isomeric metabolite. This metabolite has one – tenth to one- fortieth the HMG- CoA reductase inhibitor activity of the parent compound.

The systemic clearance of pravastatin is 0.81l/h/kg and the renal clearance is 0.38l/h/kg indicating tubular secretion.

Populations at risk:

Paediatric subject: Mean pravastatin C_{max} and AUC values for paediatric subjects pooled across age, and gender were similar to those values observed in adults after 20 mg oral dose.

Hepatic failure: Systemic exposure to pravastatin and metabolites in patients with alcoholic cirrhosis is enhanced by about 50% comparatively to patients with normal liver function.

Renal impairment: No significant modifications were observed in patients with mild renal impairment. However severe and moderate renal insufficiency may lead to a two fold increase of the systemic exposure to pravastatin and metabolites.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity on reproduction, there are no other risks for the patient than those expected due to the pharmacological mechanism of action.

Repeated dose studies indicate that pravastatin may induce varying degrees of hepatotoxicity and myopathy; in general, substantive effects on these tissues were only evident at doses 50 or more times the maximum human mg/kg dose.

In vitro and *in vivo* genetic toxicology studies have shown no evidence of mutagenic potential.

In mice a 2-year carcinogenicity study with pravastatin demonstrates at doses of 250 and 500 mg/kg/day (\geq 310 times the maximum human mg/kg dose) statistically significant increases in

the incidence of hepatocellular carcinomas in males and females, and lung adenomas in females only.

In rats a 2-year carcinogenicity study demonstrates at a dose of 100 mg/ kg/day (125 times the maximum human mg/kg/dose) a statistically significant increase in the incidence of hepatocellular carcinomas in males only.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate
croscarmellose sodium
magnesium stearate
light magnesium oxide
microcelac
povidone
yellow ferric oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep out of the reach and sight of children.

Store below 25 °C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

The immediate container for Pravastatin Sodium Tablets 10 mg is a laminated aluminium/aluminium foil pack of 28 tablets. The blister strips are packed in a carton.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319, Pinner Road
North Harrow
Middlesex HA1 4 HF
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 20075/0018

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
15/09/2008

10 **DATE OF REVISION OF THE TEXT**
15/09/2008

1 **NAME OF THE MEDICINAL PRODUCT**
Pravastatin Sodium 20 mg Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each tablet contains 20 mg pravastatin sodium.
Excipient: Lactose monohydrate 100 mg.
For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Tablet.

Pravastatin Tablets 20 mg: Yellow colored, rounded rectangular shaped, biconvex, uncoated tablets debossed 'PDT' on one side and '20' on the other side

4 **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**
Hypercholesterolaemia.

Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (eg. exercise, weight reduction) is inadequate.

Primary prevention

Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolaemia and at high risk of a first cardiovascular event, as an adjunct to diet (see section 5.1)

Secondary prevention

Reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina pectoris and with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors (see section 5.1).

Post transplantation

Reduction of post transplantation hyperlipidaemia in-patient receiving immunosuppressive therapy following solid organ transplantation (see sections 4.2, 4.5 and 5.1).

4.2 Posology and method of administration

Prior to initiating Pravastatin Tablets, secondary causes of hypercholesterolaemia should be excluded and patients should be placed on a standard lipid-lowering diet, which should be continued during treatment.

Pravastatin sodium is administered orally once daily preferably in the evening with or without food.

Hypercholesterolaemia: The recommended dose range is 10 - 40 mg once daily. The therapeutic response is seen within a week and the full effect of a given dose occurs within four weeks, therefore periodic lipid determinations should be performed and the dosage adjusted accordingly. The maximum daily dose is 40 mg.

Cardiovascular prevention: In all preventive morbidity and mortality trials, the only studied starting and maintenance dose was 40 mg daily.

Dosage after transplantation: Following organ transplantation a starting dose of 20 mg per day is recommended in patients receiving immunosuppressive therapy (see section 4.5). Depending on the response of the lipid parameters, the dose may be adjusted upto 40 mg under close medical supervision (see section 4.5).

Children and adolescents (8-18 years of age) with heterozygous familial

hypercholesterolaemia: The recommended dose range is 10 –20 mg once daily between 8 and 13 years of age as doses greater than 20 mg have not been studied in this population and 10- 40 mg daily between 14 and 18 years of age (for children and adolescent females of child –bearing potential see section 4.6; for results of the study see section 5.1).

Elderly patients: There is no dose adjustment necessary in these patients unless there are predisposing risk factors (see section 4.4).

Renal or hepatic impairment: A starting dose of 10 mg a day is recommended in patients with moderate or severe renal impairment or significant hepatic impairment. The dosage should be adjusted according to the response of lipid parameters and under medical supervision.

Concomitant therapy: The lipid lowering effects of pravastatin sodium on total cholesterol and LDL - cholesterol are enhanced when combined with a bile acid – binding resin (eg.

colestyramine, colestipol). Pravastatin sodium should be given either one hour before or at least four hours after the resin (see section 4.5).

For patients taking ciclosporin with or without other immunosuppressive medicinal products, treatment should begin with 20 mg of pravastatin sodium once daily and titration to 40 mg should be preformed with caution (see section 4.5).

4.3 **Contraindications**

Hypersensitivity to the active substance or to any of the excipients. Acute liver disease or unexplained, persistent elevations of serum transaminase elevation exceeding 3 times the upper limit of normal (see section 4.4).

Pregnancy and lactation (see section 4.6).

4.4 **Special warnings and precautions for use**

Pravastatin has not been evaluated in patients with homozygous familial hypercholesterolaemia. Therapy is not suitable when hypercholesterolaemia is due to elevated HDL-cholesterol.

As for other HMG-CoA reductase inhibitors, combination of pravastatin with fibrates is not recommended.

In children before puberty, the benefit /risk of treatment should be carefully evaluated by physicians before treatment initiation.

Hepatic disorders: As with other lipid- lowering agents, moderate increase in liver transaminase levels has been observed. In majority of cases, liver transaminase levels have returned to their baseline value without the need for treatment discontinuation. Special attention should be given to patients who develop increased transaminase levels and therapy should be discontinued if increases in alanine aminotransferase (ALT) and aspartate aminotransferase exceed three times the upper limit of normal and persist.

Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion.

Muscle disorders: As with other HMG-CoA reductase inhibitors (statins), pravastatin has been associated with the onset of myalgia, myopathy and very rarely, rhabdomyolysis. Myopathy must be considered in any patient under statin therapy presenting with unexplained muscle symptoms such as muscle weakness, or muscle cramps. In such cases creatine kinase levels should be measured. Statin therapy should be temporarily interrupted when creatine kinase levels are $> 5 \times \text{ULN}$ or when there are severe clinical symptoms. Very rarely (in about 1 case over 100,000 patients-years) rhabdomyolysis occurs, with or without secondary renal insufficiency. Rhabdomyolysis is an acute potentially fatal condition of skeletal muscle, which may develop at any time during treatment and is characterized by massive muscle destruction associated with major increase in creatine kinase (usually > 30 or $40 \times \text{ULN}$) leading to myoglobinuria.

The risk of myopathy with statins appears to be exposure- dependant and therefore may vary with individual drugs (due to lipophilicity and pharmacokinetic differences), including their dosage and potential for drug interactions.

Although there is no muscular contraindication to the prescription of a statin, certain predisposing factor may increase the risk of muscular toxicity and therefore justify a careful evaluation of benefit/risk and special clinical monitoring. CK measurement is indicated before starting statin therapy in these patients.

The risk and severity of muscular disorders during statin therapy is increased by the co administration of interacting medicines. The use of fibrates alone is occasionally associated with myopathy. The combined use of a statin and fibrates should generally be avoided. The co-administration of statins and nicotinic acid should be used with caution. An increase in the incidence of myopathy has also 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. When associated with statin therapy, muscle symptoms usually resolve following discontinuation of statin therapy.

Creatine kinase measurement and interpretation:

Routine monitoring of creatine kinase (CK) or other muscle enzyme levels is not recommended in asymptomatic patients on statin therapy. However, measurement of CK is recommended before starting statin therapy in patients with special predisposing factors, and in patient developing muscular symptoms during statin therapy as described below. If CK levels are significantly elevated at baseline ($> 5x$ ULN), Ck levels should be remeasured 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 a 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 ($> 5 x$ 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. Treatment discontinuation should also be considered if the muscular symptoms are severe and cause daily discomfort, even if the CK increase remains $\leq 5 x$ 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.

Lactose: This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 **Interaction with other medicinal products and other forms of interaction**

Fibrates: The use of fibrates alone is occasionally with myopathy. An increased risk of muscle related adverse events, including rhabdomyolysis, have been reported when fibrates are co-administered with other statins. These adverse events with pravastatin cannot be excluded, therefore the combined use of pravastatin and fibrates (e.g. gemfibrozil, fenofibrate) should generally be avoided (see section 4.4). If this combination is considered necessary, careful clinical and CK monitoring of patients on such regimen is required.

Colestyramine / Colestipol: Concomitant administration resulted in approximately 40 to 50% decrease in the bioavailability of pravastatin. There was no clinically significant decrease in bioavailability or therapeutic effect when pravastatin was administered one hour before or four hours after colestyramine or one hour before colestipol (see section 4.2).

Ciclosporin: Concomittant administration of pravastatin and ciclosporin leads to an approximately 4- fold increase in pravastatin systemic exposure. In some patients, however, the increase in pravastatin exposure may be larger. Clinical and biochemical monitoring of patients receiving this combination is recommended (see section 4.2).

Warfarin and other oral anticoagulants: Bioavailability parameters at steady state for pravastatin were not altered following administration with warfarin. Chronic dosing of the two products did not produce any changes in the anticoagulant action of warfarin.

Products metabolized by cytochrome P450: Pravastatin is not metabolized to a clinically significant extent by the cytochrome P450 system. This is why products that are metabolized by, or inhibitors of, the cytochrome P450 system can be added to a stable regimen of pravastatin without causing significant changes in the plasma levels of pravastatin as have been seen with other statins. The absence of a significant pharmacokinetic interaction with pravastatin has been specifically demonstrated for several products, particularly those that are substrates/inhibitors of CYP3A4 e.g. diltiazem, verapamil, itraconazole, Ketoconazole, protease inhibitors, grapefruit juice and CYP2C9 inhibitors (e.g. fluconazole).

In one of the two interaction studies with pravastatin and erythromycin a statistically significant increase in pravastatin AUC (70%) and C_{max} (121%) was observed. In a similar study with clarithromycin a statistically significant increase in AUC (110%) and C_{max} (127%) was observed. Although these changes were minor, caution should be exercised when associating pravastatin with erythromycin or clarithromycin.

Other products: In interaction studies no statistically significant differences in bioavailability were observed when pravastatin was administered with acetylsalicylic acid, antacids (when given one hour prior to pravastatin), nicotinic acid or probucol.

4.6 **Pregnancy and lactation**

Pregnancy: Pravastatin is contraindicated during pregnancy and should be administered to women of childbearing potential only when such patients are unlikely to conceive and have been informed of the potential risk. Special caution is recommended in adolescent females of childbearing potential to ensure proper understanding of the potential risk associated with pravastatin therapy during pregnancy. If a patient plans to become pregnant or becomes pregnant the doctor has to be informed immediately and pravastatin should be discontinued because of the potential risk to the fetus.

Lactation: A small amount of pravastatin is excreted in human breast milk, therefore pravastatin is contraindicated during breastfeeding.

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 may occur during treatment.

4.8 **Undesirable effects**

The frequencies of adverse events are ranked according to the following: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Clinical trials: Pravastatin has been studied at 40 mg in seven randomised double-blind placebo-controlled trials involving over 21,000 patients treated with pravastatin (n = 10764) or placebo (n = 10719), representing over 47,000 patients years of exposure to pravastatin. Over 19,000 patients were followed for a median of 4.8 – 5.9 years.

The following adverse drug reactions were reported; none of them occurred at a rate in excess of 0.3% in the pravastatin group compared to the placebo group.

Nervous system disorder:

Uncommon: dizziness, headache, sleep disturbance, insomnia.

Eye disorders:

Uncommon: vision disturbance (including blurred vision and diplopia).

Gastrointestinal disorders:

Uncommon: dyspepsia/heartburn, abdominal pain, nausea/ vomiting, constipation, diarrhoea, flatulence.

Skin and subcutaneous tissue disorders:

Uncommon: pruritus, rash, urticaria, scalp/hair abnormality (including alopecia).

Renal and urinary disorders:

Uncommon : abnormal urination (including dysuria, frequency, nocturia)

Reproductive system and breast disorders:

Uncommon : sexual dysfunction.

General disorders:

Uncommon: fatigue.

Events of special clinical interest:

Skeletal muscle: Effects on the skeletal muscle, eg. musculoskeletal pain including arthralgia, muscle cramps, myalgia, muscle weakness and elevated creatine kinase levels have been reported in clinical trials. The rate of myalgia (1.4% pravastatin vs. 1.4% placebo) and muscle weakness (0.1% pravastatin vs. <0.1% placebo) and the incidence of CK level > 3 x ULN and > 10 x ULN in CARE, WOSCOPS and LIPID was similar to placebo (1.6% pravastatin vs. 1.6% placebo and 1.0% pravastatin vs. 1.0% placebo, respectively) (see section 4.4).

Liver effects: Elevations of serum transaminases have been reported. In the three long-term, placebo-controlled clinical trials CARE, WOSCOPS and LIPID, marked abnormalities of ALT and AST (> 3 x ULN) occurred at similar frequency (≤ 1.2%) in both treatment groups.

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, paresthesia.

Immune system disorders:

Very rare: Hypersensitivity reactions: anaphylaxis, angioedema, lupus erythematosus- like syndrome.

Gastrointestinal disorders:

Very rare: pancreatitis.

Hepatobiliary disorders:

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 myoglobinuria, myopathy (see section 4.4) myositis, polymyositis.

Isolated cases of tendon disorders, sometimes complicated by rupture.

4.9 Overdose

The experience with overdose of Pravastatin sodium in humans is very limited. There is no specific treatment in the event of overdose. In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC Code: C10AA03.

Pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the enzyme catalyzing the early rate limiting step in cholesterol biosynthesis, and produces its lipid lowering effect in two ways. Firstly with the reversible and specific competitive inhibition of HMG-CoA reductase, it effects modest reduction in the synthesis of intracellular 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-cholesterol.

Secondly, pravastatin inhibits LDL production by inhibiting the hepatic synthesis of VLDL-cholesterol, the LDL-cholesterol precursor.

In both healthy subjects and patients with hypercholesterolaemia, pravastatin sodium lowers the following lipid values: total cholesterol, LDL-cholesterol, apolipoprotein B, VLDL-cholesterol and triglycerides; while HDL-cholesterol and apolipoprotein A are elevated.

Clinical efficacy:

Primary prevention

The "West of Scotland Coronary Prevention Study (WOSCOPS)" was a randomised, double-blind, placebo-controlled trial among 6,595 male patients aged from 45 to 64 years with moderate to severe hypercholesterolaemia (LDL-C: 155 - 232 mg/dl [4.0 - 6.0 mmol/l]) and with no history of myocardial infarction, treated for an average duration of 4.8 years with either a 40 mg daily dose of pravastatin or placebo as an adjunct to diet. In pravastatin-treated patients, results showed:

- A decrease in the risk of mortality from coronary disease and of non-lethal myocardial infarction (relative risk reduction RRR was 31%; $p = 0.0001$ with an absolute risk of 7.9% in the placebo group, and 5.5% in pravastatin treated patients); the effects on these cumulative cardiovascular events rates being evident as early as 6 months of treatment;
- A decrease in the total number of deaths from a cardiovascular event (RRR 32%; $p = 0.03$);
- When risk factors were taken into account, a RRR of 24% ($p = 0.039$) in total mortality was also observed among patients treated with pravastatin;
- A decrease in the relative risk for undergoing myocardial revascularisation procedures (coronary artery bypass graft surgery or coronary angioplasty) by 37% ($p = 0.009$) and coronary angiography by 31% ($p = 0.007$).

The benefit of the treatment on the criteria indicated above is not known in patients over the age of 65 years, who could not be included in the study.

In the absence of data in patients with hypercholesterolaemia associated with a triglyceride level of more than 6 mmol/l (5.3 g/l) after a diet for 8 weeks, in this study, the benefit of pravastatin treatment has not been established in this type of patient.

Secondary prevention

The "Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)" study was a multi-center, randomised, double-blind, placebo-controlled study comparing the effects of pravastatin (40 mg OD) with placebo in 9014 patients aged 31 to 75 years for an average duration of 5.6 years with normal to elevated serum cholesterol levels (baseline total cholesterol = 155 to 271 mg/dl [4.0 – 7.0 mmol/l], mean total cholesterol = 219 mg/dl [5.66 mmol/l]) and with variable triglyceride levels of up to 443 mg/dl [5.0 mmol/l] and with a history of myocardial infarction or unstable angina pectoris in the preceding 3 to 36 months. Treatment with pravastatin significantly reduced the relative risk of CHD death by 24% ($p = 0.0004$, with an absolute risk of 6.4% in the placebo group, and 5.3% in pravastatin treated patients), the relative risk of coronary events (either CHD death or nonfatal MI) by 24% ($p < 0.0001$) and the relative risk of fatal or nonfatal myocardial infarction by 29% ($p < 0.0001$). In pravastatin-treated patients, results showed:

- A reduction in the relative risk of total mortality by 23% ($p < 0.0001$) and cardiovascular mortality by 25% ($p < 0.0001$);
- A reduction in the relative risk of undergoing myocardial revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 20% ($p < 0.0001$);
- A reduction in the relative risk of stroke by 19% ($p = 0.048$).

The "Cholesterol and Recurrent Events (CARE)" study was a randomised, double-blind, placebo-controlled study comparing the effects of pravastatin (40 mg OD) on coronary heart disease death and nonfatal myocardial infarction for an average of 4.9 years in 4,159 patients aged 21 to 75 years, with normal total cholesterol levels (baseline mean total cholesterol < 240 mg/dl), who had experienced a myocardial infarction in the preceding 3 to 20 months. Treatment with pravastatin significantly reduced:

- The rate of a recurrent coronary event (either coronary heart disease death or nonfatal MI) by 24% ($p = 0.003$, placebo 13.3%, pravastatin 10.4%);
- The relative risk of undergoing revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 27% ($p < 0.001$).

The relative risk of stroke was also reduced by 32% ($p = 0.032$), and stroke or transient ischaemic attack (TIA) combined by 27% ($p = 0.02$).

The benefit of the treatment on the above criteria is not known in patients over the age of 75 years, who could not be included in the CARE and LIPID studies.

In the absence of data in patients with hypercholesterolaemia associated with a triglyceride level of more than 4 mmol/l (3.5 g/l) or more than 5 mmol/l (4.45 g/l) after following a diet for 4 or 8

weeks, in the CARE and LIPID studies, respectively, the benefit of treatment with pravastatin has not been established in this type of patient.

In the CARE and LIPID studies, about 80% of patients had received ASA as part of their regimen.

Heart and kidney transplantation

The efficacy of pravastatin in patients receiving an immunosuppressant treatment following:

Heart transplant was assessed in one prospective, randomised, controlled study (n = 97). Patients were treated concurrently with either pravastatin (20 - 40 mg) or not, and a standard immunosuppressive regimen of ciclosporin, prednisone and azathioprine. Treatment with pravastatin significantly reduced the rate of cardiac rejection with haemodynamic compromise at one year, improved one-year survival (p = 0.025), and lowered the risk of coronary vasculopathy in the transplant as determined by angiography and autopsy (p = 0.049).

Renal transplant was assessed in one prospective not controlled, not randomised study (n = 48) of 4 months duration. Patients were treated concurrently with either pravastatin (20 mg) or not, and a standard immunosuppressive regimen of ciclosporin, and prednisone. In patients following kidney transplantation, pravastatin significantly reduced both the incidence of multiple rejection episodes and the incidence of biopsy-proved acute rejection episodes, and the use of pulse injections of both prednisolone and Muromonab-CD3.

Children and adolescents (8 - 18 years of age):

A double-blind placebo-controlled study in 214 paediatric patients with heterozygous familial hypercholesterolaemia was conducted over 2 years. Children (8 - 13 years) were randomised to placebo (n = 63) or 20 mg of pravastatin daily (n = 65) and the adolescents (aged 14 - 18 years) were randomised to placebo (n = 45) or 40 mg of pravastatin daily (n = 41).

Inclusion in this study required one parent with either a clinical or molecular diagnosis of familial hypercholesterolaemia. The mean baseline LDL-C value was 239 mg/dl (6.2 mmol/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]). There was a significant mean percent reduction in LDL-C of -22.9% and also in total cholesterol (-17.2%) from the pooled data analysis in both children and adolescents, similar to demonstrated efficacy in adults on 20 mg of pravastatin.

The effects of pravastatin treatment in the two age groups were similar. The mean achieved LDL-C was 186 mg/dl (4.8 mmol/l) (range: 67 - 363 mg/dl [1.7 - 9.4 mmol/l]) in the pravastatin group compared to 236 mg/dl (6.1 mmol/l) (range: 105 - 438 mg/dl [2.7 - 11.3 mmol/l]) in the placebo group. In subjects receiving pravastatin, there were no differences seen in any of the monitored endocrine parameters [ACTH, cortisol, DHEAS, FSH, LH, TSH, estradiol (girls) or testosterone (boys)] relative to placebo. There were no developmental differences, testicular volume changes or Tanner score differences observed relative to placebo. The power of this study to detect a difference between the two groups of treatment was low.

The long-term efficacy of pravastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic properties

Absorption:

Pravastatin is administered orally in the active form. It is rapidly absorbed; peak serum levels are achieved 1 to 1.5 hours after ingestion. On average, 34% of the orally administered dose is absorbed, with an absolute bioavailability of 17%.

The presence of food in the gastrointestinal tract leads to a reduction in the bioavailability, but the cholesterol –lowering effect of pravastatin is the same whether taken with or without food.

After absorption, 66% of pravastatin undergoes a first pass extraction through the liver, which is the primary site of its action and the primary site of cholesterol synthesis and clearance of LDL-cholesterol. In vitro studies demonstrated that pravastatin is transported into hepatocytes and with substantially less intake in other cells. In view of this substantial first pass through the liver, plasma concentrations of pravastatin have only a limited value in predicting the lipid-lowering effect.

The plasma concentrations are proportional to the doses administered.

Distribution:

About 50% of circulating pravastatin is bound to plasma proteins. The volume of distribution is about 0.51 l/kg. A small quantity of pravastatin passes into the human breast milk.

Metabolism and elimination:

Pravastatin is not significantly metabolized by cytochrome P450 nor does it appear to be a substrate or an inhibitor of p-glycoprotein but rather a substrate of other transport proteins. Following oral administration, 20% of the initial dose is eliminated in the urine and 70% in the faeces. Plasma elimination half life of oral pravastatin is 1.5 to 2 hours.

After intravenous administration, 47% of the dose is eliminated by renal excretion and 53% by biliary excretion and transformation. The major degraded product of pravastatin is the 3- α -hydroxy isomeric metabolite. This metabolite has one – tenth to one- fortieth the HMG- CoA reductase inhibitor activity of the parent compound.

The systemic clearance of pravastatin is 0.81l/h/kg and the renal clearance is 0.38l/h/kg indicating tubular secretion.

Populations at risk:

Paediatric subject: Mean pravastatin Cmax and AUC values for paediatric subjects pooled across age, and gender were similar to those values observed in adults after 20 mg oral dose.

Hepatic failure: Systemic exposure to pravastatin and metabolites in patients with alcoholic cirrhosis is enhanced by about 50% comparatively to patients with normal liver function.

Renal impairment: No significant modifications were observed in patients with mild renal impairment. However severe and moderate renal insufficiency may lead to a two fold increase of the systemic exposure to pravastatin and metabolites.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity on reproduction, there are no other risks for the patient than those expected due to the pharmacological mechanism of action.

Repeated dose studies indicate that pravastatin may induce varying degrees of hepatotoxicity and myopathy; in general, substantive effects on these tissues were only evident at doses 50 or more times the maximum human mg/kg dose.

In vitro and *in vivo* genetic toxicology studies have shown no evidence of mutagenic potential.

In mice a 2-year carcinogenicity study with pravastatin demonstrates at doses of 250 and 500 mg/kg/day (≥ 310 times the maximum human mg/kg dose) statistically significant increases in the incidence of hepatocellular carcinomas in males and females, and lung adenomas in females only.

In rats a 2-year carcinogenicity study demonstrates at a dose of 100 mg/kg/day (125 times the maximum human mg/kg/dose) a statistically significant increase in the incidence of hepatocellular carcinomas in males only.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate
croscarmellose sodium
magnesium stearate
light magnesium oxide
microcelac
povidone
yellow ferric oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep out of the reach and sight of children.

Store below 25 °C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

The immediate container for Pravastatin Sodium Tablets 20 mg is a laminated aluminium/aluminium foil pack of 28 tablets. The blister strips are packed in a carton.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319, Pinner Road
North Harrow
Middlesex HA1 4 HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/09/2008

10 DATE OF REVISION OF THE TEXT

15/09/2008

1 NAME OF THE MEDICINAL PRODUCT

Pravastatin Sodium 40 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg pravastatin sodium.
Excipient: Lactose monohydrate 200 mg.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Pravastatin Tablets 40 mg: Yellow colored, rounded rectangular shaped, biconvex, uncoated tablets debossed 'PDT' on one side and '40' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia.

Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (eg. exercise, weight reduction) is inadequate.

Primary prevention

Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolaemia and at high risk of a first cardiovascular event, as an adjunct to diet (see section 5.1)

Secondary prevention

Reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina pectoris and with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors (see section 5.1).

Post transplantation

Reduction of post transplantation hyperlipidaemia in-patient receiving immunosuppressive therapy following solid organ transplantation (see sections 4.2, 4.5 and 5.1).

4.2 Posology and method of administration

Prior to initiating Pravastatin Tablets, secondary causes of hypercholesterolaemia should be excluded and patients should be placed on a standard lipid-lowering diet, which should be continued during treatment.

Pravastatin sodium is administered orally once daily preferably in the evening with or without food.

Hypercholesterolaemia: The recommended dose range is 10 - 40 mg once daily. The therapeutic response is seen within a week and the full effect of a given dose occurs within four weeks, therefore periodic lipid determinations should be performed and the dosage adjusted accordingly. The maximum daily dose is 40 mg.

Cardiovascular prevention: In all preventive morbidity and mortality trials, the only studied starting and maintenance dose was 40 mg daily.

Dosage after transplantation: Following organ transplantation a starting dose of 20 mg per day is recommended in patients receiving immunosuppressive therapy (see section 4.5). Depending on the response of the lipid parameters, the dose may be adjusted upto 40 mg under close medical supervision (see section 4.5).

Children and adolescents (8-18 years of age) with heterozygous familial

hypercholesterolaemia: The recommended dose range is 10 –20 mg once daily between 8 and 13 years of age as doses greater than 20 mg have not been studied in this population and 10- 40 mg daily between 14 and 18 years of age (for children and adolescent females of child –bearing potential see section 4.6; for results of the study see section 5.1).

Elderly patients: There is no dose adjustment necessary in these patients unless there are predisposing risk factors (see section 4.4).

Renal or hepatic impairment: A starting dose of 10 mg a day is recommended in patients with moderate or severe renal impairment or significant hepatic impairment. The dosage should be adjusted according to the response of lipid parameters and under medical supervision.

Concomitant therapy: The lipid lowering effects of pravastatin sodium on total cholesterol and LDL - cholesterol are enhanced when combined with a bile acid – binding resin (eg. colestyramine, colestipol). Pravastatin sodium should be given either one hour before or at least four hours after the resin (see section 4.5).

For patients taking ciclosporin with or without other immunosuppressive medicinal products, treatment should begin with 20 mg of pravastatin sodium once daily and titration to 40 mg should be preformed with caution (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Acute liver disease or unexplained, persistent elevations of serum transaminase elevation exceeding 3 times the upper limit of normal (see section 4.4).

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Pravastatin has not been evaluated in patients with homozygous familial hypercholesterolaemia. Therapy is not suitable when hypercholesterolaemia is due to elevated HDL-cholesterol.

As for other HMG-CoA reductase inhibitors, combination of pravastatin with fibrates is not recommended.

In children before puberty, the benefit /risk of treatment should be carefully evaluated by physicians before treatment initiation.

Hepatic disorders: As with other lipid- lowering agents, moderate increase in liver transaminase levels has been observed. In majority of cases, liver transaminase levels have returned to their baseline value without the need for treatment discontinuation. Special attention should be given to patients who develop increased transaminase levels and therapy should be discontinued if increases in alanine aminotransferase (ALT) and aspartate aminotransferase exceed three times the upper limit of normal and persist.

Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion.

Muscle disorders: As with other HMG-CoA reductase inhibitors (statins), pravastatin has been associated with the onset of myalgia, myopathy and very rarely, rhabdomyolysis. Myopathy must be considered in any patient under statin therapy presenting with unexplained muscle

symptoms such as muscle weakness, or muscle cramps. In such cases creatine kinase levels should be measured. Statin therapy should be temporarily interrupted when creatine kinase levels are $> 5 \times \text{ULN}$ or when there are severe clinical symptoms. Very rarely (in about 1 case over 100,000 patients-years) rhabdomyolysis occurs, with or without secondary renal insufficiency. Rhabdomyolysis is an acute potentially fatal condition of skeletal muscle, which may develop at any time during treatment and is characterized by massive muscle destruction associated with major increase in creatine kinase (usually > 30 or $40 \times \text{ULN}$) leading to myoglobinuria.

The risk of myopathy with statins appears to be exposure- dependant and therefore may vary with individual drugs (due to lipophilicity and pharmacokinetic differences), including their dosage and potential for drug interactions.

Although there is no muscular contraindication to the prescription of a statin, certain predisposing factor may increase the risk of muscular toxicity and therefore justify a careful evaluation of benefit/risk and special clinical monitoring. CK measurement is indicated before starting statin therapy in these patients.

The risk and severity of muscular disorders during statin therapy is increased by the co administration of interacting medicines. The use of fibrates alone is occasionally associated with myopathy. The combined use of a statin and fibrates should generally be avoided. The co-administration of statins and nicotinic acid should be used with caution. An increase in the incidence of myopathy has also 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. When associated with statin therapy, muscle symptoms usually resolve following discontinuation of statin therapy.

Creatine kinase measurement and interpretation:

Routine monitoring of creatine kinase (CK) or other muscle enzyme levels is not recommended in asymptomatic patients on statin therapy. However, measurement of CK is recommended before starting statin therapy in patients with special predisposing factors, and in patient developing muscular symptoms during statin therapy as described below. If CK levels are significantly elevated at baseline $> 5 \times \text{ULN}$, Ck levels should be remeasured 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 a 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 $> 5 \times \text{ULN}$ 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. Treatment discontinuation should also be considered if the muscular symptoms are severe and cause daily discomfort, even if the CK increase remains \leq 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.

Lactose: This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 **Interaction with other medicinal products and other forms of interaction**

Fibrates: The use of fibrates alone is occasionally with myopathy. An increased risk of muscle related adverse events, including rhabdomyolysis, have been reported when fibrates are co-administered with other statins. These adverse events with pravastatin cannot be excluded, therefore the combined use of pravastatin and fibrates (e.g. gemfibrozil, fenofibrate) should generally be avoided (see section 4.4). If this combination is considered necessary, careful clinical and CK monitoring of patients on such regimen is required.

Colestyramine / Colestipol: Concomitant administration resulted in approximately 40 to 50% decrease in the bioavailability of pravastatin. There was no clinically significant decrease in bioavailability or therapeutic effect when pravastatin was administered one hour before or four hours after colestyramine or one hour before colestipol (see section 4.2).

Ciclosporin: Concomittant administration of pravastatin and ciclosporin leads to an approximately 4- fold increase in pravastatin systemic exposure. In some patients, however, the increase in pravastatin exposure may be larger. Clinical and biochemical monitoring of patients receiving this combination is recommended (see section 4.2).

Warfarin and other oral anticoagulants: Bioavailability parameters at steady state for pravastatin were not altered following administration with warfarin. Chronic dosing of the two products did not produce any changes in the anticoagulant action of warfarin.

Products metabolized by cytochrome P450: Pravastatin is not metabolized to a clinically significant extent by the cytochrome P450 system. This is why products that are metabolized by, or inhibitors of, the cytochrome P450 system can be added to a stable regimen of pravastatin without causing significant changes in the plasma levels of pravastatin as have been seen with other statins. The absence of a significant pharmacokinetic interaction with pravastatin has been specifically demonstrated for several products, particularly those that are substrates/inhibitors of CYP3A4 e.g. diltiazem, verapamil, itraconazole, Ketoconazole, protease inhibitors, grapefruit juice and CYP2C9 inhibitors (e.g. fluconazole).

In one of the two interaction studies with pravastatin and erythromycin a statistically significant increase in pravastatin AUC (70%) and C_{max} (121%) was observed. In a similar study with clarithromycin a statistically significant increase in AUC (110%) and C_{max} (127%) was

observed. Although these changes were minor, caution should be exercised when associating pravastatin with erythromycin or clarithromycin.

Other products: In interaction studies no statistically significant differences in bioavailability were observed when pravastatin was administered with acetylsalicylic acid, antacids (when given one hour prior to pravastatin), nicotinic acid or probucol.

4.6 **Pregnancy and lactation**

Pregnancy: Pravastatin is contraindicated during pregnancy and should be administered to women of childbearing potential only when such patients are unlikely to conceive and have been informed of the potential risk. Special caution is recommended in adolescent females of childbearing potential to ensure proper understanding of the potential risk associated with pravastatin therapy during pregnancy. If a patient plans to become pregnant or becomes pregnant the doctor has to be informed immediately and pravastatin should be discontinued because of the potential risk to the fetus.

Lactation: A small amount of pravastatin is excreted in human breast milk, therefore pravastatin is contraindicated during breastfeeding.

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 may occur during treatment.

4.8 **Undesirable effects**

The frequencies of adverse events are ranked according to the following: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Clinical trials: Pravastatin has been studied at 40 mg in seven randomised double-blind placebo-controlled trials involving over 21,000 patients treated with pravastatin (n = 10764) or placebo (n = 10719), representing over 47,000 patients years of exposure to pravastatin. Over 19,000 patients were followed for a median of 4.8 – 5.9 years.

The following adverse drug reactions were reported; none of them occurred at a rate in excess of 0.3% in the pravastatin group compared to the placebo group.

Nervous system disorder:

Uncommon: dizziness, headache, sleep disturbance, insomnia.

Eye disorders:

Uncommon: vision disturbance (including blurred vision and diplopia).

Gastrointestinal disorders:

Uncommon: dyspepsia/heartburn, abdominal pain, nausea/ vomiting, constipation, diarrhoea, flatulence.

Skin and subcutaneous tissue disorders:

Uncommon: pruritus, rash, urticaria, scalp/hair abnormality (including alopecia).

Renal and urinary disorders:

Uncommon : abnormal urination (including dysuria, frequency, nocturia)

Reproductive system and breast disorders:

Uncommon : sexual dysfunction.

General disorders:

Uncommon: fatigue.

Events of special clinical interest:

Skeletal muscle: Effects on the skeletal muscle, eg. musculoskeletal pain including arthralgia, muscle cramps, myalgia, muscle weakness and elevated creatine kinase levels have been reported in clinical trials. The rate of myalgia (1.4% pravastatin vs. 1.4% placebo) and muscle weakness (0.1% pravastatin vs. <0.1% placebo) and the incidence of CK level > 3 x ULN and > 10 x ULN in CARE, WOSCOPS and LIPID was similar to placebo (1.6% pravastatin vs. 1.6% placebo and 1.0% pravastatin vs. 1.0% placebo, respectively) (see section 4.4).

Liver effects: Elevations of serum transaminases have been reported. In the three long-term, placebo-controlled clinical trials CARE, WOSCOPS and LIPID, marked abnormalities of ALT and AST (> 3 x ULN) occurred at similar frequency (≤ 1.2%) in both treatment groups.

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, paresthesia.

Immune system disorders:

Very rare: Hypersensitivity reactions: anaphylaxis, angioedema, lupus erythematosus- like syndrome.

Gastrointestinal disorders:

Very rare: pancreatitis.

Hepatobiliary disorders:

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 myoglobinuria, myopathy (see section 4.4) myositis, polymyositis.

Isolated cases of tendon disorders, sometimes complicated by rupture.

4.9 Overdose

The experience with overdose of Pravastatin sodium in humans is very limited. There is no specific treatment in the event of overdose. In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC Code: C10AA03.

Pravastatin is a competitive inhibitor of 3-hydroxy –3- methylglutaryl-coenzyme A reductase, the enzyme catalyzing the early rate limiting step in cholesterol biosynthesis, and produces its lipid lowering effect in two ways. Firstly with the reversible and specific competitive inhibition of HMG-CoA reductase, it effects modest reduction in the synthesis of intracellular 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-cholesterol.

Secondly, pravastatin inhibits LDL production by inhibiting the hepatic synthesis of VLDL-cholesterol, the LDL- cholesterol precursor.

In both healthy subjects and patients with hypercholesterolaemia, pravastatin sodium lowers the following lipid values: total cholesterol, LDL-cholesterol, apolipoprotein B, VLDL-cholesterol and triglycerides; while HDL-cholesterol and apolipoprotein A are elevated.

Clinical efficacy:

Primary prevention

The "West of Scotland Coronary Prevention Study (WOSCOPS)" was a randomised, double-blind, placebo-controlled trial among 6,595 male patients aged from 45 to 64 years with moderate to severe hypercholesterolaemia (LDL-C: 155 - 232 mg/dl [4.0 - 6.0 mmol/l]) and with no history of myocardial infarction, treated for an average duration of 4.8 years with either a 40 mg daily dose of pravastatin or placebo as an adjunct to diet. In pravastatin-treated patients, results showed:

- A decrease in the risk of mortality from coronary disease and of non-lethal myocardial infarction (relative risk reduction RRR was 31%; $p = 0.0001$ with an absolute risk of 7.9% in the placebo group, and 5.5% in pravastatin treated patients); the effects on these cumulative cardiovascular events rates being evident as early as 6 months of treatment;
- A decrease in the total number of deaths from a cardiovascular event (RRR 32%; $p = 0.03$);
- When risk factors were taken into account, a RRR of 24% ($p = 0.039$) in total mortality was also observed among patients treated with pravastatin;

- A decrease in the relative risk for undergoing myocardial revascularisation procedures (coronary artery bypass graft surgery or coronary angioplasty) by 37% ($p = 0.009$) and coronary angiography by 31% ($p = 0.007$).

The benefit of the treatment on the criteria indicated above is not known in patients over the age of 65 years, who could not be included in the study.

In the absence of data in patients with hypercholesterolaemia associated with a triglyceride level of more than 6 mmol/l (5.3 g/l) after a diet for 8 weeks, in this study, the benefit of pravastatin treatment has not been established in this type of patient.

Secondary prevention

The "Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)" study was a multi-center, randomised, double-blind, placebo-controlled study comparing the effects of pravastatin (40 mg OD) with placebo in 9014 patients aged 31 to 75 years for an average duration of 5.6 years with normal to elevated serum cholesterol levels (baseline total cholesterol = 155 to 271 mg/dl [4.0 – 7.0 mmol/l], mean total cholesterol = 219 mg/dl [5.66 mmol/l]) and with variable triglyceride levels of up to 443 mg/dl [5.0 mmol/l] and with a history of myocardial infarction or unstable angina pectoris in the preceding 3 to 36 months. Treatment with pravastatin significantly reduced the relative risk of CHD death by 24% ($p = 0.0004$, with an absolute risk of 6.4% in the placebo group, and 5.3% in pravastatin treated patients), the relative risk of coronary events (either CHD death or nonfatal MI) by 24% ($p < 0.0001$) and the relative risk of fatal or nonfatal myocardial infarction by 29% ($p < 0.0001$). In pravastatin-treated patients, results showed:

- A reduction in the relative risk of total mortality by 23% ($p < 0.0001$) and cardiovascular mortality by 25% ($p < 0.0001$);
- A reduction in the relative risk of undergoing myocardial revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 20% ($p < 0.0001$);
- A reduction in the relative risk of stroke by 19% ($p = 0.048$).

The "Cholesterol and Recurrent Events (CARE)" study was a randomised, double-blind, placebo-controlled study comparing the effects of pravastatin (40 mg OD) on coronary heart disease death and nonfatal myocardial infarction for an average of 4.9 years in 4,159 patients aged 21 to 75 years, with normal total cholesterol levels (baseline mean total cholesterol < 240 mg/dl), who had experienced a myocardial infarction in the preceding 3 to 20 months. Treatment with pravastatin significantly reduced:

- The rate of a recurrent coronary event (either coronary heart disease death or nonfatal MI) by 24% ($p = 0.003$, placebo 13.3%, pravastatin 10.4%);
- The relative risk of undergoing revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 27% ($p < 0.001$).

The relative risk of stroke was also reduced by 32% ($p = 0.032$), and stroke or transient ischaemic attack (TIA) combined by 27% ($p = 0.02$).

The benefit of the treatment on the above criteria is not known in patients over the age of 75 years, who could not be included in the CARE and LIPID studies.

In the absence of data in patients with hypercholesterolaemia associated with a triglyceride level of more than 4 mmol/l (3.5 g/l) or more than 5 mmol/l (4.45 g/l) after following a diet for 4 or 8 weeks, in the CARE and LIPID studies, respectively, the benefit of treatment with pravastatin has not been established in this type of patient.

In the CARE and LIPID studies, about 80% of patients had received ASA as part of their regimen.

Heart and kidney transplantation

The efficacy of pravastatin in patients receiving an immunosuppressant treatment following:

Heart transplant was assessed in one prospective, randomised, controlled study (n = 97). Patients were treated concurrently with either pravastatin (20 - 40 mg) or not, and a standard immunosuppressive regimen of ciclosporin, prednisone and azathioprine. Treatment with pravastatin significantly reduced the rate of cardiac rejection with haemodynamic compromise at one year, improved one-year survival (p = 0.025), and lowered the risk of coronary vasculopathy in the transplant as determined by angiography and autopsy (p = 0.049).

Renal transplant was assessed in one prospective not controlled, not randomised study (n = 48) of 4 months duration. Patients were treated concurrently with either pravastatin (20 mg) or not, and a standard immunosuppressive regimen of ciclosporin, and prednisone. In patients following kidney transplantation, pravastatin significantly reduced both the incidence of multiple rejection episodes and the incidence of biopsy-proved acute rejection episodes, and the use of pulse injections of both prednisolone and Muromonab-CD3.

Children and adolescents (8 - 18 years of age):

A double-blind placebo-controlled study in 214 paediatric patients with heterozygous familial hypercholesterolaemia was conducted over 2 years. Children (8 - 13 years) were randomised to placebo (n = 63) or 20 mg of pravastatin daily (n = 65) and the adolescents (aged 14 - 18 years) were randomised to placebo (n = 45) or 40 mg of pravastatin daily (n = 41).

Inclusion in this study required one parent with either a clinical or molecular diagnosis of familial hypercholesterolaemia. The mean baseline LDL-C value was 239 mg/dl (6.2 mmol/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]). There was a significant mean percent reduction in LDL-C of -22.9% and also in total cholesterol (-17.2%) from the pooled data analysis in both children and adolescents, similar to demonstrated efficacy in adults on 20 mg of pravastatin.

The effects of pravastatin treatment in the two age groups were similar. The mean achieved LDL-C was 186 mg/dl (4.8 mmol/l) (range: 67 - 363 mg/dl [1.7 - 9.4 mmol/l]) in the pravastatin group compared to 236 mg/dl (6.1 mmol/l) (range: 105 - 438 mg/dl [2.7 - 11.3 mmol/l]) in the placebo group. In subjects receiving pravastatin, there were no differences seen in any of the monitored endocrine parameters [ACTH, cortisol, DHEAS, FSH, LH, TSH, estradiol (girls) or testosterone (boys)] relative to placebo. There were no developmental differences, testicular volume changes or Tanner score differences observed relative to placebo. The power of this study to detect a difference between the two groups of treatment was low.

The long-term efficacy of pravastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic properties

Absorption:

Pravastatin is administered orally in the active form. It is rapidly absorbed; peak serum levels are achieved 1 to 1.5 hours after ingestion. On average, 34% of the orally administered dose is absorbed, with an absolute bioavailability of 17%.

The presence of food in the gastrointestinal tract leads to a reduction in the bioavailability, but the cholesterol –lowering effect of pravastatin is the same whether taken with or without food.

After absorption, 66% of pravastatin undergoes a first pass extraction through the liver, which is the primary site of its action and the primary site of cholesterol synthesis and clearance of LDL-cholesterol. In vitro studies demonstrated that pravastatin is transported into hepatocytes and with substantially less intake in other cells. In view of this substantial first pass through the liver, plasma concentrations of pravastatin have only a limited value in predicting the lipid-lowering effect.

The plasma concentrations are proportional to the doses administered.

Distribution:

About 50% of circulating pravastatin is bound to plasma proteins. The volume of distribution is about 0.51 l/kg. A small quantity of pravastatin passes into the human breast milk.

Metabolism and elimination:

Pravastatin is not significantly metabolized by cytochrome P450 nor does it appear to be a substrate or an inhibitor of p-glycoprotein but rather a substrate of other transport proteins. Following oral administration, 20% of the initial dose is eliminated in the urine and 70% in the faeces. Plasma elimination half life of oral pravastatin is 1.5 to 2 hours.

After intravenous administration, 47% of the dose is eliminated by renal excretion and 53% by biliary excretion and transformation. The major degraded product of pravastatin is the 3- α -hydroxy isomeric metabolite. This metabolite has one – tenth to one- fortieth the HMG- CoA reductase inhibitor activity of the parent compound.

The systemic clearance of pravastatin is 0.81l/h/kg and the renal clearance is 0.38l/h/kg indicating tubular secretion.

Populations at risk:

Paediatric subject: Mean pravastatin C_{max} and AUC values for pediatric subjects pooled across age, and gender were similar to those values observed in adults after 20 mg oral dose.

Hepatic failure: Systemic exposure to pravastatin and metabolites in patients with alcoholic cirrhosis is enhanced by about 50% comparatively to patients with normal liver function.

Renal impairment: No significant modifications were observed in patients with mild renal impairment. However severe and moderate renal insufficiency may lead to a two fold increase of the systemic exposure to pravastatin and metabolites.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity on reproduction, there are no other risks for the patient than those expected due to the pharmacological mechanism of action.

Repeated dose studies indicate that pravastatin may induce varying degrees of hepatotoxicity and myopathy; in general, substantive effects on these tissues were only evident at doses 50 or more times the maximum human mg/kg dose.

In vitro and *in vivo* genetic toxicology studies have shown no evidence of mutagenic potential.

In mice a 2-year carcinogenicity study with pravastatin demonstrates at doses of 250 and 500 mg/kg/day (≥ 310 times the maximum human mg/kg dose) statistically significant increases in the incidence of hepatocellular carcinomas in males and females, and lung adenomas in females only.

In rats a 2-year carcinogenicity study demonstrates at a dose of 100 mg/kg/day (125 times the maximum human mg/kg/dose) a statistically significant increase in the incidence of hepatocellular carcinomas in males only.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate
croscarmellose sodium
magnesium stearate
light magnesium oxide
microcelac
povidone
yellow ferric oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep out of the reach and sight of children.

Store below 25 °C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

The immediate container for Pravastatin Sodium Tablets 40 mg is a laminated aluminium/aluminium foil pack of 28 tablets. The blister strips are packed in a carton.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
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North Harrow
Middlesex HA1 4 HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/09/2008

10 DATE OF REVISION OF THE TEXT

15/09/2008

Module 3

Product Information Leaflet

accord

PACKAGE LEAFLET:
INFORMATION FOR THE USER

PRAVASTATIN SODIUM

10 mg TABLETS

PRAVASTATIN SODIUM

20 mg TABLETS

PRAVASTATIN SODIUM

40 mg TABLETS

Pravastatin Sodium

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Pravastatin Sodium Tablets is and what it is used for
2. Before you take Pravastatin Sodium Tablets
3. How to take Pravastatin Sodium Tablets
4. Possible side effects
5. How to store Pravastatin Sodium Tablets
6. Further information

1. What Pravastatin Sodium Tablets is and what it is used for

Pravastatin Sodium Tablets belongs to a group of medicines known as HMG-CoA reductase inhibitors (or statins), which work by reducing your body's production of "bad cholesterol" and raising levels of "good cholesterol". Cholesterol is a lipid that can cause coronary heart disease by narrowing the vessels that supply the heart with blood. This condition, called hardening of the arteries or atherosclerosis, may lead to angina, a heart attack (myocardial infarction) or stroke.

If you have already had a heart attack or have unstable angina (chest pain), Pravastatin Sodium reduces the risk of you having another heart attack or stroke in the future, regardless of your cholesterol level.

If you have raised levels of cholesterol but do not have coronary heart disease, Pravastatin Sodium reduces the risk of this occurring or of you having a heart attack or stroke in the future.

When you use Pravastatin Sodium, your doctor will recommend other actions as part of your treatment, such as a low fat diet, exercise and weight reduction.

If you have had an organ transplant and are taking medication to stop your body rejecting the transplant, Pravastatin Sodium reduces increased lipid levels.

2. Before you take Pravastatin Sodium Tablets

Do not use Pravastatin Sodium Tablets in following conditions:

- You have any liver problems.
- You are hypersensitive (allergic) to Pravastatin Sodium or any of the other ingredients of Pravastatin Sodium.
- You are pregnant or there is a possibility that you may become pregnant.
- You are breast-feeding.

Take special care with Pravastatin Sodium Tablets

Tell your doctor if you have ever had any of the following:

- Kidney disease or an underactive thyroid.
- Past history of liver disease.
- Alcohol problems (If you regularly drink large amounts of alcohol).
- A hereditary muscle disorder in yourself or a blood relative.
- Side effects affecting your muscles when taking another cholesterol-lowering medicine such as statin or fibrate.

If you have suffered any of these problems, your doctor will need to carry out a blood test before and possibly during Pravastatin Sodium treatment to assess your risk of muscle-related side effects. You may also need this blood test if you are aged older than 70 years. Go back to your doctor as soon as possible to discuss your concerns and follow the advice given.

Using other medicines:

If you are already being treated with any of the following talk to your doctor before you start to take Pravastatin Sodium Tablets as the combination may result in an increased risk of developing muscle problems.

- A group of cholesterol lowering drugs called fibrates (e.g. gemfibrozil, fenofibrate) or nicotinic acid.
- The immunosuppressant ciclosporin.
- The antibiotics erythromycin or clarithromycin.
- A resin type lipid-lowering agent such as colestyramine or colestipol, Pravastatin Sodium

Tablets should be taken at least one hour before or four hours after you have taken the resin.

- Warfarin and other oral anticoagulants (agents that help in thinning the blood).
- Product metabolized by cytochrome P450 (diltiazem, verapamil, itraconazole, ketoconazole, protease inhibitors and CYP2C9 inhibitors like fluconazole).

It is important that you tell your doctor about all the medicines you are taking, including those you have bought without a prescription.

Using Pravastatin Sodium Tablets with food and drink:

- Taking food and drink has no influence on your treatment with Pravastatin Sodium Tablets.
- Take the advice of your doctor before taking grape fruit juice with Pravastatin Sodium Tablets.
- Discuss with your doctor if you drink alcohol and seek his advice.

Pregnancy and breast-feeding:

Do not take Pravastatin if you are pregnant, trying to become pregnant or suspect you may be pregnant, as the safety in pregnant women has not been established, if you become pregnant while using Pravastatin, you must stop taking tablets immediately and contact your doctor.

A small amount of the active substance of Pravastatin passes into breast milk. Therefore, you must not take Pravastatin while breast-feeding.

Ask your pharmacist or doctor for advice before taking any medicine.

Driving and using machines:

- Pravastatin Sodium Tablets usually does not affect your ability to drive but if you experience dizziness make sure you are fit to drive or operate machinery.

Important information about some of the ingredients of Pravastatin Sodium Tablets.

This medicine contains lactose. If you have been told by your doctor that you have intolerance to some sugars (eg. Lactose), contact your doctor before taking this medicinal product.

3. How to take Pravastatin Sodium Tablets

Always take your tablets exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

- Pravastatin Sodium Tablets can be taken

with or without food. Swallow the correct number of tablets with some liquid.

- You should continue taking Pravastatin Sodium Tablets as long as your doctor has advised you to do so. This will vary from person to person and your doctor will adjust the number and strength of the tablets to suit you.

Dose instructions for adults and adolescents (14-18 years)

The usual dose of Pravastatin Sodium is 10-40 mg once a day preferably in the evening.

Dose instructions for children (8-13 years)

The usual dose is 10-20 mg once a day. Following organ transplantation the usual dose is 20 mg once a day.

If you take more Pravastatin Sodium Tablets than you should

If you take more tablets than you have been told to take, or if someone else accidentally takes your medicine, contact accident and emergency department of your nearest hospital. Take any left over tablets or empty box with you for easier identification.

If you forget to take Pravastatin Sodium Tablets

Do not take a double dose to make up for the forgotten dose, take your next dose as usual and continue your course.

4. Possible side effects

Like all medicines, Pravastatin Sodium Tablets can cause side effects, although not everybody gets them.

Common side effects ($\geq 1/100$, $< 1/10$):

- High levels of an enzyme serum transaminase in blood

Uncommon side effects ($\geq 1/1000 < 1/100$)

- Dizziness
- Headache
- Sleep disturbances
- Insomnia (sleeplessness)
- Vision disturbance (blurred vision or double vision)
- Dyspepsia (difficulty in digesting food)/ heartburn
- Abdominal pain
- Nausea (urge to vomit)/ Vomiting
- Constipation
- Diarrhoea
- Flatulence
- Skin reactions like itching and rashes
- Scalp and hair problems (including hair loss)

- Abnormal urination (pain, frequent urination at night)
- Disturbed sexual functions
- Fatigue (tiredness)

Very rare side effects ($< 1/10,000$):

- Hypersensitivity reactions (angioneurotic oedema, anaphylaxis) such as serious allergic reactions with swelling of the face, tongue and wind pipe which can cause great difficulty in breathing. This is a very rare reaction which can be very serious. You should seek medical attention immediately if this occurs.
- Problems with touch (burning / tingling sensation or numbness or pins and needles (paresthesia) may occur which may be a sign of damage to the nerve endings (peripheral polyneuropathy)
- Rarely, patients have developed muscle wasting or inflammation, and very rarely this has progressed to become a serious potentially life-threatening condition (called 'rhabdomyolysis'). Acute renal failure secondary to myoglobinuria (the presence of myoglobin in the urine), myositis (inflammation of muscles), myopathy (muscle disease), polymyositis (chronic muscle inflammation) may be associated with rhabdomyolysis). If you have muscle weakness, tenderness or pain and particularly at the same time, you feel unwell or have a high temperature, stop taking Pravastatin Sodium Tablets and tell your doctor immediately
- Pancreatitis (Inflammation of the pancreas)
- Chronic inflammatory autoimmune disorder (An illness that occurs when the body tissues are attacked by its own immune system), a certain type of chronic skin disorder (lupus like syndrome).
- Yellowish discolouration of the skin (jaundice), tissues and body fluids.
- Hepatitis (Inflammation of liver), acute liver failure
- Tendon disorders complicated by rupture.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Pravastatin Sodium Tablets

- Keep out of reach and sight of children.
- Store below 25°C. Store in the original package in order to protect from light and moisture.
- Do not use the tablets after the expiry date stated on the carton and blister (EXP). The expiry date refers to the last day of that month
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment

6. Further Information

What Pravastatin Sodium Tablets contains:

The active ingredient is Pravastatin Sodium. Pravastatin Sodium tablets have either 10 mg, 20 mg or 40 mg Pravastatin Sodium in them. The other ingredients in the tablet are: microcelac, lactose monohydrate, povidone, croscarmellose sodium, magnesium stearate, magnesium oxide light and yellow iron oxide (E 172).

What Pravastatin Sodium Tablets looks like and content of the pack:

Pravastatin Sodium 10 mg Tablets are yellow coloured, rounded rectangular shaped, biconvex, uncoated tablets debossed 'PDT' on one side and '10' on the other side. Pravastatin Sodium 20 mg Tablets are yellow coloured, rounded rectangular shaped, biconvex, uncoated tablets debossed 'PDT' on one side and '20' on the other side. Pravastatin Sodium 40 mg Tablets are yellow coloured, rounded rectangular shaped, biconvex, uncoated tablets debossed 'PDT' on one side and '40' on the other side. Pravastatin Sodium Tablets are packed in blisters in pack of 28 tablets.

Marketing Authorization Holder and Manufacturer: Accord Healthcare Limited, Sage House, 319, Pinner Road, North Harrow, Middlesex HA14HF, UK.

This leaflet was last approved in September 2008.

Module 4

Labelling

Label:

Numeric Code	accord PRAVASTATIN SODIUM 10 MG TABLETS	accord PRAVASTATIN SODIUM 10 MG TABLETS
	accord PRAVASTATIN SODIUM 10 MG TABLETS	accord PRAVASTATIN SODIUM 10 MG TABLETS
Code : Guj/Drugs/1339	PL 20075/0018 PA 1390/002/001 XXXXXXXXX	PL 20075/0018 PA 1390/002/001 XXXXXXXXX

Carton:



Label:

Numeric Code	accord PRAVASTATIN SODIUM 20 MG TABLETS	accord PRAVASTATIN SODIUM 20 MG TABLETS
	accord PRAVASTATIN SODIUM 20 MG TABLETS	accord PRAVASTATIN SODIUM 20 MG TABLETS
Code : Guj/Drugs/1339	PL 20075/0019 PA 1390/002/002 XXXXXXXXX	PL 20075/0019 PA 1390/002/002 XXXXXXXXX

Carton:



Label:

Numeric Code	accord PRAVASTATIN SODIUM 40 MG TABLETS	accord PRAVASTATIN SODIUM 40 MG TABLETS
	accord PRAVASTATIN SODIUM 40 MG TABLETS	accord PRAVASTATIN SODIUM 40 MG TABLETS
Code : Guj/Drugs/1399	PL 20075/0020 PA 1390/002/003 XXXXXXXXX	PL 20075/0020 PA 1390/002/003 XXXXXXXXX

Carton:



Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Pravastatin Sodium 10 mg, 20 mg and 40 mg Tablets, in the treatment of hypercholesterolaemia, could be approved.

EXECUTIVE SUMMARY

Problem statement

This abridged decentralised application concerns a generic version of pravastatin sodium tablets, submitted under Article 10.1 of Directive 2001/83/EC. The reference product is Lipostat® Tablets, authorised to Bristol-Myers Squibb on 10 January 1997. Hence the 10 year rule is fulfilled and the legal basis of this application is satisfactory.

With the UK as the reference Member State in this decentralised procedure, Accord Healthcare Limited applied for a marketing authorisation for Pravastatin Sodium 10 mg, 20 mg and 40 mg Tablets in Belgium, Germany, Greece, Spain, Hungary, Ireland, Italy, Latvia, Malta, The Netherlands and Portugal.

About the product

Pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyses the early rate-limiting step in cholesterol biosynthesis. Pravastatin is a member of the drug class known as statins (or HMG-CoA reductase inhibitors), a class of hypolipidemic agents used as pharmaceuticals to lower cholesterol levels in people at risk of cardiovascular disease due to hypercholesterolemia.

Pravastatin has been used for the proposed indications for many years.

General comments on the submitted dossier

The dossier submitted was of ~~reasonable~~ acceptable quality.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities as certification that

acceptable standards of GMP are in place at those non-Community sites.

The applicant has given an undertaking that the bioequivalence study was conducted in compliance with the GLP and GCP.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Active substance

The control tests and specifications for the active substance are adequately drawn up and are in line with the Ph. Eur. The quality of the active substance is assured by the supporting Ph. Eur. Certificate of Suitability.

Drug Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed and the results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 36 months with the storage condition 'Do not store above 25 °C.' for the drug product is considered acceptable.

Non-clinical aspects

Specific non-clinical studies have not been performed, which is acceptable for this application for a generic product. The non-clinical overview provides a reasonable review of the known pharmacological, pharmacokinetic and toxicological properties of pravastatin sodium.

Clinical aspects

No new efficacy and safety data were submitted and none is required for this type of application.

The applicant has provided biowaver justification for the 10 mg and 20 mg strength tablets. This is acceptable. Bioequivalence data from studies using highest strength 40 mg formulation can be extrapolated to the lower strengths.

Pharmacokinetics

The first bioequivalence study was a randomised, open label, two treatment, two period, two sequence, single dose, crossover, oral bioavailability study in healthy, adult, male subjects. The test (Pravastatin 40 mg) and the reference (Lipostat 40 mg) products were administered under fasting conditions. The results were as follows:-

Table 1: Pharmacokinetic parameters (ln-transformed values; arithmetic mean ± SD, t_{max})

Treatment	AUC _{0-t} ng/ml/h	AUC _{0-∞} ng/ml/h	C _{max} ng/ml	t _{max} h	T _{1/2} h
Test	395 ± 190	420 ± 188	173 ± 91	1.00	2.2 ± 0.8
Reference	373 ± 185	399 ± 184	165 ± 90	1.00	2.3 ± 1.0
*Ratio (90% CI)	107.97 (100.84 – 115.61)	107.20 (100.59 – 114.25)	106.80 (97.34 – 117.18)		
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity				
AUC _{0-t}	area under the plasma concentration-time curve from time zero to t hours				
C _{max}	maximum plasma concentration				
T _{max}	time for maximum concentration				
T _{1/2}	half-life				

**ln-transformed values*

Based on the above data, the bioequivalence of the test product with the reference product has been shown.

A second bio-study was performed with a new bio-analytical method which is specific for pravastatin and its metabolite, 3α-hydroxyisomer of pravastatin.

A summary of the results of the second bioequivalence study were as follows:-

Table 2: Geometric least square means, ratios and 90 % confidence interval for pravastatin (n=63)

Parameters	Geometric Least Square Mean (ln-transformed values)			90 % Confidence Interval (Parametric)
	Reference Product A	Test Product B	Ratio (B/A) %	
C _{max} (ng/ml)	107.561	105.164	97.8	88.38-108.16%
AUC _{0-t} (ng.h/ml)	245.880	235.365	95.7	88.81-103.18%
AUC _{0-inf} (ng.h/ml)	257.082 [#]	247.082 [#]	95.8	88.94-103.14%

Based on the above data, bioequivalence of the test product with the reference product has been shown.

BENEFIT RISK ASSESSMENT

The risk: benefit ratio for this product is considered favourable and approval is recommended.

Overall conclusion

QUALITY

The important quality characteristics of Pravastatin Sodium 10 mg, 20 mg and 40 mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No preclinical data is needed for these applications.

No new or unexpected safety concerns arise from these applications.

EFFICACY

Clinical studies have demonstrated the efficacy of pravastatin sodium in the treatment of hypercholesterolaemia.

The product literature is satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.