Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

PRAVASTATIN SODIUM 10MG TABLETS
PRAVASTATIN SODIUM 20MG TABLETS
PRAVASTATIN SODIUM 40MG TABLETS

Procedure No: UK/H/2810, 2811 and 2875/001-3/DC

UK Licence No: PL 20692/0055-63

VALE PHARMACEUTICALS LIMITED

LAY SUMMARY

On 17 May 2010, Austria, Belgium, Czech Republic, Finland, Germany, Spain, France, Ireland, Italy, Netherlands, Norway, Portugal and Romania, Sweden and the UK agreed to grant a Marketing Authorisation to Vale Pharmaceuticals Limited for the medicinal products Pravastatin Sodium 10mg, 20mg and 40mg Tablets (PL 20692/0055-63; UK/H/2810, 2811 and 2875/001-3/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, Marketing Authorisations were granted in the UK on 15 June 2010.

Pravastatin belongs to a group of medicines called statins, which work by reducing high cholesterol levels in the blood. Cholesterol is a fatty substance (lipid) that can cause the narrowing of blood vessels in the heart causing coronary heart disease.

Pravastatin is used:

- to lower high cholesterol levels in your blood if diet, exercise or weight loss has not lowered your cholesterol level.
- to lower the fatty substances (lipids) in your blood if you have had an organ transplant and are receiving therapy to suppress immune response.
- to reduce the chance of having heart related problems if you have high cholesterol and are at higher risk of having cardiovascular event.
- to reduce the chance of having another heart attack or if you suffer from chest pain attacks (unstable angina pectoris).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Pravastatin Sodium 10mg, 20mg and 40mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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Module 1

Product Name	Pravastatin Sodium 10mg, 20mg and 40mg Tablets
Type of Application	Generic, Article 10.1
Active Substances	Pravastatin sodium
Form	Tablet
Strength	10, 20 and 40mg Tablets
MA Holder	Vale Pharmaceuticals Ltd, Unit 1b, Gurtnafleur Business Park, Gurtnafleur, Clonmel, Co. Tipperary, Ireland.
Reference Member State (RMS)	UK
CMS	UK/H/2810/001/DC: Belgium, Czech Republic, Germany, Spain, France, Ireland, Netherlands, Portugal and Romania. UK/H/2810/002-3/DC:Austria, Belgium, Czech Republic, Finland, Germany, Spain, France, Ireland, Italy, Netherlands, Norway, Portugal, Romania and Sweden UK/H/2811/001-3/DC: France and Portugal. UK/H/2875/001-3/DC: Belgium .
Procedure Number	UK/H/2810, 2811 and 2875/001-3/DC
Timetable	Day 188 – 17 May 2010

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 of pravastatin sodium.

Excipient: 76.7 mg of lactose monohydrate / tablet
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablets

Pravastatin sodium 10 mg tablets: Light pink colour, mottled, round, flat, bevelled tablets debossed with "10" on one side and plain on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypercholesterolaemia
Treatment of primary hypercholesterolemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Primary prevention
Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolemia 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 patients receiving immunossupressive 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 sodium Tablets, secondary causes of hypercholesterolaemia should be excluded and patients should be placed on a standard lipid-lowering diet that should be continued during treatment.

Pravastatin sodium Tablets are 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 up to 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 childbearing 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 Tablets on total cholesterol and LDL-cholesterol are enhanced when combined with a bile acid-binding resin (e.g. cholestyramine, colestipol). Pravastatin sodium Tablets should be given either one hour before or at least four hours after the resin (see section 4.5).

For patients taking cyclosporine 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 performed with caution (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Active liver disease including unexplained persistent elevations of serum transaminase elevation exceeding 3 x the upper limit of normal (ULN) (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 others 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 increases in liver transaminase levels have been observed. In the 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 (AST) 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 others 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 pain or tenderness, muscle weakness, or muscle cramps. In such cases creatine kinase (CK) levels should be measured (see below).

Statin therapy should be temporarily interrupted when CK levels are > 5 x ULN or when there are severe clinical symptoms. Very rarely (in about 1 case over 100 000 patient-years), rhabdomyolysis occurs, with or without secondary renal insufficiency. Rhabdomyolysis is an acute potentially fatal condition of skeletal muscle which may develop at any time during treatment and is characterised by massive muscle destruction associated with major increase in CK (usually > 30 or 40 x ULN) leading

to myoglobinuria.

The risk of myopathy with statins appears to be exposure-dependent and therefore may vary with individual active substances (due to lipophilicity and pharmacokinetic differences), including their dosage and potential for interactions with medicinal products. Although there is no muscular contraindication to the prescription of a statin, certain predisposing factors may increase the risk of muscular toxicity and therefore justify a careful evaluation of the benefit/risk and special clinical monitoring. CK measurement is indicated before starting statin therapy in these patients (see below).

The risk and severity of muscular disorders during statin therapy is increased by the co-administration of interacting medicinal products. 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 (see section 4.5). 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 patients developing muscular symptoms during statin therapy, as described below. If CK levels are significantly elevated at baseline (> 5 x ULN), CK levels should be re-measured about 5 to 7 days later to confirm the results. When measured, CK levels should be interpreted in the context of other potential factors that can cause transient muscle damage, such as strenuous exercise or muscle trauma.

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

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 < 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 patient, 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 associated 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 can not 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.

Cholestyramine/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 cholestyramine or one hour before colestipol (see section 4.2).

Cyclosporin
Concomitant administration of pravastatin and cyclosporin leads to an approximately 4fold 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 metabolised by cytochrome P450
Pravastatin is not metabolised to a clinically significant extent by the cytochrome P450 system. This is why products that are metabolised 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 two interaction studies with pravastatin and erythromycin a statistically significant increase in pravastatin AUC (70 %) and Cmax (121 %) was observed. In a similar study with clarithromycin a statistically significant increase in AUC (110 %) and Cmax (127 %) was observed. Although these changes were minor, caution should be exercised when associating pravastatin with erythromycin or clarithromycin.

Other products
In interaction studies with aspirin, antacids (one hour prior to pravastatin sodium) cimetidine, gemfibrozil, nicotinic acid or probucol, no statistically significant differences in bioavailability were seen.

4.6 Pregnancy and lactation

Pregnancy
Pravastatin is contraindicated during pregnancy and should be administered to women of childbearing potential only when these 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 must be discontinued because of the potential risk to the foetus (see section 4.3).

Lactation
A small amount of pravastatin is excreted in human breast milk; therefore pravastatin is contraindicated during breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following: very common (> 1/10); common (> 1/100, <1/10); uncommon (> 1/1000, <1/100); rare (> 1/10000, <1/1000); very rare (<1/10000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Clinical trials
Pravastatin tablets have been studied at 40 mg in seven randomized double-blind placebo-controlled trials involving over 21000 patients treated with pravastatin (N=10764) or placebo (N=10719), representing over 47000 patient-years of exposure to pravastatin. Over 19000 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 pravastatin group compared to the placebo group.

Nervous system disorders:
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, e.g. musculoskeletal pain including arthralgia, muscle cramps, myalgia, muscle weakness and elevated CK 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 erythematouslike 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, sometime complicated by rupture.

The following adverse events have been reported with some statins:
- Nightmares
- Memory loss
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

4.9 Overdose

To date there has been limited experience with overdosage of pravastatin. There is no specific treatment in the event of overdose. In the event of 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.

Mechanism of action:
Pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalysing 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 6595 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 patients.

Secondary prevention:
The "Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)" 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 coronary heart disease (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 myocardial infarction (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-c ontrolled study comparing the effects of pravastatin (40 mg OD) on coronary heart disease death and n onfatal myocardial infarction for an average of 4.9 years in 4159 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 patients.

In the CARE and LIPID studies, about 80 % of patients had received acetylsalicylic acid (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 sodium (20-40 mg) or not, and a standard immunosuppressive regimen of cyclosporine, 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 sodium (20 mg) or not, and a standard immunosuppressive regimen of cyclosporin, 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 was 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 identical whether taken with or without food.

After absorption, 66% of pravastatin undergoes extensive 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 0.5 l/kg. A small quantity of pravastatin passes into the human breast milk.

Metabolism and elimination:
Pravastatin is not significantly metabolised 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 the renal excretion and 53% by biliary excretion and biotransformation. The major degradation 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 0.81 l/H/kg and the renal clearance is 0.38 l/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 observed in adults after a 20 mg oral dose.

Hepatic failure:
Systemic exposure to pravastatin and metabolites in patients with alcoholic cirrhosis is enhanced by about 50% comparatively to patient 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, measurable 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 increase 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
Dihydroxy Aluminium Sodium Carbonate
Sodium Stearyl Fumarate
Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original packaging in order to protect from moisture.

6.5 Nature and contents of container

PL 20692/0055 and 0061:
Polyamide/aluminium/PVC-aluminium foil blisters in pack sizes of 10, 14, 20, 28, 30, 50, 60, 84, 90, 98 or 100 tablets.

PL 20692/0058:
Polyamide/aluminium/PVC-aluminium foil blisters in pack sizes of 20, 28, 30, 60, 84 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Vale Pharmaecuticals Ltd
1B Gurtnafleur Business Park,
Gurtnafleur, Clonmel, Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 20692/0055
PL 20692/0058
PL 20692/0061

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/06/2010

10 DATE OF REVISION OF THE TEXT

15/06/2010

1 NAME OF THE MEDICINAL PRODUCT

Pravastatin sodium 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of pravastatin sodium.

Excipient: 153.5 mg of lactose monohydrate / tablet
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Pravastatin sodium 20 mg tablets: Light yellow colour, mottled, round tablet debossed with "20" on one side and break line on the other side. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Primary prevention
Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolemia 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 patients receiving immunossupressive 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 sodium Tablets, secondary causes of hypercholesterolaemia should be excluded and patients should be placed on a standard lipid-lowering diet that should be continued during treatment.

Pravastatin sodium Tablets are 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 up to 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 childbearing 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 Tablets on total cholesterol and LDL-cholesterol are enhanced when combined with a bile acid-binding resin (e.g. cholestyramine, colestipol). Pravastatin sodium Tablets should be given either one hour before or at least four hours after the resin (see section 4.5).

For patients taking cyclosporine 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 performed with caution (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Active liver disease including unexplained persistent elevations of serum transaminase elevation exceeding 3 x the upper limit of normal (ULN) (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 others 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 increases in liver transaminase levels have been observed. In the 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 (AST) 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 others 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 pain or tenderness, muscle weakness, or muscle cramps. In such cases creatine kinase (CK) levels should be measured (see below).

Statin therapy should be temporarily interrupted when CK levels are > 5 x ULN or when there are severe clinical symptoms. Very rarely (in about 1 case over 100 000 patient-years), rhabdomyolysis occurs, with or without secondary renal insufficiency. Rhabdomyolysis is an acute potentially fatal condition of skeletal muscle which may develop at any time during treatment and is characterised by massive muscle destruction associated with major increase in CK (usually > 30 or 40 x ULN) leading

to myoglobinuria.

The risk of myopathy with statins appears to be exposure-dependent and therefore may vary with individual active substances (due to lipophilicity and pharmacokinetic differences), including their dosage and potential for interactions with medicinal products. Although there is no muscular contraindication to the prescription of a statin, certain predisposing factors may increase the risk of muscular toxicity and therefore justify a careful evaluation of the benefit/risk and special clinical monitoring. CK measurement is indicated before starting statin therapy in these patients (see below).

The risk and severity of muscular disorders during statin therapy is increased by the co-administration of interacting medicinal products. 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 (see section 4.5). 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 patients developing muscular symptoms during statin therapy, as described below. If CK levels are significantly elevated at baseline (> 5 x ULN), CK levels should be re-measured about 5 to 7 days later to confirm the results. When measured, CK levels should be interpreted in the context of other potential factors that can cause transient muscle damage, such as strenuous exercise or muscle trauma.

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

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 < 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 patient, 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 associated 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 can not 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.

Cholestyramine/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 cholestyramine or one hour before colestipol (see section 4.2).

Cyclosporin
Concomitant administration of pravastatin and cyclosporin leads to an approximately 4fold 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 metabolised by cytochrome P450
Pravastatin is not metabolised to a clinically significant extent by the cytochrome P450 system. This is why products that are metabolised 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 two interaction studies with pravastatin and erythromycin a statistically significant increase in pravastatin AUC (70 %) and Cmax (121 %) was observed. In a similar study with clarithromycin a statistically significant increase in AUC (110 %) and Cmax (127 %) was observed. Although these changes were minor, caution should be exercised when associating pravastatin with erythromycin or clarithromycin.

Other products
In interaction studies with aspirin, antacids (one hour prior to pravastatin sodium) cimetidine, gemfibrozil, nicotinic acid or probucol, no statistically significant differences in bioavailability were seen.

4.6 Pregnancy and lactation

Pregnancy
Pravastatin is contraindicated during pregnancy and should be administered to women of childbearing potential only when these 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 must be discontinued because of the potential risk to the foetus (see section 4.3).

Lactation
A small amount of pravastatin is excreted in human breast milk; therefore pravastatin is contraindicated during breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following: very common (> 1/10); common (> 1/100, <1/10); uncommon (> 1/1000, <1/100); rare (> 1/10000, <1/1000); very rare (<1/10000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Clinical trials
Pravastatin tablets have been studied at 40 mg in seven randomized double-blind placebo-controlled trials involving over 21000 patients treated with pravastatin (N=10764) or placebo (N=10719), representing over 47000 patient-years of exposure to pravastatin. Over 19000 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 pravastatin group compared to the placebo group.

Nervous system disorders:
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, e.g. musculoskeletal pain including arthralgia, muscle cramps, myalgia, muscle weakness and elevated CK 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 erythematouslike 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, sometime complicated by rupture.

The following adverse events have been reported with some statins:
- Nightmares
- Memory loss
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

4.9 Overdose

To date there has been limited experience with overdosage of pravastatin. There is no specific treatment in the event of overdose. In the event of 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.

Mechanism of action:
Pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalysing 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 6595 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 patients.

Secondary prevention:
The "Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)" 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 coronary heart disease (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 myocardial infarction (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 4159 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 patients.

In the CARE and LIPID studies, about 80 % of patients had received acetylsalicylic acid (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 sodium (20-40 mg) or not, and a standard immunosuppressive regimen of cyclosporine, 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 sodium (20 mg) or not, and a standard immunosuppressive regimen of cyclosporin, 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 was 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 identical whether taken with or without food.

After absorption, 66% of pravastatin undergoes extensive 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 0.5 l/kg. A small quantity of pravastatin passes into the human breast milk.

Metabolism and elimination:
Pravastatin is not significantly metabolised 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 the renal excretion and 53% by biliary excretion and biotransformation. The major degradation 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 0.81 l/H/kg and the renal clearance is 0.38 l/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 observed in adults after a 20 mg oral dose.

Hepatic failure:
Systemic exposure to pravastatin and metabolites in patients with alcoholic cirrhosis is enhanced by about 50% comparatively to patient 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, measurable 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 increase 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
Dihydroxy Aluminium Sodium Carbonate
Sodium Stearyl Fumarate
Iron Oxide Yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original packaging in order to protect from moisture.

6.5 Nature and contents of container

PL 20692/0056 and 0062
Polyamide/aluminium/PVC-aluminium foil blisters in pack sizes of 10, 14, 20, 28, 30, 50, 60, 84, 90, 98 or 100 tablets

PL 20692/0059:
Polyamide/aluminium/PVC-aluminium foil blisters in pack sizes of 20, 28, 30, 60, 84 or 90 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Vale Pharmaecuticals Ltd
1B Gurtnafleur Business Park,
Gurtnafleur, Clonmel, Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 20692/0056
PL 20692/0059
PL 20692/0062

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/06/2010

10 DATE OF REVISION OF THE TEXT

15/06/2010

1 NAME OF THE MEDICINAL PRODUCT

Pravastatin sodium 40 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg of pravastatin sodium.

Excipient: 307.1 mg of lactose monohydrate / tablet
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Pravastatin sodium 40 mg tablets: Light pink colour, mottled, round tablet debossed with "40" on one side and break line on the other side. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Primary prevention
Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolemia 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 patients receiving immunossupressive 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 sodium Tablets, secondary causes of hypercholesterolaemia should be excluded and patients should be placed on a standard lipid-lowering diet that should be continued during treatment.

Pravastatin sodium Tablets are 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 up to 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 childbearing 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 Tablets on total cholesterol and LDL-cholesterol are enhanced when combined with a bile acid-binding resin (e.g. cholestyramine, colestipol). Pravastatin sodium Tablets should be given either one hour before or at least four hours after the resin (see section 4.5).

For patients taking cyclosporine 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 performed with caution (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Active liver disease including unexplained persistent elevations of serum transaminase elevation exceeding 3 x the upper limit of normal (ULN) (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 others 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 increases in liver transaminase levels have been observed. In the 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 (AST) 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 others 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 pain or tenderness, muscle weakness, or muscle cramps. In such cases creatine kinase (CK) levels should be measured (see below).

Statin therapy should be temporarily interrupted when CK levels are > 5 x ULN or when there are severe clinical symptoms. Very rarely (in about 1 case over 100 000 patient-years), rhabdomyolysis occurs, with or without secondary renal insufficiency. Rhabdomyolysis is an acute potentially fatal condition of skeletal muscle which may develop at any time during treatment and is characterised by massive muscle destruction associated with major increase in CK (usually > 30 or 40 x ULN) leading

to myoglobinuria.

The risk of myopathy with statins appears to be exposure-dependent and therefore may vary with individual active substances (due to lipophilicity and pharmacokinetic differences), including their dosage and potential for interactions with medicinal products. Although there is no muscular contraindication to the prescription of a statin, certain predisposing factors may increase the risk of muscular toxicity and therefore justify a careful evaluation of the benefit/risk and special clinical monitoring. CK measurement is indicated before starting statin therapy in these patients (see below).

The risk and severity of muscular disorders during statin therapy is increased by the co-administration of interacting medicinal products. 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 (see section 4.5). 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 patients developing muscular symptoms during statin therapy, as described below. If CK levels are significantly elevated at baseline (> 5 x ULN), CK levels should be re-measured about 5 to 7 days later to confirm the results. When measured, CK levels should be interpreted in the context of other potential factors that can cause transient muscle damage, such as strenuous exercise or muscle trauma.

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

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 < 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 patient, 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 associated 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 can not 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.

Cholestyramine/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 cholestyramine or one hour before colestipol (see section 4.2).

Cyclosporin
Concomitant administration of pravastatin and cyclosporin leads to an approximately 4fold 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 metabolised by cytochrome P450
Pravastatin is not metabolised to a clinically significant extent by the cytochrome P450 system. This is why products that are metabolised 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 two interaction studies with pravastatin and erythromycin a statistically significant increase in pravastatin AUC (70 %) and Cmax (121 %) was observed. In a similar study with clarithromycin a statistically significant increase in AUC (110 %) and Cmax (127 %) was observed. Although these changes were minor, caution should be exercised when associating pravastatin with erythromycin or clarithromycin.

Other products
In interaction studies with aspirin, antacids (one hour prior to pravastatin sodium) cimetidine, gemfibrozil, nicotinic acid or probucol, no statistically significant differences in bioavailability were seen.

4.6 Pregnancy and lactation

Pregnancy
Pravastatin is contraindicated during pregnancy and should be administered to women of childbearing potential only when these 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 must be discontinued because of the potential risk to the foetus (see section 4.3).

Lactation
A small amount of pravastatin is excreted in human breast milk; therefore pravastatin is contraindicated during breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following: very common (> 1/10); common (> 1/100, <1/10); uncommon (> 1/1000, <1/100); rare (> 1/10000, <1/1000); very rare (<1/10000).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Clinical trials
Pravastatin tablets have been studied at 40 mg in seven randomized double-blind placebo-controlled trials involving over 21000 patients treated with pravastatin (N=10764) or placebo (N=10719), representing over 47000 patient-years of exposure to pravastatin. Over 19000 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 pravastatin group compared to the placebo group.

Nervous system disorders:
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, e.g. musculoskeletal pain including arthralgia, muscle cramps, myalgia, muscle weakness and elevated CK 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 erythematouslike 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, sometime complicated by rupture.

The following adverse events have been reported with some statins:
- Nightmares
- Memory loss
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

4.9 Overdose

To date there has been limited experience with overdosage of pravastatin. There is no specific treatment in the event of overdose. In the event of 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.

Mechanism of action:
Pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalysing 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 6595 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 patients.

Secondary prevention:
The "Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)" 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 coronary heart disease (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 myocardial infarction (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 4159 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 patients.

In the CARE and LIPID studies, about 80 % of patients had received acetylsalicylic acid (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 sodium (20-40 mg) or not, and a standard immunosuppressive regimen of cyclosporine, 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 sodium (20 mg) or not, and a standard immunosuppressive regimen of cyclosporin, 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 was 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 identical whether taken with or without food.

After absorption, 66% of pravastatin undergoes extensive 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 0.5 l/kg. A small quantity of pravastatin passes into the human breast milk.

Metabolism and elimination:
Pravastatin is not significantly metabolised 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 the renal excretion and 53% by biliary excretion and biotransformation. The major degradation 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 0.81 l/H/kg and the renal clearance is 0.38 l/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 observed in adults after a 20 mg oral dose.

Hepatic failure:
Systemic exposure to pravastatin and metabolites in patients with alcoholic cirrhosis is enhanced by about 50% comparatively to patient 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, measurable 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 increase 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
Dihydroxy Aluminium Sodium Carbonate
Sodium Stearyl Fumarate
Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original packaging in order to protect from moisture.

6.5 Nature and contents of container

PL 20692/0057 and 0063
Polyamide/aluminium/PVC-aluminium foil blisters in pack sizes of 10, 14, 20, 28, 30, 50, 60, 84, 90, 98 or 100 tablets

PL 20692/0060:
Polyamide/aluminium/PVC-aluminium foil blisters in pack sizes of 20, 28, 30, 60, 84 or 90 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Vale Pharmaecuticals Ltd
1B Gurtnafleur Business Park,
Gurtnafleur, Clonmel, Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 20692/0057
PL 20692/0060
PL 20692/0063

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/06/2010

10 DATE OF REVISION OF THE TEXT

15/06/2010

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

PRAVASTATIN SODIUM 10 mg FILM-COATED TABLETS
PRAVASTATIN SODIUM 20 mg FILM-COATED TABLETS
PRAVASTATIN SODIUM 40 mg FILM-COATED 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 any further questions, ask your doctor. • 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.

In this leaflet:

1. WHAT PRAVASTATIN SODIUM IS AND WHAT IT IS USED FOR

Pravastatin, the active substance of Pravastatin Sodium, belongs to a group of medicines called statins which work by reducing high cholesterol levels in the blood. Cholesterol is a fatty substance (lipid) that can cause the narrowing of blood vessels in the heart causing coronary heart disease.

Pravastatin Sodium is used:
- to lower high cholesterol levels in your blood if diet, exercise or weight loss has not lowered your cholesterol level
- to lower the fatty substances (lipids) in your blood if you have had an organ transplant
- to reduce the chance of having another heart attack if you have previously had a heart attack or if you suffer from chest pain attacks (unstable angina pectoris).

2. BEFORE YOU TAKE PRAVASTATIN SODIUM

Do not take Pravastatin Sodium:
- if you are hypersensitive (allergic) to pravastatin sodium or any of the other ingredients of Pravastatin Sodium Tablets
- if you suffer from a liver disease or if liver function tests keep showing excessive values without any identifiable reason (your doctor will advise you about this)
- if you are pregnant or breastfeeding.

Take special care with Pravastatin Sodium:
- if you suffer from a kidney disease or have a history of liver disease
- if you regularly drink large amounts of alcohol
- if you suffer from a low function of your thyroid gland
- if you are taking medication (eg. fibrates) to lower fatty substances in your blood
- if you have experienced muscle problems during previous treatment to lower the fatty substances in your blood or if you or anyone in your family suffers from a hereditary muscle disease.

If you have suffered from any of these problems, your doctor will need to carry out a blood test before and possibly during Pravastatin treatment to assess your risk of muscle-related side effects. You may also need this blood test if you are 70 years or older.
- if you suffer from muscle weakness or cramps during your treatment or if certain parts of your body become unusually sensitive to touch.

Check with your doctor or pharmacist before taking pravastatin if you:
- have severe respitory failure.

Consult your doctor immediately if, while using Pravastatin Sodium, you get unexplained muscle ache, muscle weakness or muscle cramps, particularly in combination with tiredness, fever and red-brown discolouration of urine (rhabdomyolysis), which can be a sign of kidney problems. These symptoms may be caused by the use of Pravastatin Sodium.

Use in children - This medicine is not recommended for children younger than 8 years old.

Taking other medicines - Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
If you take Pravastatin Sodium together with certain other medicines, the effect either of Pravastatin Sodium or of the other medicine or of both may be influenced.

Inform your doctor or pharmacist especially if you are taking or have recently taken any of the following medicines:
- Medicines known as fibrates (eg. Gemfibrozil and Fenofibrate) which decrease fat levels in the blood or nicotinic acid. Taking these medicines with pravastatin may cause severe muscle disorders.
- Medicines such as Colestyramine and Colestipol used for the treatment of a high cholesterol level because they may reduce the effectiveness of pravastatin. Pravastatin sodium should be taken at least one hour before or four hours after you have taken these medicines.
- Ciclosporin (a medicine used to suppress the immune system) because the effect of pravastatin may be increased and your doctor may need to change your dose.
- Antibiotics such as Erythromycin and Clarithromycin because these increase the effect of pravastatin.

Taking Pravastatin Sodium with food and drink - This medicine can be taken with or without food. You should always keep your alcohol intake to a minimum. If you are concerned about how much alcohol you can drink while you are taking this medicine, you should discuss this with your doctor.

Pregnancy and breast-feeding - You should not use Pravastatin Sodium during pregnancy or whilst breast-feeding as pravastatin may harm your baby. Before you start using Pravastatin Sodium, you should inform your doctor if you are pregnant or intend to become pregnant. If you become pregnant during treatment, you should stop using Pravastatin Sodium and consult your doctor. Women of childbearing age should use a reliable contraceptive whilst taking this medicine. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines - Pravastatin Sodium does not usually affect the ability to drive and use machines. You may, however, feel a bit dizzy. Avoid driving or operating machines if you feel unwell after taking pravastatin.

Important information about some of the ingredients of Pravastatin Sodium - This medicine contains lactose. If you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE PRAVASTATIN SODIUM

Always take Pravastatin Sodium exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Take Pravastatin Sodium once daily, preferably in the evening, with or without food. Swallow the tablets with a sufficient quantity of liquid (e.g. one glass of water).

Unless otherwise prescribed by your doctor, the usual dose is:
For lowering an increased cholesterol level in the blood - The recommended dose is 10-40 mg pravastatin taken once per day. The maximum daily dose is 40 mg pravastatin.

To prevent heart and vessel disease - the recommended dose is 40 mg pravastatin taken once per day.

Following a transplant - the recommended dose is 20 mg pravastatin taken once per day. The dosage can be adjusted up to 40 mg pravastatin. Your doctor will tell you how much to take.

Children and adolescents with hereditary increased cholesterol in the blood (heterozygous familial hypercholesterolaemia) - The recommended dose is 10-20 mg pravastatin taken once per day for children 8-13 years of age and 10-40 mg pravastatin taken once per day in adolescents 14-18 years of age.

Elderly - No dosage adjustment is required for this group. The same dosage as for adult patients can be used. Your doctor will tell you how much to take.

Dosage adjustment in kidney or liver disorder - The typical dose is 10 mg pravastatin taken once per day but may be higher. Your doctor will tell you how much to take.

Taking Pravastatin with other medicines - If you take Pravastatin and other medicines containing colestyramine or colestipol (medicines also used for the treatment of high cholesterol levels), you should take Pravastatin Sodium at least one hour before or four hours after these medicines.

If you are also taking a medicine which lowers the body's immune system (ciclosporin), your doctor may prescribe a starting dose of 20 mg once a day. The dose may be adjusted up to 40 mg by your doctor. Your doctor will tell you how much to take.

Your doctor will tell you how long you have to take Pravastatin Sodium. This depends on why you are taking this medicine.

If you have the impression that the effect of Pravastatin Sodium is too strong or too weak, talk to your doctor or pharmacist.

If you take more Pravastatin Sodium than you should - If you have taken too many tablets, or if someone has accidentally taken your tablets, **contact your doctor or pharmacist immediately.**

If you forget to take Pravastatin Sodium - If you miss a dose do not worry. Simply take your normal dose when it is next due. **Do not** take a double dose to make up for a forgotten dose.

If you stop taking Pravastatin Sodium - Take Pravastatin Sodium as long as your doctor has told you. If you stop taking Pravastatin Sodium, your cholesterol levels may increase again.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Pravastatin Sodium can cause side effects, although not everybody gets them. Generally, these are mild and transient. However, the following side effects may occur in some patients during treatment.

You might experience inflammation of the pancreas (pancreatitis), muscle inflammation, muscle cramps, fever that may be associated with kidney problems (rhabdomyolysis). **Contact your doctor immediately** if you develop one of these symptoms during the use of Pravastatin Sodium, because muscle disorders may be serious in rare cases (see also 2. Before you take Pravastatin Sodium).

You might get a serious allergic reaction causing swelling of the face, throat, tongue and excessive fluid in your body which can produce difficulty in swallowing or breathing. This is a very rare reaction which can be serious if it occurs, you **should see a doctor immediately if you have these symptoms.**

Uncommon side effects (affecting 1 to 10 users in 1000) include:
- dizziness, headache, sleep disturbances, difficulty sleeping
- problems with eyesight, blurred vision or double vision
- digestive problems or slow digestion, indigestion /heartburn, abdominal pain, feeling/being sick, difficulty or delay emptying bowels, diarrhoea, wind
- itching, rash, hives, scalp and hair problems (inclusive of hair loss)
- abnormal urination, eg. pain, frequency, frequent urination at night
- problems with sexual functions
- tiredness.

Very Rare side effects (affecting 1 to 10 users in 10,000) include:
- problems with touch including burning/tingling sensation, numbness or pins and needles (paresthesia)
- inflamed tendons, sometimes associated with tearing
- tender muscles and bones, painful joints (arthralgia), muscle cramps, muscle pain and muscle weakness
- increased production of liver enzymes
- yellowing of the skin or whites of eyes (jaundice), tissues and body fluids, liver inflammation (hepatitis), sudden rapid destruction of all liver tissue (hepatitis necrosis)
- a certain type of chronic skin disorder (lupus like syndrome).

Other possible side effects include:
- sleep disturbances, including insomnia and nightmares
- memory loss
- depression
- breathing problems including persistant cough and/or shortness of breath and fever.

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

Keep out of the reach and sight of children.
Store in the original packaging in order to protect from moisture.

Do not use Pravastatin Sodium after the expiry date which is stated on the carton and blister after '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 contains:
The active substance is: Pravastatin sodium.
Pravastatin Sodium 10 mg tablets: each tablet contains 10 mg of pravastatin sodium.
Pravastatin Sodium 20 mg tablets: each tablet contains 20 mg of pravastatin sodium.
Pravastatin Sodium 40 mg tablets: each tablet contains 40 mg of pravastatin sodium.
The other ingredients are Lactose Monohydrate, Dihydroxy Aluminium Sodium Carbonate, Sodium Stearyl Fumarate, Iron Oxide Red (E 172) (for the 10 mg and 40 mg tablets only) and Iron Oxide Yellow (E172) (for the 20 mg tablet only).

What Pravastatin Sodium looks like and contents of the pack - 10 mg Tablets - Light pink colour, mottled, round, flat, bevelled tablets debossed with '10' on one side and plain on the other.
20 mg Tablets - Light yellow colour, mottled, round tablet debossed with '20' on one side and break line on the other side. The tablet can be divided into equal halves.
40 mg Tablets - Light pink colour, mottled, round tablet debossed with '40' on one side and break line on the other side. The tablet can be divided into equal halves.
Pravastatin Sodium is available in blister packs with 10, 14, 20, 28, 30, 50, 60, 84, 90, 98 or 100 tablets. Not all pack sizes may be marketed.

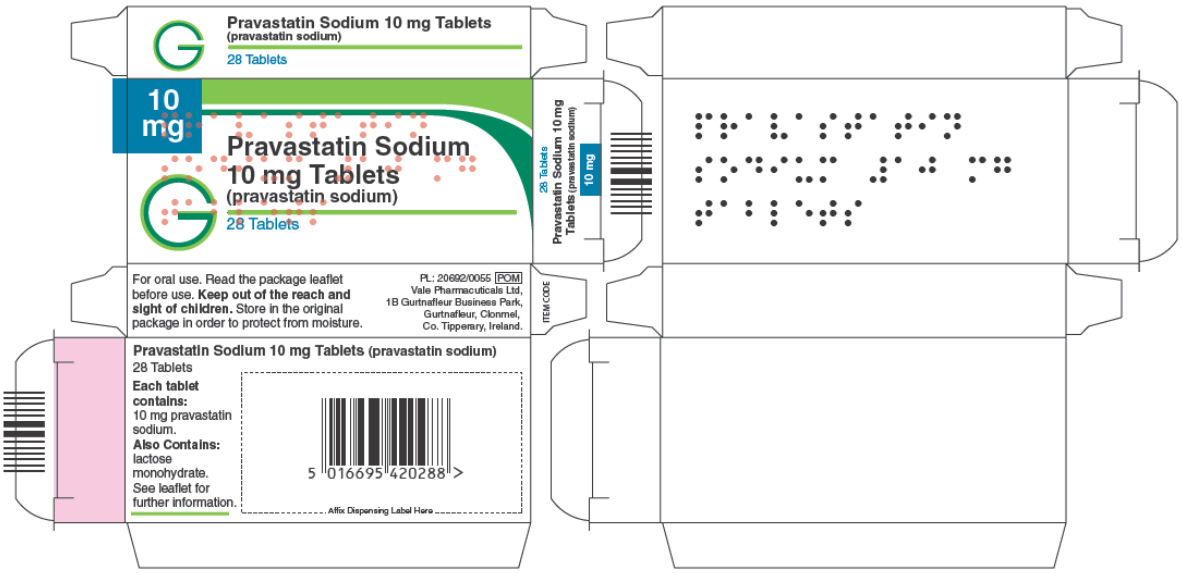
Marketing Authorisation Holder - Vale Pharmaceuticals Ltd, 1B Gurtnafleur Business Park, Gurtnafleur, Clonmel, Co. Tipperary, Ireland
Tel: +353 (0)52 80664 Fax: +353 (0)52 80665

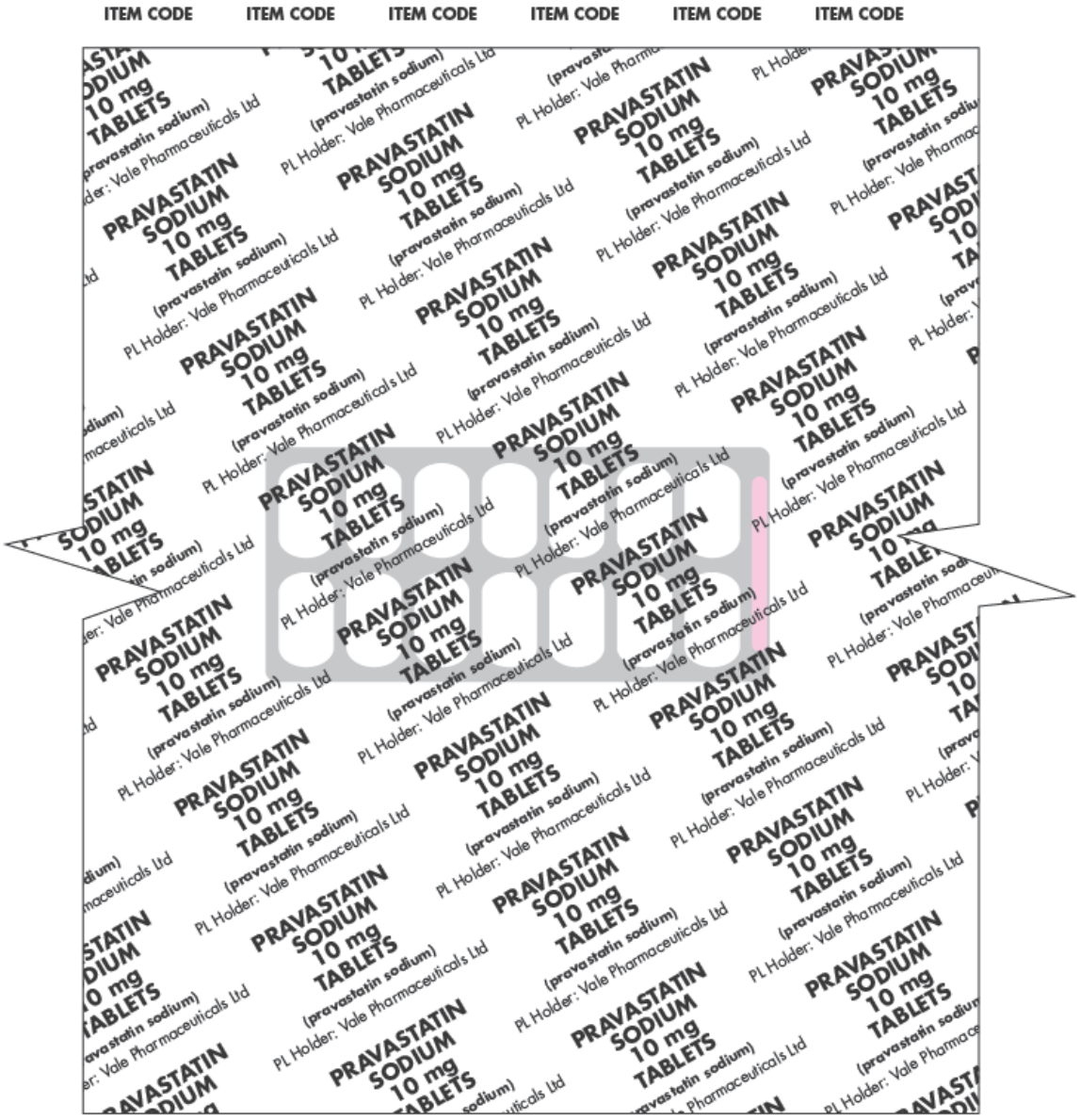
Manufacturer - McDermott Laboratories trading as Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.
Tel: +353 1839 8600 Fax: +353 1839 9651
Mylan B.V, Distelweg 25, 3752 LB Bunschoten The Netherlands
Tel: +31 332 997080 Fax: +31 332 997085
Mylan dura GmbH, Wittichstraße 6, D-64295 Darmstadt, Germany
Tel: +49 61 51 9512-0 Fax: +49 61 51 9512-302
Mylan S.A.S (Saint Priest), 117 allee des parcs, 69 800 Saint Priest, France
Tjoa Pack Hungary Kft, 2040 Budaors, Vasut u. 13.
Tel: +36 23 501 441 Fax: +36 23 430 659

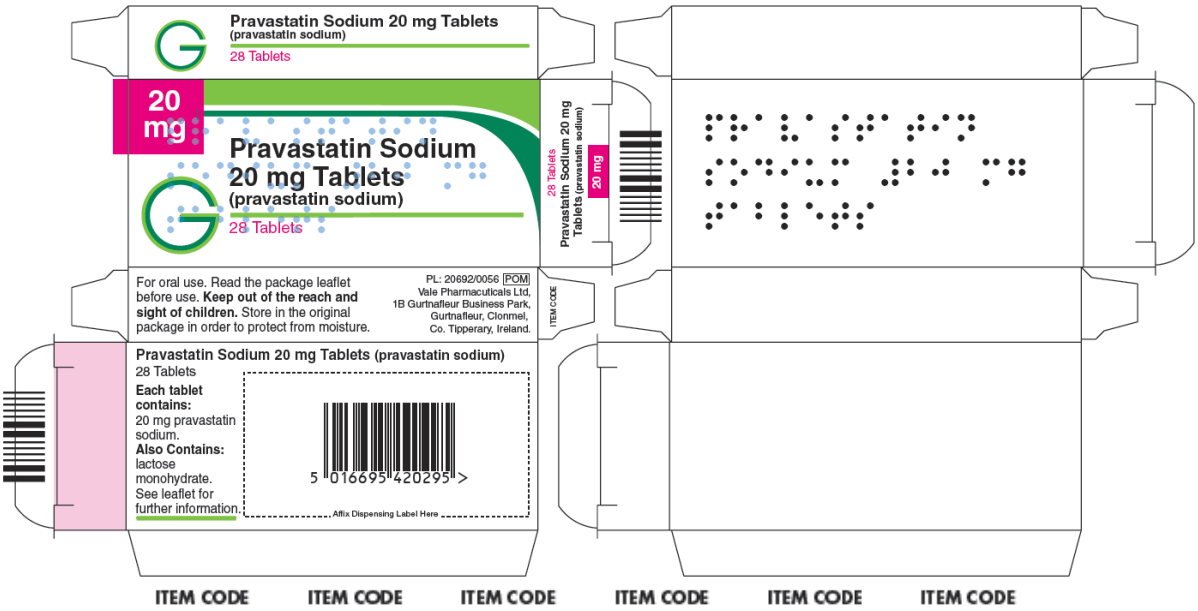
This medicinal product is authorised in the Member States of the EEA under the following names:
Austria - Pravastatin Vale 20 mg, 40 mg Tabletten
Belgium - Pravastatin Vale 10 mg, 20 mg, 40 mg Tablets
Czech Republic - Pravastatin Vale 10 mg, 20 mg Tablets
Finland - Pravastatin Vale 20 mg, 40 mg Tablets
France - Pravastatine Vale Pharmaceuticals 10 mg, 20 mg, 40 mg Tablets
Germany - Pravastatin Vale 10 mg, 20 mg, 40 mg Tabletten
Ireland - Pravastatin Sodium 10 mg, 20 mg, 40 mg Tablets
Italy - Pravastatina Vale Pharmaceuticals 20 mg, 40 mg Tablets
Netherlands - Pravastatine Natrium Vale 10 mg, 20 mg, 40 mg Tabletten
Norway - Pravastatin Vale 20 mg, 40 mg Tablets
Portugal - Pravastatina Vale 10 mg, 20 mg, 40 mg comprimidos
Romania - Pravastatina Sodica Vale 10 mg, 20 mg, 40 mg comprimate
Spain - Pravastatina Valera 10 mg, 20 mg, 40 mg comprimidos EFG
Sweden - Pravastatin Vale 20 mg, 40 mg Tablets
United Kingdom - Pravastatin Sodium 10 mg, 20 mg, 40 mg Tablets.

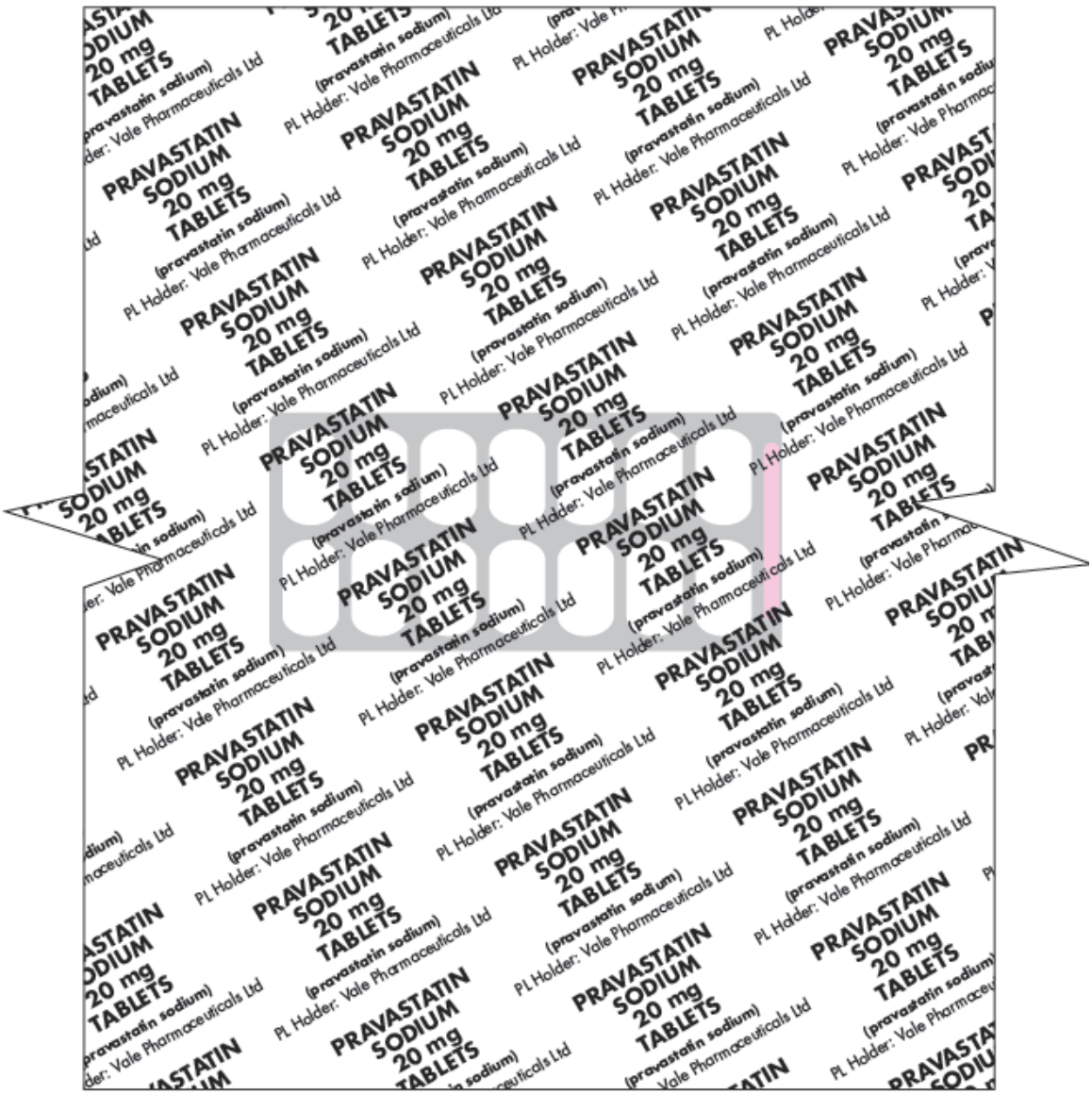
This leaflet was last approved in: May 2010 PRPRPR

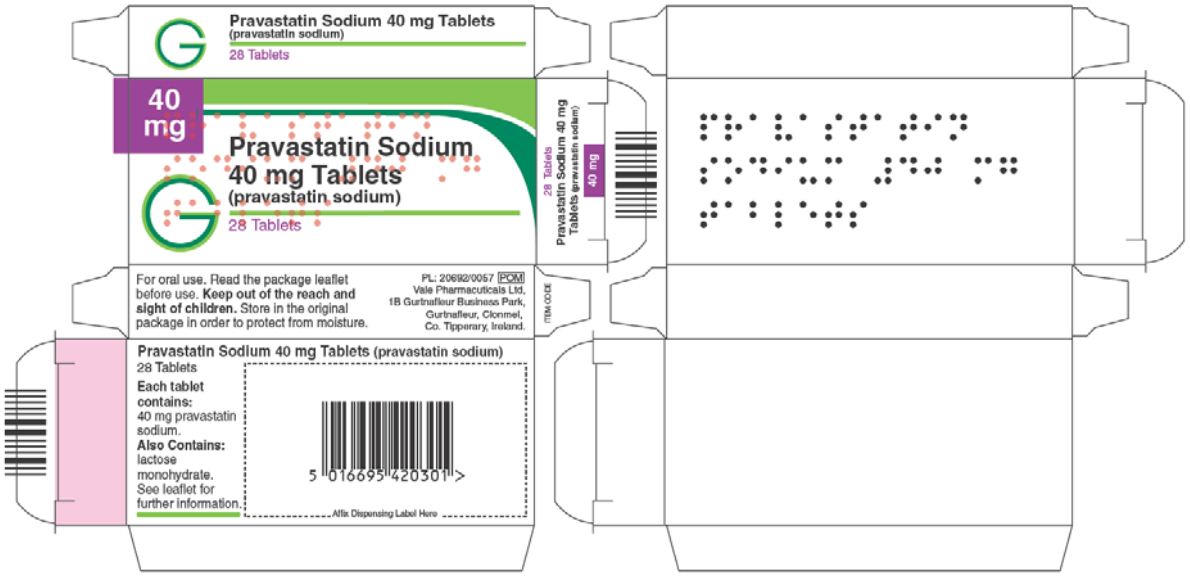
Module 4
Labelling






Pravastatin Sodium 20 mg Tablets
(pravastatin sodium)
28 Tablets
20 mg
Pravastatin Sodium
20 mg Tablets
(pravastatin sodium)
28 Tablets
Pravastatin Sodium 20 mg Tablets (pravastatin sodium)
28 Tablets
20 mg
For oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Store in the original package in order to protect from moisture.
PL: 20692/0056 POM
Vale Pharmaceuticals Ltd,
1B Gurtnafleur Business Park,
Gurtnafleur, Clonmel,
Co. Tipperary, Ireland.
ITEM CODE
Pravastatin Sodium 20 mg Tablets (pravastatin sodium)
28 Tablets
Each tablet contains:
20 mg pravastatin sodium.
Also Contains:
lactose monohydrate.
See leaflet for further information.
5 016695 420295
Affix Dispensing Label Here
ITEM CODE
ITEM CODE
ITEM CODE
ITEM CODE
ITEM CODE
ITEM CODE


PRAVASTATIN SODIUM 20 mg TABLETS
(pravastatin sodium)
PL Holder: Vale Pharmaceuticals Ltd



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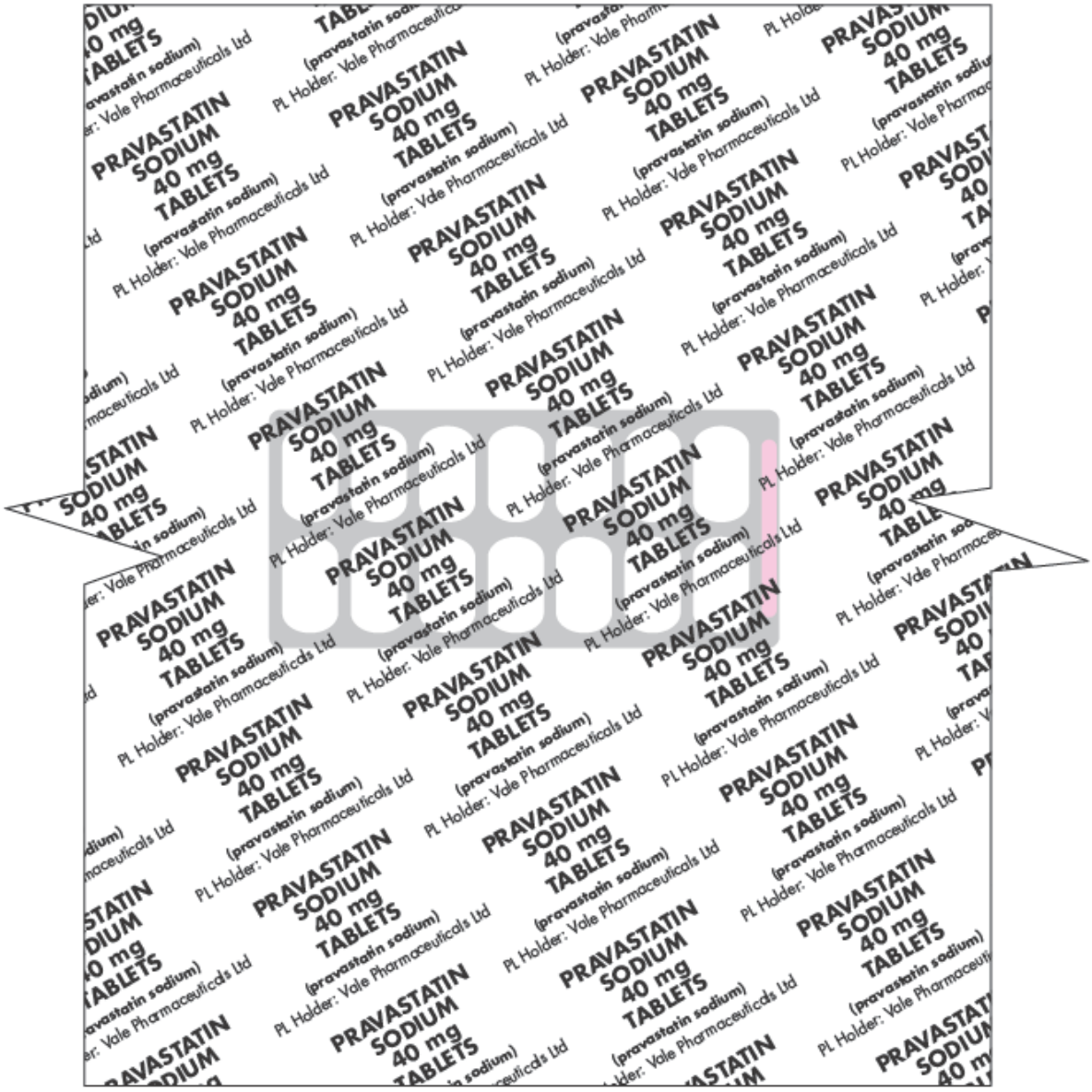


Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Pravastatin Sodium 10mg, 20mg and 40mg Tablets (PL 20692/0055-63; UK/H/2810, 2811 and 2875/001-3/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as reference member state (RMS), and Austria, Belgium, Czech Republic, Germany, Spain, Finland, France, Ireland, Italy, Netherlands, Norway, Portugal, Romania and Sweden as concerned member states (CMS).

The products are prescription-only medicines for the treatment of:

- hypercholesterolaemia,
- primary prevention (reduction of cardiovascular mortality and morbidity) in patients with moderate to severe hypercholesterolaemia
- secondary prevention (reduction of cardiovascular mortality and morbidity) in patients with a history of myocardial infarction or unstable angina pectoris and with normal or increased cholesterol levels
- reduction of post transplantation hyperlipidaemia in patients receiving immunosupressive therapy following solid organ transplantation.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Lipostat 10mg, 20mg and 40mg Tablets, which were originally granted licences in 1997 to Bristol Myers Squibb Pharmaceuticals Ltd, UK.

Pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A(HMG-CoA) reductase, the enzyme catalysing the early rate-limiting step in the 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.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 188) on 17 May 2010. After a subsequent national phase, the licences were granted in the UK on 15 June 2010.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Pravastatin Sodium 10, 20 and 40mg Tablets
Name(s) of the active substance(s) (INN)	Pravastatin sodium
Pharmacotherapeutic classification (ATC code)	Cardiovascular system – lipid modifying (C10AA03)
Pharmaceutical form and strength(s)	10, 20 and 40mg Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/2810, 2811 and 2875/001-3/DC
Reference Member State	United Kingdom
Member States concerned	UK/H/2810/001/DC: Belgium, Czech Republic, Germany, Spain, France, Ireland, Netherlands, Portugal and Romania. UK/H/2810/002-3/DC:Austria, Belgium, Czech Republic, Finland, Germany, Spain, France, Ireland, Italy, Netherlands, Norway, Portugal, Romania and Sweden UK/H/2811/001-3/DC: France and Portugal. UK/H/2875/001-3/DC: Belgium
Marketing Authorisation Number(s)	PL 20692/0055-63
Name and address of the authorisation holder	Vale Pharmaceuticals Ltd. Unit 1b, Gurtnafleur Business Park, Gurtnafleur, Clonnel, Co. Tipperary, Ireland.

III SCIENTIFIC OVERVIEW AND DISCUSSION

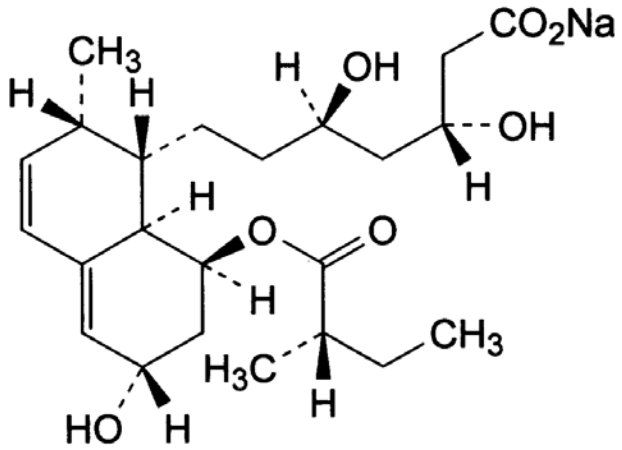
III.1 QUALITY ASPECTS

S. Active substance

INN: Pravastatin sodium

Chemical name: Sodium (3*R*,5*R*)-3,5-dihydroxy-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-6-hydroxy-2-methyl-8-[[(2*S*)-2-methylbutanoyl]oxy]-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]heptanoate

Structure:



Molecular formula: $C_{23}H_{35}NaO_7$

Molecular mass: 446.5

Appearance: Appearance: off white crystalline powder, hygroscopic.Solubility: freely soluble in water and in methanol, soluble in ethanol

Pravastatin sodium is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, dihydroxy aluminium sodium carbonate, sodium stearyl fumarate, iron oxide red (E172 - 10 and 40mg strength only) and iron oxide yellow (E172 - 20mg strength only).

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of iron oxide red and yellow (E172), which are compliant with US Pharmacopoeia/National Formulary monographs. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent tablet dosage form of Pravastatin sodium Tablets, comparable to Lipostat Tablets (Bristol Myers Squibb Pharmaceuticals Ltd)

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System

PL 20692/0055-57 and 0061-63:
Polyamide/aluminium/polyvinylchloride blisters in pack sizes of 10, 14, 20, 28, 30, 50, 60, 84, 90, 98 or 100 tablets.

PL 20692/0058-60:
Polyamide/aluminium/polyvinylchloride blisters in pack sizes of 20, 28, 30, 60, 84 or 90 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage conditions "Store in the original packaging in order to protect from moisture".

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of pravastatin sodium are well-known, no further preclinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a preclinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose crossover study to compare the pharmacokinetics of the test product Pravastatin Sodium 40mg Tablets versus the reference product Lipostat 40mg Tablets (Bristol-Myers Squibb, UK) in healthy adult male volunteers under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours post dose. The two treatment arms were separated by at least a 5-day washout period.

The pharmacokinetic results (presented as geometric least-squares means, ratios and 90% confidence intervals) are presented below:

Parameters (Units)	In-transformed Data			90% Confidence Interval (Parametric
	Geometric Least Squares Mean			
	Test Product-A	Reference Product-B	Ratio (A/B)%	
C_{max} (ng/mL)	114.44	118.19	96.83%	87.22-107.50
AUC_{0-t} (ng.h/mL)	244.51	254.23	96.18%	88.81-104.16
$AUC_{0-\infty}$ (ng.h/mL)	255.54	264.20	96.72%	89.62-104.39

The 90% confidence intervals for C_{max} and AUC for test versus reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.

As the 10, 20 and 40mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the extrapolation of results and conclusions from the bioequivalence study on the 40mg strength to the 10 and 20mg strengths is justified.

Efficacy

No new data on the efficacy have been submitted and none are required for these types of applications.

Safety

No new or unexpected safety issues were raised by the bioequivalence data.

SPC, PIL, Labels

The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Pravastatin Sodium 10, 20 and 40mg 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 risk-benefit balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant's 40mg Tablets and its respective reference product. As the 10mg and 20mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 40mg strength can be extrapolated to the 10 and 20mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the originator products are interchangeable. Extensive clinical experience with pravastatin sodium is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome