ANNEX I

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

Member State	Marketing Authorisation Holders/Applicants	Invented Name	Strength	Pharmaceutical Form	Route of administration
Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 Postfach 153, A-1037 Vienna Austria	Crestor	5 mg	Film coated tablet	oral use
Belgium	AstraZeneca Belgium Egide Van Ophemstraat 110 B-1180 Brussels, Belgium	Crestor	5 mg	Film coated tablet	oral use
Denmark	AstraZeneca A/SRoskildevej 22 DK-2620 Albertslund Denmark	Crestor	5 mg	Film coated tablet	oral use
Finland	AstraZeneca Oy Luomanportti 3 FIN-02200 Espoo Finland	Crestor	5 mg	Film coated tablet	oral use
France	AstraZeneca France Place Renault F-92844 Rueil-Malmaison Cedex France	Crestor	5 mg	Film coated tablet	oral use
Greece	AstraZeneca S A 4, Theotokopoulou & Astronafton str GR-151 25 Maroussi Athens Greece	Crestor	5 mg	Film coated tablet	oral use

Member State	Marketing Authorisation Holders/Applicants	Invented Name	Strength	Pharmaceutical Form	Route of administration
Iceland	AstraZeneca A/S Roskildevej 22 DK-2620 Albertslund Denmark	Crestor	5 mg	Film coated tablet	oral use
Ireland	AstraZeneca UK Limited Horizon Place, 600 Capability Green, Luton, Bedfordshire LU1 3LU England UK	Crestor	5 mg	Film coated tablet	oral use
Italy	AstraZeneca Netherlands P O Box 599 NL-2700 An Zoetermeer Netherlands	Crestor	5 mg	Film coated tablet	oral use
Luxembourg	AstraZeneca Belgium Egide Van Ophemstraat 110 B-1180 Brussels Belgium	Crestor	5 mg	Film coated tablet	oral use
The Netherlands	AstraZeneca Netherlands P O Box 599 NL-2700 An Zoetermeer Netherlands	Crestor	5 mg	Film coated tablet	oral use
Portugal	AstraZeneca – Produtos Farmacéuticos, Lda Rua Humberto Madeira 7	Crestor	5 mg	Film coated tablet	oral use

Member State	Marketing Authorisation Holders/Applicants	Invented Name	Strength	Pharmaceutical Form	Route of administration
	Valejas 2745-663 Barcarena Portugal				
Sweden	AstraZeneca AB 151 85 Södertälje Södertälje Sweden	Crestor	5 mg	Film coated tablet	oral use
UK	AstraZeneca UK Limited Horizon Place, 600 Capability Green, Luton, Bedfordshire LU1 3LU England UK	Crestor	5 mg	Film coated tablet	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 CRESTOR 5 mg (see Annex I)

Rosuvastatin (Crestor) 10 mg is currently authorised in the majority of MS as a start and maintenance dose with acceptable risk/benefit ratio. Updated clinical trials information and post-marketing data do not provide grounds to change this assessment or to recommend specific amendments to the prescribing information for this dose level.

The difference in lipid-lowering efficacy between rosuvastatin 5 mg and 10 mg is that anticipated with a statin, *i.e.* a doubling of the dose from 5 mg to 10 mg (either through start dose or through up-titration) produces an average incremental reduction of LDL-C of 6%, from an average 41% to 47%. The assessment of relevance of this incremental reduction is complex, and must take into account the body of evidence available from outcome trials for this class of agents. This is reflected in available treatment guidelines from learned societies. Available data do not allow conclusion on a general threshold level beyond which further reduction of LDL-C is futile. The potential relevance of need of >45% reduction of LDL-C, and that this could be taken into account in an individualised choice of start dose, has already been acknowledged by CHMP for other products of this class.

The overall experience with rosuvastatin 5 mg is more limited than that with 10 mg but available clinical trials information and post-marketing data do not support relevant safety benefit at group level of the 5 mg dose, in comparison with the 10 mg dose. There are no data to support a steeper dose relationship for adverse reactions (myopathy, hepatotoxicity) for rosuvastatin, compared with other statins. It is not considered necessary to request a generally higher ratio between start dose and maximum dose for rosuvastatin (20 mg in the general target population, 40 mg in selected patients) than has been requested for other statins assessed by CHMP (simvastatin, pravastatin). Rather, the choice of start dose should take into account potential safety concerns in the individual patient based e.g. on sensitivity to adverse reactions and pharmacokinetic considerations.

In conclusion, the benefit/risk ratio is favourable for Crestor 5 or Crestor 10 mg as alternative start doses. The choice of start dose in the individual patient should take into account aspects of efficacy and safety, as detailed in the SPC.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Based on the finding that

⇒ Crestor 10 mg daily dose leads to a higher reduction in LDL-C compared with 5 mg

⇒ No important safety or tolerability difference between rosuvastatin 5 mg and 10 mg is evident on the basis of post-marketing or clinical trial data

The conclusion is that the benefit/risk ratio is favourable for Crestor 5 mg or Crestor 10 mg as alternative start doses. The choice of start dose in the individual patient should take into account aspects of efficacy and safety, as detailed in the SPC.

ANNEX III

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

1. NAME OF THE MEDICINAL PRODUCT

Crestor 5 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg rosuvastatin (as rosuvastatin calcium).

For excipients see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Round, yellow coloured, intagliated with 'ZD4522' and '5' on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

4.2 Posology and method of administration

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines.

The recommended start dose is 5 or 10 mg orally once daily in both statin naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions (see below). A dose adjustment to the next dose level can be made after 4 weeks, if necessary (see Section 5.1 Pharmacodynamic properties). In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses (see Section 4.8 Undesirable effects), a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed (see Section 4.4 Special warnings and precautions). Specialist supervision is recommended when the 40 mg dose is initiated.

Crestor may be given at any time of day, with or without food.

Paediatric use
Safety and efficacy have not been established in children. Paediatric experience is limited to a small number of children (aged 8 years or above) with homozygous familial hypercholesterolaemia. Therefore, Crestor is not recommended for paediatric use at this time.

Use in the elderly
A start dose of 5 mg is recommended in patients > 70 years (see section 4.4 Special warnings and precautions for use).
No other dose adjustment is necessary in relation to age.

Dosage in patients with renal insufficiency
No dose adjustment is necessary in patients with mild to moderate renal impairment.
The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of Crestor in patients with severe renal impairment is contraindicated for all doses. (See Section 4.3 Contraindications and Section 5.2 Pharmacokinetic properties).

Dosage in patients with hepatic impairment
There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9 (see Section 5.2 Pharmacokinetic properties). In these patients an assessment of renal function should be considered (see Section 4.4 Special warnings and special precautions for use). There is no experience in subjects with Child-Pugh scores above 9. Crestor is contraindicated in patients with active liver disease (see Section 4.3 Contraindications).

Race
Increased systemic exposure has been seen in Japanese and Chinese subjects (see section 4.4 Special warnings and special precautions for use and section 5.2 Pharmacokinetic properties). The recommended start dose is 5 mg for patients of Japanese and Chinese ancestry. The 40 mg dose is contraindicated in Japanese and Chinese patients (see sections 4.3 Contraindications and 5.2 Pharmacokinetic properties).

Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is 5 mg in patients with predisposing factors to myopathy (see Section 4.4 Special warnings and special precautions for use).
The 40 mg dose is contraindicated in some of these patients (see Section 4.3 Contraindications).

4.3 Contraindications

Crestor is contraindicated:

- in patients with hypersensitivity to rosuvastatin or to any of the excipients.
- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN).
- in patients with severe renal impairment (creatinine clearance <30 ml/min).
- in patients with myopathy.
- in patients receiving concomitant cyclosporin.
- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

The 40 mg dose is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- moderate renal impairment (creatinine clearence < 60 ml/min)
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- situations where an increase in plasma levels may occur
- Japanese and Chinese patients
- concomitant use of fibrates.

(See sections 4.4 Special warnings and special precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction and 5.2 Pharmacokinetic properties).

4.4 Special warnings and special precautions for use

Renal Effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of Crestor, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease (see Section 4.8 Undesirable effects). An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Skeletal Muscle Effects

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Crestor-treated patients with all doses and in particular with doses > 20 mg.

Creatine Kinase Measurement

Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK >5xULN, treatment should not be started.

Before Treatment

Crestor, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- renal impairment
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- age >70 years
- situations where an increase in plasma levels may occur (see section 5.2 Pharmacokinetic properties)
- concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (>5xULN) treatment should not be started.

Whilst on Treatment

Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Crestor or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring.Routine monitoring of CK levels in asymptomatic patients is not warranted.

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with Crestor and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, cyclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of Crestor and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of

Crestor with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40 mg dose is contraindicated with concomitant use of a fibrate.
(See Section 4.5 Interaction with other medicinal products and other forms of interaction and Section 4.8 Undesirable effects.)

Crestor should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Liver Effects
As with other HMG-CoA reductase inhibitors, Crestor should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.
It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Crestor should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with Crestor.

Race
Pharmacokinetic studies show an increase in exposure in Japanese and Chinese subjects compared with Caucasians (see section 4.2 Posology and Method of administration and section 5.2 Pharmacokinetic properties)

4.5 Interaction with other medicinal products and other forms of interaction

Cyclosporin: During concomitant treatment with Crestor and cyclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Section 4.3 Contraindications).

Concomitant administration did not affect plasma concentrations of cyclosporin.

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

Gemfibrozil and other lipid-lowering products: Concomitant use of Crestor and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC (see Section 4.4 Special warnings and special precautions for use).
Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur.
Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. The 40 mg dose is contraindicated with concomitant use of a fibrate (see Section 4.3 Contraindications and Section 4.4 Special warnings and special precautions for use). These patients should also start with the 5 mg dose.

Antacid: The simultaneous dosing of Crestor with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after Crestor. The clinical relevance of this interaction has not been studied.

Erythromycin: Concomitant use of Crestor and erythromycin resulted in a 20% decrease in AUC (0-t) and a 30% decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of Crestor and an oral contraceptive resulted in an increase in ethinyl oestradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant Crestor and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

Other medicinal products: Based on data from specific interaction studies no clinically relevant interaction with digoxin is expected.

Cytochrome P450 enzymes: Results from *in vitro* and *in vivo* studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4). Concomitant administration of itraconazole (an inhibitor of CYP3A4) and rosuvastatin resulted in a 28% increase in AUC of rosuvastatin. This small increase is not considered clinically significant. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected.

4.6 Pregnancy and lactation

Crestor is contraindicated in pregnancy and lactation.
Women of child bearing potential should use appropriate contraceptive measures.
Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity (see Section 5.3 Preclinical safety data). If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.
Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.
(see Section 4.3 Contraindications).

4.7 Effects on ability to drive and use machines

Studies to determine the effect of Crestor on the ability to drive and use machines have not been conducted . However, based on its pharmacodynamic properties, Crestor is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

The adverse events seen with Crestor are generally mild and transient. In controlled clinical trials, less than 4% of Crestor-treated patients were withdrawn due to adverse events.

The frequencies of adverse events are ranked according to the following: Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Rare (>1/10,000, <1/1000);

Immune system disorders
Rare: hypersensitivity reactions including angioedema

Nervous system disorders
Common: headache, dizziness

Gastrointestinal disorders
Common: constipation, nausea, abdominal pain

Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash and urticaria

Musculoskeletal, connective tissue and bone disorders
Common: myalgia
Rare: myopathy and rhabdomyolysis

General disorders
Common: asthenia

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

Renal Effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with Crestor. Shifts in urine protein from none or trace to ++ or more were seen in <1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy, and has not been shown to be predictive of acute or progressive renal disease.

Skeletal muscle effects: Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Crestor-treated patients with all doses and in particular with doses > 20 mg.

A dose-related increase in CK levels has been observed in patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5xULN), treatment should be discontinued (see Section 4.4 Special warnings and special precautions for use).

Liver Effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient.

4.9 Overdose

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. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors

ATC code: C10A A07

Mechanism of action
Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Pharmacodynamic effects
Crestor reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 1). Crestor also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 1 Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	Apo B	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Clinical efficacy
Crestor is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex, or age and in special populations such as diabetics, or patients with familial hypercholesterolaemia.

From pooled phase III data, Crestor has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (mean baseline LDL-C about 4.8 mmol/l) to recognised European Atherosclerosis Society (EAS; 1998) guideline targets; about 80% of patients treated with 10 mg reached the EAS targets for LDL-C levels (<3 mmol/l).

In a large study, 435 patients with heterozygous familial hypercholesterolaemia were given Crestor from 20 mg to 80 mg in a force-titration design. All doses showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to a daily dose of 40 mg (12 weeks of treatment), LDL-C was reduced by 53%. 33% of patients reached EAS guidelines for LDL-C levels (<3 mmol/l).

In a force-titration, open label trial, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to Crestor 20 - 40 mg. In the overall population, the mean LDL-C reduction was 22%.

In clinical studies with a limited number of patients, Crestor has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin (see Section 4.4 Special warnings and special precautions for use).

Rosuvastatin has not been proven to prevent the associated complications of lipid abnormalities, such as coronary heart disease as mortality and morbidity studies with Crestor have not yet been completed.

5.2 Pharmacokinetic properties

Absorption: Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%.

Distribution: Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Metabolism: Rosuvastatin undergoes limited metabolism (approximately 10%). *In vitro* metabolism studies using human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Excretion: Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7%). As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

Linearity: Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Special populations:

Age and sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin.

Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC compared with western Caucasians in both Japanese subjects residing in Japan, and Chinese subjects living in Singapore. The contribution of environmental and genetic factors to these observed differences has not been determined. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal insufficiency: In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (CrCl <30 ml/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

Hepatic insufficiency: In a study with subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity potential. In a rat pre- and postnatal study, reproductive toxicity was evident from reduced litter sizes, litter weight and pup

survival. These effects were observed at maternotoxic doses at systemic exposures several times above the therapeutic exposure level.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Calcium phosphate
Crospovidone
Magnesium stearate

Tablet coat
Lactose monohydrate
Hypromellose
Glycerol triacetate
Titanium dioxide (E171)
Ferric oxide, yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Blisters: Do not store above 30°C. Store in the original package.
HDPE bottles: Do not store above 30°C. Keep container tightly closed.

6.5 Nature and contents of container

Blisters of aluminium laminate/aluminium foil of 7, 14, 15, 20, 28, 30, 42, 50, 56, 60, 84, 98 and 100 tablets and HDPE bottles of 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling < and disposal>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[See Annex I- to be completed nationally]>

{Name and address}

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT