ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Austria	Bristol-Myers Squibb GesmbH Columbusgasse 4 A-1101 Wien	Pravachol	10 mg	Tablets	Oral use
Austria	Bristol-Myers Squibb GesmbH Columbusgasse 4 A-1101 Wien	Pravachol	20 mg	Tablets	Oral use
Austria	Bristol-Myers Squibb GesmbH Columbusgasse 4 A-1101 Wien	Pravachol	40 mg	Tablets	Oral use
Austria	Bristol-Myers Squibb GesmbH Columbusgasse 4 A-1101 Wien	Selipran	10 mg	Tablets	Oral use
Austria	Bristol-Myers Squibb GesmbH Columbusgasse 4 A-1101 Wien	Selipran	20 mg	Tablets	Oral use
Austria	Bristol-Myers Squibb GesmbH Columbusgasse 4 A-1101 Wien	Selipran	40 mg	Tablets	Oral use
Belgium	Bristol-Myers Squibb Belgium sa/nv Chaussée de La Hulpe,185 B-1170 Bruxelles	Pravasine	10 mg	Tablets	Oral use
Belgium	Bristol-Myers Squibb Belgium sa/nv Chaussée de La Hulpe,185 B-1170 Bruxelles	Pravasine	20 mg	Tablets	Oral use
Belgium	Bristol-Myers Squibb Belgium sa/nv Chaussée de La Hulpe,185 B-1170 Bruxelles	Pravasine	40 mg	Tablets	Oral use
Denmark	Bristol-Myers Squibb AB	Pravachol	10 mg	Tablets	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Gustavslundsvägen 145 Box 15200 S-167 15 Bromma				
Denmark	Bristol-Myers Squibb AB Gustavslundsvägen 145 Box 15200 S-167 15 Bromma	Pravachol	20 mg	Tablets	Oral use
Denmark	Bristol-Myers Squibb AB Gustavslundsvägen 145 Box 15200 S-167 15 Bromma	Pravachol	40 mg	Tablets	Oral use
Finland	Bristol-Myers Squibb AB Gustavslundsvägen 145 Box 15200 S-167 15 Bromma	Pravachol	20 mg	Tablets	Oral use
Finland	Bristol-Myers Squibb AB Gustavslundsvägen 145 Box 15200 S-167 15 Bromma	Pravachol	40 mg	Tablets	Oral use
France	Bristol-Myers Squibb 1, parvis de La Défence F-92800 Puteaux	Elisor	10 mg	Tablets	Oral use
France	Bristol-Myers Squibb 1, parvis de La Défence F-92800 Puteaux	Elisor	20 mg	Tablets	Oral use
France	Bristol-Myers Squibb 1, parvis de La Défence F-92800 Puteaux	Elisor	40 mg	Tablets	Oral use
Germany	Bristol-Myers Squibb GmbH	Pravasin	10 mg	Tablets	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Sapporobogen 6-8 D-80809 München				
Germany	Bristol-Myers Squibb GmbH Sapporobogen 6-8 D-80809 München	Pravasin	20 mg	Tablets	Oral use
Germany	Bristol-Myers Squibb GmbH Sapporobogen 6-8 D-80809 München	Pravasin	40 mg	Tablets	Oral use
Germany	Bristol-Myers Squibb GmbH Sapporobogen 6-8 D-80809 München	Pravasin Protect	10 mg	Tablets	Oral use
Germany	Bristol-Myers Squibb GmbH Sapporobogen 6-8 D-80809 München	Pravasin Protect	20 mg	Tablets	Oral use
Germany	Bristol-Myers Squibb GmbH Sapporobogen 6-8 D-80809 München	Pravasin Protect	40 mg	Tablets	Oral use
Germany	Bristol-Myers Squibb GmbH Sapporobogen 6-8 D-80809 München	Selip	10 mg	Tablets	Oral use
Germany	Bristol-Myers Squibb GmbH Sapporobogen 6-8 D-80809 München	Selip	20 mg	Tablets	Oral use
Germany	Bristol-Myers Squibb GmbH Sapporobogen 6-8 D-80809 München	Selip	40 mg	Tablets	Oral use
Germany	Bristol-Myers Squibb GmbH Sapporobogen 6-8	Liprevil	10 mg	Tablets	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	D-80809 München				
Germany	Bristol-Myers Squibb GmbH Sapporobogen 6-8 D-80809 München	Liprevil	20 mg	Tablets	Oral use
Germany	Bristol-Myers Squibb GmbH Sapporobogen 6-8 D-80809 München	Liprevil	40 mg	Tablets	Oral use
Greece	Bristol-Myers Squibb AEBE 102 Tatoiou and Kolokotroni Sreet 14671 Nea Erythrea Attikis	Pravachol	10 mg	Tablets	Oral use
Greece	Bristol-Myers Squibb AEBE 102 Tatoiou and Kolokotroni Sreet 14671 Nea Erythrea Attikis	Pravachol	20 mg	Tablets	Oral use
Greece	Bristol-Myers Squibb AEBE 102 Tatoiou and Kolokotroni Sreet 14671 Nea Erythrea Attikis	Pravachol	40 mg	Tablets	Oral use
Iceland	Bristol-Myers Squibb AB Gustavslundsvägen 145 Box 15200 S-167 15 Bromma	Pravachol	20 mg	Tablets	Oral use
Iceland	Bristol-Myers Squibb AB Gustavslundsvägen 145 Box 15200 S-167 15 Bromma	Pravachol	40 mg	Tablets	Oral use
Ireland	Bristol-Myers Squibb Pharmaceuticals Ltd Watery Lane IRL-Swords, Co. Dublin	Lipostat	10 mg	Tablets	Oral use
Ireland	Bristol-Myers Squibb Pharmaceuticals Ltd	Lipostat	20 mg	Tablets	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Watery Lane IRL-Swords, Co. Dublin				
Ireland	Bristol-Myers Squibb Pharmaceuticals Ltd Watery Lane IRL-Swords, Co. Dublin	Lipostat	40 mg	Tablets	Oral use
Italy	Bristol-Myers Squibb, S.p.A. Via Virgilio Maroso, 50 I-00142	Selectin	10 mg	Tablets	Oral use
Italy	Bristol-Myers Squibb, S.p.A. Via Virgilio Maroso, 50 I-00142	Selectin	20 mg	Tablets	Oral use
Italy	Bristol-Myers Squibb, S.p.A. Via Virgilio Maroso, 50 I-00142	Selectin	40 mg	Tablets	Oral use
Luxembourg	Bristol-Myers Squibb Belgium sa/nv Chaussée de La Hulpe,185 B-1170 Bruxelles	Pravasine	10 mg	Tablets	Oral use
Luxembourg	Bristol-Myers Squibb Belgium sa/nv Chaussée de La Hulpe,185 B-1170 Bruxelles	Pravasine	20 mg	Tablets	Oral use
Luxembourg	Bristol-Myers Squibb Belgium sa/nv Chaussée de La Hulpe,185 B-1170 Bruxelles	Pravasine	40 mg	Tablets	Oral use
Netherlands	Bristol-Myers Squibb B.V. Vijzelmolenlaan 9 NL-3447 GX Woerden	Selektine	10 mg	Tablets	Oral use
Netherlands	Bristol-Myers Squibb B.V. Vijzelmolenlaan 9	Selektine	20 mg	Tablets	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	NL-3447 GX Woerden				
Netherlands	Bristol-Myers Squibb B.V. Vijzelmolenlaan 9 NL-3447 GX Woerden	Selektine	40 mg	Tablets	Oral use
Norway	Bristol-Myers Squibb AB Gustavslundsvägen 145 Box 15200 S-167 15 Bromma	Pravachol	20 mg	Tablets	Oral use
Norway	Bristol-Myers Squibb AB Gustavslundsvägen 145 Box 15200 S-167 15 Bromma	Pravachol	40 mg	Tablets	Oral use
Portugal	Bristol-Myers Squibb Farmacêutica Portuguesa, LDA Quinta da Fonte P-2780 730 Paço de Arcos	Pravacol	10 mg	Tablets	Oral use
Portugal	Bristol-Myers Squibb Farmacêutica Portuguesa, LDA Quinta da Fonte P-2780 730 Paço de Arcos	Pravacol	20 mg	Tablets	Oral use
Portugal	Bristol-Myers Squibb Farmacêutica Portuguesa, LDA Quinta da Fonte P-2780 730 Paço de Arcos	Pravacol	40 mg	Tablets	Oral use
Portugal	Bristol-Myers Squibb Farmacêutica Portuguesa, LDA Quinta da Fonte P-2780 730 Paço de Arcos	Pravasin	10 mg	Tablets	Oral use
Portugal	Bristol-Myers Squibb	Pravasin	20 mg	Tablets	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Farmacêutica Portuguesa, LDA Quinta da Fonte P-2780 730 Paço de Arcos				
Portugal	Bristol-Myers Squibb Farmacêutica Portuguesa, LDA Quinta da Fonte P-2780 730 Paço de Arcos	Pravasin	40 mg	Tablets	Oral use
Spain	Grupo Bristol-Myers Squibb c/ Almansa, 101 E-28040 Madrid	Bristacol	10 mg	Tablets	Oral use
Spain	Grupo Bristol-Myers Squibb c/ Almansa, 101 E-28040 Madrid	Bristacol	20 mg	Tablets	Oral use
Spain	Grupo Bristol-Myers Squibb c/ Almansa, 101 E-28040 Madrid	Bristacol	40 mg	Tablets	Oral use
Spain	Grupo Bristol-Myers Squibb c/ Almansa, 101 E-28040 Madrid	Lipemol	10 mg	Tablets	Oral use
Spain	Grupo Bristol-Myers Squibb c/ Almansa, 101 E-28040 Madrid	Lipemol	20 mg	Tablets	Oral use
Spain	Grupo Bristol-Myers Squibb c/ Almansa, 101 E-28040 Madrid	Lipemol	40 mg	Tablets	Oral use
Sweden	Bristol-Myers Squibb AB Gustavslundsvägen 145 Box 15200 S-167 15 Bromma	Pravachol	20 mg	Tablets	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Sweden	Bristol-Myers Squibb AB Gustavslundsvägen 145 Box 15200 S-167 15 Bromma	Pravachol	40 mg	Tablets	Oral use
United Kingdom	Bristol-Myers Squibb Pharmaceuticals Ltd 141-149 Staines Road Hounslow TW3 3JA	Lipostat	10 mg	Tablets	Oral use
United Kingdom	Bristol-Myers Squibb Pharmaceuticals Ltd 141-149 Staines Road Hounslow TW3 3JA	Lipostat	20 mg	Tablets	Oral use
United Kingdom	Bristol-Myers Squibb Pharmaceuticals Ltd 141-149 Staines Road Hounslow TW3 3JA	Lipostat	40 mg	Tablets	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF PRAVACHOL AND ASSOCIATED NAMES (See Annex I)

Quality issues

No significant issues relating to Quality were identified.

The pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC (section 6).

Efficacy issues

The divergences that previously existed across the SPCs of EU Member States included:

Section 4.1 Therapeutic Indications

The MAH was requested to propose and scientifically justify a common EU wide approach as there were divergences between national approvals regarding the use of Pravachol in:

Isolated or mixed hypercholesterolaemia. This indication was approved in all EU Member States, Iceland and Norway. However the wording (and therefore the precise meaning) of the approved indication is very different in the different nationally approved summaries of product characteristics.

Primary prevention in Coronary Heart Disease. This indication was approved as an indication only in some Member States and in others the data are described only under section 5.1 Pharmacodynamic properties.

Secondary prevention in Coronary Heart Disease. This indication was approved in all Member States, Iceland and Norway. However, the wording (and therefore the precise meaning) of the indication was different from member state to member state. Furthermore, within the Coronary Heart Disease indication "*slowing of the progression of coronary artery sclerosis and reduction of the incidence of cardiac events*" were approved as separate indications only in some Member States.

Finally, only some Member States approved an indication in the *treatment of hyperlipidaemia following solid organ transplant*. This indication was restricted to a treatment following cardiac and renal transplantation in some of these Member States and in some others restricted to a treatment following a cardiac transplant.

Primary hypercholesterolaemia and mixed dyslipidaemia

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. First, with the reversible and specific competitive inhibition of HMG-CoA reductase, it induces a 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 the low-density lipoproteins (LDL) production by inhibiting the hepatic synthesis of very low-density lipoproteins (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 high-density lipoprotein (HDL)-cholesterol and apolipoprotein A are elevated.

Primary prevention of coronary heart disease

This indication is based on the results of one outcome study, WOSCOPS (the West of Scotland Coronary Prevention Study).

The "West of Scotland Coronary Prevention Study (WOSCOPS)" was a randomised, double-blind, placebo-controlled trial among 6,595 male patients aged from 45 to 64 years with moderate to severe hypercholesterolaemia (LDL-C: 155-232 mg/dl [4.0-6.0 mmol/l]) and with no history of myocardial infarction, treated for an average duration of 4.8 years with either a 40 mg daily dose of pravastatin or placebo as an adjunct to diet. In pravastatin-treated patients, results showed:
- a decrease in the risk of mortality from coronary disease and of non-lethal myocardial infarction (relative risk reduction RRR was 31%; p = 0.0001 with an absolute risk of 7.9% in the placebo group, and 5.5% in pravastatin treated patients); the effects on these cumulative cardiovascular events rates being evident as early as 6 months of treatment;
- a decrease in the total number of deaths from a cardiovascular event (RRR 32%; p = 0.03)
- when risk factors were taken into account, a RRR of 24% (p = 0.039) in total mortality was also observed among patients treated with pravastatin;
- a decrease in the relative risk for undergoing myocardial revascularisation procedures (coronary artery bypass graft surgery or coronary angioplasty) by 37% (p = 0.009) and coronary angiography by 31% (p = 0.007).

The benefit of the treatment on the criteria indicated above is not known in patients over the age of 65 years, who were not included in the study. In this study, the benefit of pravastatin treatment was not established 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.

Reservations have been expressed about the extrapolation of such findings for all patients with hypercholesterolaemia; because of the age-adjusted mortality among Scottish men aged 45 to 74 years at the time WOSCOPS was conducted, i.e., 1990-1992. The mortality was highest in Europe with 886 cases per 100 000 compared with 330 cases per 100 000 in France and 542 cases per 100 000 in Belgium.

Using Belgium as a case study for a risk analysis, it was shown that the WOSCOPS Scottish men population, although selected from a population with a higher risk of cardiovascular disease, was not so different in observed risk than in other countries, such as Belgium, when using the selection criteria of the study. Based on these overall findings, It was concluded that the WOSCOPS findings observed in Scottish men could be extrapolated to men of other European countries. The generalisation of these results to women was more problematic as the Belgium case report study did not investigate the applicability of the relative risk reduction observed in the WOSCOPS study to other populations such as women. However, CARE (Cholesterol and Recurrent Events) and LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) studies also included both men and women.

The CPMP agreed to generalise the use of pravastatin to men and women at high risk of cardiovascular events such as family history of early cardiovascular events, continued smoking, constant hypertension, diabetes mellitus, low HDL-cholesterol levels. However, the CPMP did not want to include any reference to “myocardial revascularisation procedure” as the techniques used depend on medical practice and cannot be considered as a “hard” endpoint contrary to both other criteria: fatal and non-fatal myocardial infarction.

Finally, a cross-reference to section 5.1 Pharmacodynamic describing the methodology and the main results of the WOSCOPS study was included in section 4.1 since this information was considered to be highlighted for prescribers to know the real benefits that can be expected with that statin in this indication.

Secondary prevention of coronary heart disease

This indication is based from the results of six controlled studies: PLAC I (Pravastatin Limitation of Atherosclerosis in the Coronary Arteries), PLAC II (Pravastatin, Lipids and Atherosclerosis in the Carotid Arteries), REGRESS (Regression Growth Evaluation Statin Study), KAPS (Kuopio Atherosclerosis Prevention Study), CARE and LIPID studies.

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% ($p = 0.02$).

Based on the CARE study, the secondary prevention indication was extended to include the reduction of cardiovascular and cerebrovascular events in patients at risk with normal cholesterol levels.

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 CHD death by 24% ($p = 0.0004$, with an absolute risk of 6.4% in the placebo group, and 5.3% in pravastatin treated patients), the relative risk of coronary events (either CHD death or nonfatal MI) by 24% ($p < 0.0001$) and the relative risk of fatal or nonfatal myocardial infarction by 29% ($p < 0.0001$). In pravastatin-treated patients, results showed:
- a reduction in the relative risk of total mortality by 23% ($p < 0.0001$) and cardiovascular mortality by 25% ($p < 0.0001$);
- a reduction in the relative risk of undergoing myocardial revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 20% ($p < 0.0001$);
- a reduction in the relative risk of stroke by 19% ($p = 0.048$).

Based on this study, the secondary prevention indication was extended to include patients with unstable angina pectoris.

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 was not established in this type of patients.

Some issues were also more specifically discussed by the CPMP:

- *Need for myocardial revascularisation (CARE, LIPID)*

In the CARE study, treatment with pravastatin significantly reduced the rate of a recurrent coronary event (either coronary heart disease death or non-fatal MI) by 24% ($p = 0.003$) and was associated with a decrease in the rate of coronary bypass surgery by 14.1% in the pravastatin group, compared to 18.8% in the placebo group (coronary bypass surgery or angioplasty). In the LIPID study, a decrease in 13% in myocardial revascularisation (bypass or angioplasty) in the pravastatin group compared to 15.7% in the placebo group, was observed.

However, as for primary prevention, the CPMP disagreed to mention "myocardial revascularisation" in the indication section as the effects of revascularisation depends on medical practice and should be considered as a consequence of the myocardial infarction reduction risk.

- *Stroke, transient ischaemic attack*

A separate analysis of AIT (transient strokes) and AVC as secondary criteria was performed by a specific Committee board as a *post-hoc* analysis in the CARE study. In this study, the population was not considered representative of a high-risk population of strokes (prevalence of 43% of patients with hypertension compared to a 60% rate in an at risk population). In the LIPID study, an analysis of strokes and non-haemorrhagic strokes was also performed as secondary criteria.

- *Reduction of the number of hospitalisation*

The effects of pravastatin treatment in the number of hospitalisation (both in frequency and duration) were studied in the WOSCOPS study. Pravastatin treatment had no effect on hospital admissions for any non-cardiovascular category, relative to the placebo group. However, for cardiovascular causes (1,234 or 28% of the total), there was a significant 10.8% reduction in admissions (95% CI [4-17.4], $p = 0.01$) in the pravastatin group. A similar analysis was performed in the LIPID study (hospital days and the number of admissions). However, as it was a secondary prevention population there were more admissions for cardiovascular causes. In the pravastatin group there were 12516 fewer hospital days and 1075 fewer admissions. The mean number of hospitalisation days per 100 person-years of follow-up in the placebo group was 349 days compared to 296 days in the pravastatin group (a 15% reduction; $p < 0.001$). In fact, this was not due to shorter but more frequent admissions in the pravastatin group, as the median number of admissions (two) was the same in both groups.

Solid organ transplant

Hyperlipidaemia is a common post transplantation concern and untreated it can lead to death and/or loss of the graft from accelerated atherosclerosis or generalised vascular morbidity and mortality.

The treatment of post-transplantation hyperlipidaemia (PTHL) in the transplant population has become the primary focus in the management of the patient, as improvements in immunosuppressant therapy have significantly reduced acute rejection episodes. PTHL typically develops 3-6 months post-transplantation. It is a particularly atherogenic mixture of elevated LDL-cholesterol and VLDL-cholesterol. The incidence is particularly high in heart transplant patients (80%), who needed a transplant because of atherosclerotic heart disease in the native heart. However, PTHL is a distinct clinical entity, which is associated with the use of calcineurin inhibitors, such as cyclosporine, and other mediators of the rejection process such as sirolimus. As pravastatin has only a modest increase in its exposure in the presence of cyclosporine, it seems the right statin in the initial management of PTHL.

- *Cardiac transplantation*

One study was performed in cardiac transplantation (Kobashigawa study). In this open study, within two weeks after transplantation, patients were randomised to receive either a 20 mg pravastatin dose or placebo; the pravastatin dose was increased to 40 mg if well tolerated after 4 weeks (47 patients) in addition to the immunosuppressive treatment with cyclosporine, prednisone and azathioprine. After two months all patients were on a 40 mg pravastatin dose.

Results showed that 12 months after transplantation, the pravastatin group had lower mean (+/-) SD cholesterol levels than the control group (193 ± 36 versus 248 ± 49 mg/dL, p < 0.001), less frequent cardiac rejection accompagnied by haemodynamic compromise (3 versus 14 patients, p= 0.005), better survival (94 % versus 78 %, p=0.025) and a lower incidence of coronary vasculopathy in the transplant as determined by angiography and by autopsy (3 versus 10 patients, p=0.049). Furthermore, in a subgroup of study patients, intracoronary ultrasound measurements at baseline and one year after transplantation showed less progression in the pravastatin group in maximal intimal thickness, 0,11+/-0,09 mm versus 0,23+/-0,16 mm in the control group; p=0.002).

Survival was an objective end point and the findings on intracoronary ultrasonography were interpreted blindly. These results showed that if pravastatin did not change the overall incidence of cardiac rejection, it decreased the rate of rejection accompanied by haemodynamic compromise, resulting in better survival.

Furthermore, a 5-year follow-up of this study was also performed. After the first year of the study, 71% of the placebo-treated patients switched to a pravastatin treatment based on first results of the study. Five year survival continues to be superior in the pravastatin group with greater divergence in survival compared to the first year and the intimal area of the plaque was significantly reduced relative to the patient's baseline (see table below). The safety profile of pravastatin was similar to placebo.

	5-year		Delta IVUS (baseline to 5 years)		
	survival	freedom form TCAD and/or death	IA (mm²)	II	LA (mm²)
Pravastatin Group	83%	64%	0.42*	0.06	-3.14
Control group group	62%	55%	1.36	0.11	-3.49

* P<0,05; IVUS intravascular ultrasound; IA intimal area; II intimal index; LA lumen area/ TCAD = transplant coronary artery disease

In conclusion, the use of pravastatin early after heart transplantation appears to have continued benificial effects in survival, rejection, and the development of TCAD 5 years after a transplantation. A large cross over to pravastatin from the control group suggests that early use of pravastatin appears important for good outcome.

- *Renal transplantation*

Only one study (Katznelson *and al.)* was performed in this indication. In this prospective, non blinded study, performed in 48 consecutive cadaver renal transplant patients (similar design than the cardiac transplant patients), patients were randomised to receive in an alternating fashion either a 20 mg pravastatin daily dose (n=24) or placebo (control group; n=24). All patients were immunosuppressed with cyclosporine and prednisone. Results showed that in renal transplant patients early treated with pravastatin, there is a lower tendency in acute rejection and extra renal vascular complications.

- *Liver transplantation*

No study was provided to support the indication after liver transplantation. Moreover, the management of post liver transplant hyperlipidaemia is poorly documented in literature.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Pravachol, the following was considered to be the most suitable harmonised Section 4.1 indications text:

4.1 Therapeutic indications

Hypercholesterolemia

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).

Section 4.2. Posology and method of administration

Different dose recommendations have been approved by Member States with regards the starting dose, daily dose, dosing in the elderly and dosing during moderate renal and hepatic impairment.

The MAH was requested to substantiate scientifically the divergent information across member states and justify a proposed common wording, especially with regard to therapeutic daily dose range.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Pravachol the following was considered to be the most suitable harmonised Section 4.2 Posology text:

4.2 Posology and method of administration

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

<(TRADENAME)> is administered orally once daily preferably in the evening with or without food.

Hypercholestrolaemia: 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 40mg.

Cardiovascular prevention : In all preventive morbidity and mortality trials, the only studied starting and maintenance dose was 40mg 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: The documentation on efficacy and safety in patients less than 18 years old is limited; therefore, the use of <(TRADENAME)> is not recommended in these patients.

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

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

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

- Safety issues

Section 4.3 Contraindications

The MAH was requested to propose and scientifically justify a common EU wide approach as the contraindications text was considered to differ to a large extent between Member States especially relating to:

- the use in children
- severe renal impairment
- liver disease
- pregnancy
- lactation
- myopathy.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Pravachol, the following was considered to be the most suitable harmonised Section 4.3 Contraindications, the text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices:

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).

Section 4.4. Special warnings and precautions for use

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Pravachol, the most suitable harmonised Section 4.4 Special Warnings and Precautions for Use text was approved (See Annex III). The text in the

harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices.

All other sections of the SPC were harmonised as a result of the referral procedure (except See Below; Administrative Issues).

Finally, the CPMP considered that all presentations may be useful to treat the patients in the approved indications.

- Administrative issues

Other sections of the SPC which were not harmonised and which need to be introduced nationally by the Member States when implementing the harmonised SPC are the following: MAH, MA number, date of first authorisation/renewal of authorisation, Date of revision of the text.

Benefit/Risk considerations

Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Pravachol is favourable for use relating to:

Hypercholesterolemia

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).

GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the CPMP Opinion for Pravachol and associated names (see Annex I). The divergences identified at the start of the referral have been resolved.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This summary of product characteristics is the summary of product characteristics that was annexed to the Commission Decision issued on 2 March 2004 concerning this referral; this text was valid at that time. It is not subsequently varied or updated by the EMEA, and therefore may not necessarily be the summary of product characteristics currently approved in the EU member states.

1. NAME OF THE MEDICINAL PRODUCT

<(PRAVACHOL and associated names)> <(strength)> mg tablets.
[See Annex I. To be implemented nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains <(STRENGTH)> mg pravastatin sodium.
[See Annex I. To be implemented nationally]
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolemia
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 <(TRADENAME)>, secondary causes of hypercholesterolaemia should be excluded and patients should be placed on a standard lipid-lowering diet which should be continued during treatment.
<(TRADENAME)> is administered orally once daily preferably in the evening with or without food.

Hypercholesterolemia: 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 40mg.

Cardiovascular prevention: In all preventive morbidity and mortality trials, the only studied starting and maintenance dose was 40mg 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: The documentation on efficacy and safety in patients less than 18 years old is limited; therefore, the use of <(TRADENAME)> is not recommended in these patients.

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

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 <(TRADENAME)> on total cholesterol and LDL-cholesterol are enhanced when combined with a bile acid-binding resin (e.g. cholestyramine, colestipol). <(TRADENAME)> should be given either one hour before or at least four hours after the resin (see section 4.5).
For patients taking cyclosporin with or without other immunosuppressive medicinal products, treatment should begin with 20 mg of pravastatin 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 special 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.

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 drugs (due to lipophilicity and pharmacokinetic differences), including their dosage and potential for drug interactions. Although there is no muscular contraindication to the prescription of a statin, certain predisposing 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 medicines. The use of fibrates alone is occasionally associated with myopathy. The combined use of a statin and fibrates should generally be avoided. The co-administration of statins and nicotinic acid should be used with caution. An increase in the incidence of myopathy has also been described in patients receiving other statins in combination with inhibitors of cytochrome P450 metabolism. This may result from pharmacokinetic interactions that have not been documented for pravastatin (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.

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.

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.

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 4-fold increase in pravastatin systemic exposure. In some patients, however, the increase in pravastatin exposure may be larger. Clinical and biochemical monitoring of patients receiving this combination is recommended (see section 4.2).

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

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

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

4.6 Pregnancy and lactation

Pregnancy: Pravastatin is contraindicated during pregnancy and should be administered to women of childbearing potential only when these patients are unlikely to conceive and have been informed of the potential risk. 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 taking 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 (≥1/1000 <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000).

Clinical trials: <(TRADENAME)> has been studied at 40mg in seven randomized double-blind placebo-controlled trials involving over 21000 patients treated with pravastatin (N=10764) or placebo (N=10719), representing over 47000 patients 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 >3xULN and >10xULN in CARE, WOSCOP 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, WOSCOP 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, sometime complicated by rupture

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 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 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 CHD death by 24% (p = 0.0004, with an absolute risk of 6.4% in the placebo group, and 5.3% in pravastatin treated patients), the relative risk of coronary events (either CHD death or nonfatal MI) by 24% (p < 0.0001) and the relative risk of fatal or nonfatal myocardial infarction by 29% (p < 0.0001). In pravastatin-treated patients,

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

The "Cholesterol and Recurrent Events (CARE)" study was a randomised, double-blind, placebo-controlled study comparing, the effects of pravastatin (40 mg OD) on coronary heart disease death and nonfatal myocardial infarction for an average of 4.9 years in 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 ASA as part of their regimen.

Heart and kidney transplantation

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

- Renal transplant was assessed in one prospective not controlled, not randomised study (n=48) of 4 months duration. Patients were treated concurrently with either pravastatin (20 mg) or not, and a standard immunosuppressive regimen of 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.

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:
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, 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

[To be implemented nationally]

6.2 Incompatibilities

[To be implemented nationally]

6.3 Shelf life

[To be implemented nationally]

6.4 Special precautions for storage

[To be implemented nationally]

6.5 Nature and contents of container

Not all pack sizes may be marketed
[To be implemented nationally]

6.6 Instructions for use and handling

[To be implemented nationally]

7. MARKETING AUTHORIZATION HOLDER

[To be implemented nationally]

8. MARKETING AUTHORIZATION NUMBER

[To be implemented nationally]

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

[To be implemented nationally]

10. DATE OF (PARTIAL) REVISION OF THE TEXT

