Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pravat 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains pravastatin sodium 20 mg

Excipient with known effect: Contains Lactose Monohydrate 80.6mg
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Off-white to light yellow, round, unscored tablet, engraved “APO” on one side and “PRA” over “20” on the other side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

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

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

4.2 Posology and method of administration

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

<u>Posology</u>

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 child-bearing potential, see section 4.6; for results of the study see section 5.1).

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

Patients with 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 on total cholesterol and LDL-cholesterol are enhanced when combined with a bile acid-binding resin (e.g. colestyramine, colestipol). Pravastatin should be given either one hour before or at least four hours after the resin (see section 4.5).
For patients taking ciclosporin with or without other immunosuppressive medicinal products, treatment should begin with 20 mg of Pravastatin sodium once daily and titration to 40 mg should be performed with caution (see section 4.5).

Method of administration
Pravastatin is administered orally once daily preferably in the evening with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active liver disease 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 other HMG-CoA reductase inhibitors, combination of Pravastatin with fibrates is not recommended.

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

Hepatic disorders: as with other lipid-lowering agents, moderate 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 other HMG-CoA reductase inhibitors (statins), Pravastatin has been associated with the onset of myalgia, myopathy and very rarely, rhabdomyolysis.

Myopathy must be considered in any patient under statin therapy presenting with unexplained muscle symptoms such as 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 medicinal products (due to lipophilicity and pharmacokinetic differences), including their dosage and potential for drug interactions. Although there is no muscular contraindication to the prescription of a statin, certain predisposing 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 coadministration 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.

Pravastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of Pravastatin sodium tablets and fusidic acid should only be considered on a case by case basis and under close medical supervision.

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

Diabetes mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hypoglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L. BMI> 30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

<u>Interstitial lung disease</u>
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.

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.

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 remeasured 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 patients, restarting statin therapy is not recommended.

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactosemalabsorption should not take this medicine.

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 cannot be excluded; therefore the combined use of Pravastatin and fibrates (e.g. gemfibrozil, fenofibrate) should generally be avoided *(see section 4.4).* If this combination is considered necessary, careful clinical and CK monitoring of patients on such regimen is required.

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

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

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

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.
If treatment with systemic fusidic acid is necessary, Pravastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4

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.

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

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

4.6 Fertility, 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 should be discontinued because of the potential risk to the foetus.

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 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 (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000).

Clinical trials: Pravastatin has been studied at 40 mg in seven randomized doubleblind placebo-controlled trials involving over 21,000 patients treated with Pravastatin (N = 10764) or placebo (N = 10719), representing over 47,000 patients years of exposure to Pravastatin. Over 19,000 patients were followed for a median of 4.8 - 5.9 years. The following adverse drug reactions were reported; none of them occurred at a rate in excess of 0.3% in 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: dermatomyositis.
Endocrine disorders
Diabetes mellitus
Frequency will depend on the presence or absence of risk factors (fasting blood glucose at 5.6 mmol/L, BMI>30kg/m 2, raised triglycerides, history of hypertension).
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 erythematous-like syndrome
Gastrointestinal disorders:
Very rare: pancreatitis
Hepatobiliary disorders:
Very rare: jaundice, hepatitis, fulminant hepatic necrosis
Musculoskeletal and connective tissue disorders
Very rare: rhabdomyolysis, which can be associated with acute renal failure secondary to myoglobinuria, myopathy (see section 4.4)
Isolated cases of tendon disorders, sometimes complicated by rupture
Musculoskeletal disorders:
Frequency not known: Immune-mediated necrotizing myopathy (see section 4.4)

The following adverse events have been reported with Pravastatin:

- Nightmares
- Memory loss
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)
- Diabetes mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥5.6 mmol/L, BMI> 30kg/m^2, raised triglycerides, history of hypertension).

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

IMB Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

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 LDLcholesterol. 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, VLDLcholesterol 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, doubleblind, placebo-controlled trial among 6,595 male patients aged from 45 to 64 years with moderate to severe hypercholesterolaemia (LDL-C: 155-232 mg/dl [4.0-6.0 mmol/l]) and with no history of myocardial infarction, treated for an average duration of 4.8 years with either a 40 mg daily dose of Pravastatin or placebo as an adjunct to diet. In Pravastatin-treated patients, results showed:

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

The benefit of the treatment on the criteria indicated above is not known in patients over the age of 65 years, who could not be included in the study.
In the absence of data in patients with hypercholesterolaemia associated with a triglyceride level of more than 6 mmol/l (5.3 g/l) after a diet for 8 weeks, in this study, the benefit of Pravastatin treatment has not been established in this type of patients.

Secondary prevention
The "Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)" was a multicenter, randomised, double-blind, placebo-controlled study comparing the effects of Pravastatin sodium (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 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 coronary heart disease death or nonfatal myocardial infarction) 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 sodium (40 mg OD) on coronary heart disease death and nonfatal myocardial infarction for an average of 4.9 years in 4,159 patients aged 21 to 75 years, with normal total cholesterol levels (baseline mean total cholesterol < 240 mg/dl), who had experienced a myocardial infarction in the preceding 3 to 20 months. Treatment with Pravastatin significantly reduced:

- the rate of a recurrent coronary event (either coronary heart disease death or nonfatal myocardial infarction) 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 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 - 40mg) or not, and a standard immunosuppressive regimen of ciclosporin, prednisone and azathioprine. Treatment with Pravastatin significantly reduced the rate of cardiac rejection with haemodynamic compromise at one year, improved one-year survival ($p = 0.025$), and lowered the risk of coronary vasculopathy in the transplant as determined by angiography and autopsy ($p = 0.049$).
- Renal transplant was assessed in one prospective not controlled, not randomised study (n = 48) of 4 months duration. Patients were treated concurrently with either Pravastatin sodium (20 mg) or not, and a standard immunosuppressive regimen of ciclosporin, and prednisone. In patients following kidney transplantation, Pravastatin significantly reduced both the incidence of multiple rejection episodes and the incidence of biopsy-proved acute rejection episodes, and the use of pulse injections of both prednisolone and Muromonab-CD3.

Paediatric population:

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

Inclusion in this study required one parent with either a clinical or molecular diagnosis of familial hypercholesterolaemia. The mean baseline LDL-C value was 239 mg/dl (6.2 mmol/l) and 237 mg/dl (6.1 mmol/l) in the pravastatin (range 151 – 405 mg/dl [3.9 – 10.5 mmol/l]) and placebo (range 154 – 375 mg/dl [4.0 – 9.7 mmol/l]). There was a significant mean percent reduction in LDL-C of -22.9% and also in total cholesterol (-17.2%) from the pooled data analysis in both children and adolescents, similar to demonstrated efficacy in adults on 20 mg of pravastatin.

The effects of pravastatin treatment in the two age groups were similar. The mean achieved LDL-C was 186 mg/dl (4.8 mmol/l) (range: 67 – 363 mg/dl [1.7 – 9.4 mmol/l]) in the pravastatin group compared to 236 mg/dl (6.1 mmol/l) (range: 105 – 438 mg/dl [2.7 – 11.3 mmol/l]) in the placebo group. In subjects receiving pravastatin, there were no differences seen in any of the monitored endocrine parameters [ACTH, cortisol, DHEAS, FSH, LH, TSH, estradiol

(girls) or testosterone (boys)] relative to placebo. There were no developmental differences, testicular volume changes or Tanner score differences observed relative to placebo. The power of this study to detect a difference between the two groups of treatment was low.
The long-term efficacy of pravastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic properties

Absorption:
Pravastatin is administered orally in the active form. It is rapidly absorbed; peak serum levels are achieved 1 to 1.5 hours after ingestion. On average, 34% of the orally administered dose is absorbed, with an absolute bioavailability of 17%. The presence of food in the gastrointestinal tract leads to a reduction in the bioavailability, but the cholesterol-lowering effect of Pravastatin is identical whether taken with or without food.
After absorption, 66% of Pravastatin undergoes a first-pass extraction through the liver, which is the primary site of its action and the primary site of cholesterol synthesis and clearance of LDL-cholesterol. *In vitro* studies demonstrated that Pravastatin is transported into hepatocytes and with substantially less intake in other cells. In view of this substantial first pass through the liver, plasma concentrations of Pravastatin have only a limited value in predicting the lipid-lowering effect.
The plasma concentrations are proportional to the doses administered.

Distribution:
About 50% of circulating Pravastatin is bound to plasma proteins.
The volume of distribution is about 0.5 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 population: mean pravastatin Cmax and AUC values for paediatric subjects pooled across age and gender were similar to those values observed in adults after a 20 mg oral dose.
Hepatic impairment: systemic exposure to Pravastatin and metabolites in patients with alcoholic cirrhosis is enhanced by about 50% comparatively to patients with normal liver function.
Renal impairment: no significant modifications were observed in patients with mild renal impairment. However severe and moderate renal insufficiency may lead to a two fold increase of the systemic exposure to Pravastatin and metabolites.

5.3 Preclinical safety data

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

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

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

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

males and females, and lung adenomas in females only. In rats a 2-year carcinogenicity study demonstrates at a dose of 100mg/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
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store below 25^{o}C. Store in the original package.

6.5 Nature and contents of container

4, 10, 14, 20, 28, 30, 50, 56, 98, 100, 200 tablets in a PVC/PVAC/Aluminium blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Apotex Europe BV
Darwinweg 20
Leiden
2233 CR
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1513/008/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 April 2005

Date of last renewal: 15 June 2009

10 DATE OF REVISION OF THE TEXT

June 2016