Clinical Pharmacology Study Protocol

Drug Substance	Rosuvastatin calcium
Study Code	D3560C00004
Date	

A phase I, randomized, open label, single dose, 3-way crossover pharmacokinetic study comparing plasma exposure of rosuvastatin calcium, atorvastatin calcium, and simvastatin in healthy Chinese, Japanese, and Caucasian volunteers.

Sponsor:

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	**Date of Amendment**
Administrative Change No.	**Date of Administrative Change**

ASTRAZENECA PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

In the case of a medical emergency you may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Role in the study	**Name**	**Address and Telephone number**
Study Delivery Team Leader	Senior Study Delivery Operations Specialist	
Study Delivery Team Physician	Executive Director Clinical Pharmacology	
Drug Safety Physician	Senior Medical Director Drug Safety	

For further clarifications regarding:

- Procedures in case of medical emergency see Section 8.2
- Procedures in case of pregnancy see Section 8.3

PROTOCOL SYNOPSIS

A phase I, randomized, open label, single dose, 3-way crossover pharmacokinetic study comparing plasma exposure of rosuvastatin calcium, atorvastatin calcium, and simvastatin in healthy Chinese, Japanese, and Caucasian volunteers.

Investigator

Study centre(s), type and number of subjects planned

This will be a single center study conducted in the United States. Approximately 90 Healthy Chinese, Japanese, and Caucasian volunteers will be recruited to obtain at least 27 evaluable volunteers for each ethnic group. An evaluable volunteer is defined as a volunteer completing all study procedures from the screening period to the final blood sampling of the final crossover period.

Study period	Phase of development
Estimated date of first subject enrolled	I
Estimated date of last subject completed	

Objectives

The primary objective of this study is to:

- summarize and compare the plasma exposure of rosuvastatin, atorvastatin, and simvastatin after a single dose in healthy Chinese and Japanese volunteers to the plasma exposure of Caucasian volunteers following a single dose by measuring maximum concentration (C_{max}) and area under the concentration curve from zero to infinity (AUC).

The secondary objectives of this study are to:

- summarize the pharmacokinetics of rosuvastatin, atorvastatin, and simvastatin and the relevant metabolites of each by calculating area under the curve of plasma concentration against time from zero to time of last quantifiable concentration ($AUC_{(0-t)}$), terminal elimination half-life ($t_{½\lambda z}$), time of maximum concentration (t_{max}), terminal elimination rate constant (λ_z) and, (for parent compound only), apparent oral clearance (CL/F).

- calculate parent to metabolite ratios of rosuvastatin metabolites (N-desmethyl rosuvastatin, and rosuvastatin lactone), atorvastatin metabolites (ortho-hydroxy atorvastatin and para-hydroxy atorvastatin) and simvastatin acid.

- obtain deoxyribonucleic acid (DNA) samples.

- assess safety and tolerability

Study design

This is a single center, randomized, open label, 3-way crossover study in healthy Chinese, Japanese, and Caucasian volunteers.

Investigational product, dosage and mode of administration

Rosuvastatin calcium will be administered as a 20 milligram (mg) oral tablet. Atorvastatin calcium will be administered as a 40 mg oral tablet. Simvistatin will be administered as a 40 mg oral tablet.

Duration of treatment

Volunteers meeting inclusion/exclusion criteria and satisfactorily completing screening evaluations during the screening period will participate in a 29-day study that will include 3 in-patient periods (Treatment Periods A, B, C) lasting 4 nights and 5 days with washout periods of at least 7 days between each in-patient period.

Variables

- Pharmacokinetic

C_{max} and AUC of rosuvastatin, atorvastatin, and simvastatin will be the primary endpoints for this study to summarize exposure in the selected populations. A detailed description of the summaries will be described in the Statistical Analyses Plan (SAP).

Along with C_{max} and AUC**,** $AUC_{(0-t)}$, $t_{½\lambda z}$, t_{max}, λ_z and, (for parent compound only), CL/F of rosuvastatin, atorvastatin, and simvastatin and relevant metabolites will be determined to summarize the pharmacokinetics in the selected populations**.**

Parent to metabolite ratios will also be determined and summarized in the selected populations.

- Safety

Safety and tolerability will be assessed by physical examination, clinical laboratory tests, vital signs, and collection of adverse events.

- Pharmacogenetics

Blood samples will be obtained from consenting volunteers and may be used to study genetic polymorphisms in metabolizing enzymes and/or transporters that could affect the disposition of rosuvastatin, atorvastatin and simvastatin.

Volunteers who decline to provide such consent may not participate in the main pharmacokinetic study.

- Pharmacokinetic methods

C_{max} and t_{max} for each volunteer will be determined by inspection of the plasma concentration-time profile. The terminal elimination rate constant (λ_z) will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data (a minimum of 3 plasma concentration values in the terminal log-linear phase, spanning an interval of at least 2 half-lives.) Terminal elimination half-life ($t_{½\lambda z}$) will be calculated as $0.693/\lambda_z$. The $AUC_{(0-t)}$ will be calculated by the linear trapezoidal rule ($AUC = AUC_{(0-t)} + C_{last}/\lambda_z$). $AUC_{(0-t)}$ will be extrapolated to infinity using λ_z to obtain AUC where there are sufficient data. Following the single dose administration of rosuvastatin, atorvastatin and simvastatin, the CL/F will be calculated as Dose/AUC.

Statistical methods

Demographics and baseline endpoints will be summarized by study medications and ethnic groups using descriptive statistics (number [n], mean, standard deviation, median, minimum and maximum) for continuous variables and frequency counts and percentages for categorical variables.

All pharmacokinetic parameters, except t_{max}, will be summarized by study medications and ethnic groups using descriptive statistics (n, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation [CV] percentages); t_{max} will be summarized using n, minimum, median, and maximum.

Log-transformed C_{max}, $AUC_{(0-t)}$, and AUC will be analyzed using a mixed model with the fixed effect of ethnicity, sequence, treatment, and period and random effect subject. Appropriate contrasts and their 90% CIs will be produced from the model. These estimates will then be anti-log transformed to obtain the geometric means and their 90% CIs for the quantities of interest. In addition, 95% confidence intervals (CI) for the mean pharmacokinetic parameters will also be presented.

Genetic data will not be included in the statistical analyses. Genetic data will be recorded and reported separately.

Safety data will be summarized and listed by study medications and ethnic groups.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
λ_z	Terminal elimination rate constant
ad libatum	As desired
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
Assessment	An observation made on a variable involving a subjective judgment
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration curve from zero to infinity
$AUC_{(0-24)}$	Area under the plasma concentration time curve from time zero to 24 hours post-dose
$AUC_{(0-t)}$	Area under the curve of plasma concentration against time from zero to time of last quantifiable concentration
BMI	Body mass index
°C	Degrees Celsius
CGG	Clinical Genotyping Group
CI	Confidence interval
CK	Creatine kinase
CL/F	Apparent oral clearance
C_{last}	Last quantifiable plasma concentration after a single dose or last administration
C_{max}	Maximum concentration
CRC	Clinical research center
CRF	Case report form
DMPK	Drug metabolism and pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EDTA K2	Potassium Ethylenediaminetetraacetic acid
G	Relative centrifugal force

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
HBsAG	Hepatitis B surface antigen
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3methlglutaryl coenzyme A
IB	Investigators Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
kg	Kilogram
LDH	Lactic dehydrogenase
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LC/MS/MS	Liquid chromatography/mass spectrometry/mass spectrometry
LIMS	Laboratory Information Management System
M	Molar concentration measured by the number of mols of solute per liter of solvent
m^2	Meters squared
m	Meter
mg	Milligram
mL	Milliliter
MRP-2	Multidrug resistance-associated protein 2
NCS	Not clinically significant
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the volunteer from study treatment; see definition in section 4.7)
OATP1B1	Organic anion transporting polypeptide (OATP) 1B1
OTC	Over-the-counter
Outcome variable	A, usually derived, variable specifically defined to be used in the analysis of a study objective
Parameter	A quantity (usually unknown) that characterizes the distribution of a variable in a population of subjects
pCRFs	Paper case report forms
PIB	Professional information brochure
Principal investigator	A person responsible for the conduct of a clinical study at a study site. Every study center has a principal

Abbreviation or special term	Explanation
	investigator.
SAE	Serious adverse event
SAP	Statistical analysis plan
TC	Total cholesterol
TG	Triglycerides
$t_{½\lambda z}$	Terminal elimination half life
t_{max}	Time of maximum concentration
ULN	Upper limit of normal
Variable	A characteristic or a property of a subject that may vary e.g., from time to time or between subject

1. INTRODUCTION

During the clinical development of rosuvastatin calcium, Phase I studies conducted in healthy Japanese volunteers living in Japan indicated an approximate 2-fold increase in rosuvastatin maximum concentration (C_{max}) and area under the plasma concentration time curve from time zero to 24 hours post-dose ($AUC_{(0-24)}$) compared to similar studies conducted in western Caucasian volunteers and the absolute bioavailability in Japanese volunteers in Japan was 29% compared to 20% in Caucasians. The population pharmacokinetic analysis that incorporated race as a categorical variable also demonstrated an approximate 2-fold increase in rosuvastatin plasma concentrations in Asian volunteers, most of whom were Japanese residing in Japan.

The clinical development program for rosuvastatin calcium has continued exploring the phenomenon of increased rosuvastatin plasma exposure among Asians as compared to Caucasians and has now completed two additional Phase I studies comparing plasma exposure between these groups.

Study D3560C00101 was conducted at 2 sites in Singapore and included Chinese, Malay, Indian, and Caucasian volunteers living in the same environment. This study also included controls for diet (at least 10% of total caloric intake in saturated fat and a mean daily dietary cholesterol of ≥ 300 milligrams [mg] in order to participate in the study), as determined by a 3-day diet assessment. The plasma exposure of rosuvastatin, (after a single dose of 40 mg rosuvastatin calcium), again was approximately 2-fold higher in the Asian volunteers compared to the Caucasian volunteers.

Study D3560C00001 was conducted at a single center in Long Beach, California and included Chinese, Filipino, Asian Indian, Korean, Vietnamese, Japanese, and Caucasian volunteers. This study also included a 3-day diet assessment but was not exclusionary based upon the amount of saturated fat and cholesterol consumed by the volunteers as in the Singapore study. Rosuvastatin C_{max} and area under the curve of plasma concentration against time from zero to time of last quantifiable concentration ($AUC_{(0-t)}$) were consistently higher, (after a single dose of 20 mg rosuvastatin calcium), across the Asian ethnic groups and in the pooled Asian group compared to the Caucasian group, except for the Asian-Indians (excluded from the pooled Asian group), who were intermediate.

Diet and environment were considered highly unlikely to have affected the differences in exposure for these 2 studies.

In the Singapore trial, SLCOB1 genotypes did not account for the observed pharmacokinetic differences between Asian and Caucasian subjects. These gene encodes for the hepatic influx transporter Organic Anion Transporting Polypeptide 1B1 (OATP1B1) which has been shown to transport rosuvastatin, atorvastatin and simvastatin.

Since little data exists for other statins and their exposure in Asians versus Caucasians, it is important to investigate if other drugs in this class will be similar to rosuvastatin.

1.1 Background

1.1.1 Clinical pharmacology of rosuvastatin

Rosuvastatin has been studied in North American, European, and Asian volunteers. In clinical pharmacology studies in volunteers, peak plasma concentrations of rosuvastatin are reached 3 to 5 hours following oral dosing. Both C_{max} and area under the concentration curve from zero to infinity (AUC) increase in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin in Caucasian and Japanese volunteers is approximately 20% and 29% respectively.

Administration of rosuvastatin with food decreased the rate of drug absorption by 20% as assessed by C_{max} but there was no effect on the extent of absorption as assessed by AUC. Plasma concentrations of rosuvastatin do not differ following evening or morning drug administration. Significant LDL-C reductions are seen when rosuvastatin is given with or without food, and regardless of the time of day of drug administration.

Mean volume of distribution at steady state of rosuvastatin is approximately 134 litres and 69 litres in Caucasian and Japanese volunteers respectively. Rosuvastatin is approximately 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Rosuvastatin is not extensively metabolised; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9. In vitro studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. Overall, greater than 90% of plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin.

Following oral administration, rosuvastatin and its metabolites are primarily excreted in the faeces (90%). The terminal elimination half-life ($t_{½\lambda z}$) of rosuvastatin is approximately 19 hours.

After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

In vitro and in vivo data indicate that rosuvastatin clearance is not dependent on metabolism by cytochromes P450 3A4 and 2C9 to a clinically significant extent. Rosuvastatin also does not interact to a clinically significant extent with the p-glycoprotein transporter.

Please refer to the investigator's brochure (IB) for additional information.

1.1.2 Clinical pharmacology of atorvastatin

Please refer to the professional information brochure (PIB) in Appendix D.

1.1.3 Clinical pharmacology of simvastatin

Please refer to the PIB in Appendix E.

1.1.4 Safety of rosuvastatin

Review of adverse event data show that rosuvastatin is well tolerated. The overall frequency of alanine aminotransferase (ALT) elevations is low. Clinically significant ALT elevations (>3 x the upper limit of normal [ULN] on two or more occasions) are uncommon and for the most part resolve with either continued therapy with or without dose reduction or after an interruption of treatment. No cases of irreversible liver injury secondary to rosuvastatin therapy have been identified.

Muscle-related findings (i.e., creatine kinase [CK] increases, myalgia, and myopathy) are a well-recognized complication of statin therapy. As with other HMG-CoA reductase inhibitors, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and, rarely rhabdomyolysis have been reported in patients treated with rosuvastatin. The reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose, which is consistent with other HMG-CoA reductase inhibitors.

The analysis of renal data indicates that proteinuria, predominantly tubular in nature, occurs at a low frequency among volunteers receiving rosuvastatin in doses up to and including 40 mg. A low frequency of proteinuria was also observed in volunteers treated with other statins in the rosuvastatin clinical program. The proteinuria seen with rosuvastatin is not associated with clinically significant increases in serum creatinine or worsening renal function. The 40 mg rosuvastatin dose is well tolerated in terms of renal effect with both shorter-term and longer-term treatment.

Please refer to the IB for additional information.

1.1.5 Safety of atorvastatin

Please refer to the PIB in Appendix D.

1.1.6 Safety of simvastatin

Please refer to the PIB in Appendix E.

1.2 Rationale

Previous studies have demonstrated that for the same dose of rosuvastatin calcium, systemic exposure in Asian volunteers living in Japan, and of varying Asian ethnic origin living in Singapore and the United States is approximately two-fold higher than the exposure observed in Caucasian volunteers.

The purpose of this trial is to determine whether the pattern of differential pharmacokinetics of rosuvastatin in Japanese and Chinese volunteers versus Caucasian volunteers holds true for atorvastatin calcium and simvastatin as well.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to summarize and compare the plasma exposure of rosuvastatin, atorvastatin, and simvastatin, after a single dose in healthy Chinese and Japanese volunteers to the plasma exposure of Caucasian volunteers following a single dose by measuring C_{max} and AUC.

2.2 Secondary objective(s)

The secondary objectives of this study are to:

1. summarize the pharmacokinetics of rosuvastatin, atorvastatin, and simvastatin and the relevant metabolites of each by calculating $AUC_{(0-t)}$, $t_{½\lambda z}$, time of maximum concentration (t_{max}), terminal elimination rate constant (λ_z) and, (for parent compound only), apparent oral clearance (CL/F).

2. calculate parent to metabolite ratios of rosuvastatin metabolites (N-desmethyl rosuvastatin, and rosuvastatin lactone), atorvastatin metabolites (ortho-hydroxy atorvastatin and para-hydroxy atorvastatin) and simvastatin acid.

3. obtain DNA samples from volunteers who consent separately to pharmacogenetic research; genes of interest include those that may be involved with the absorption, distribution, metabolism, and excretion (ADME) of statins. Genetic information will not be included in the SAP or study report.

4. assess safety and tolerability

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design

This is a single-center, open label, randomized, 3-way crossover, pharmacokinetic study comparing plasma exposure in healthy Chinese, Japanese, and Caucasian volunteers after a single dose of rosuvastatin calcium, atorvastatin calcium and simvastatin. Approximately 90 volunteers will be recruited to obtain a minimum of 27 evaluable volunteers per ethnic group.

Volunteers that have met all of the inclusion/exclusion criteria and that have satisfactorily completed the screening evaluations will be randomly assigned, within each ethnic group, to

one of three treatment sequences as determined by a randomization schedule that will be prepared by AstraZeneca.

The study will be completed in 3 Treatment Periods, (A, B, C) each lasting 5 days and 4 nights separated by a washout period of at least 7 days.

Treatment sequences are described as follows:

- Treatment Sequence 1
  - 20 mg rosuvastatin calcium during Treatment Period A
  - 40 mg atorvastatin calcium during Treatment Period B
  - 40 mg simvastatin during Treatment Period C
- Treatment Sequence 2
  - 40 mg atorvastatin calcium during Treatment Period A
  - 40 mg simvastatin during Treatment Period B
  - 20 mg rosuvastatin calcium during Treatment Period C
- Treatment Sequence 3
  - 40 mg simvastatin during Treatment Period A
  - 20 mg rosuvastatin calcium during Treatment Period B
  - 40 mg atorvastatin calcium during Treatment Period C

The study will proceed as follows:

Treatment Period A: Volunteers will come to the clinical research center (CRC) and complete Day –1A assessments as described in the Study Plan (Table 1).

Prior to dosing on Day 1A, a 10-milliliter (mL) fasting (10 hour) blood sample will be taken for a lipid profile that will include total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C).

On Day 1A, volunteers will receive a single dose of study drug (according to their Treatment Sequence) under fasting conditions. Blood samples for those volunteers taking rosuvastatin calcium and atorvastatin calcium will be taken pre-dose (within 30 minutes) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48, 54, 60, and 72 hours post dose. Blood samples for those volunteers taking simvastatin will be taken pre-dose (within 30 minutes) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, and 48, hours post-dose. Volunteers will be discharged after

completion of the final blood sample and all safety assessments are completed on Day 4A. Volunteers taking simvastatin will be discharged after the final blood sample and all safety assessments are completed on Day 3A.

Treatment Period B: After a washout period of at least 7 days, volunteers will return to the CRC for Treatment Period B. Day –1B assessments will be completed as described in the Study Plan (Table 1). On Day 1B, volunteers will receive a single dose of study drug (according to their Treatment Sequence) under fasting conditions. Blood samples will be taken and volunteers discharged as described in Treatment Period A.

Treatment Period C: After a washout period of at least 7 days, volunteers will return to the CRC for Treatment Period C. Day –1C assessments will be completed as described in the Study Plan (Table 1). On Day 1C, volunteers will receive a single dose of study drug (according to their Treatment Sequence) under fasting conditions. Blood samples will be taken as described in Treatment Period A. Volunteers will be discharged from the study after completion of the final blood sample and all safety assessments are completed on Day 4C. Volunteers taking simvastatin will be discharged from the study after the final blood sample and all safety assessments are completed on Day 3C.

Figure 1 Study flow chart

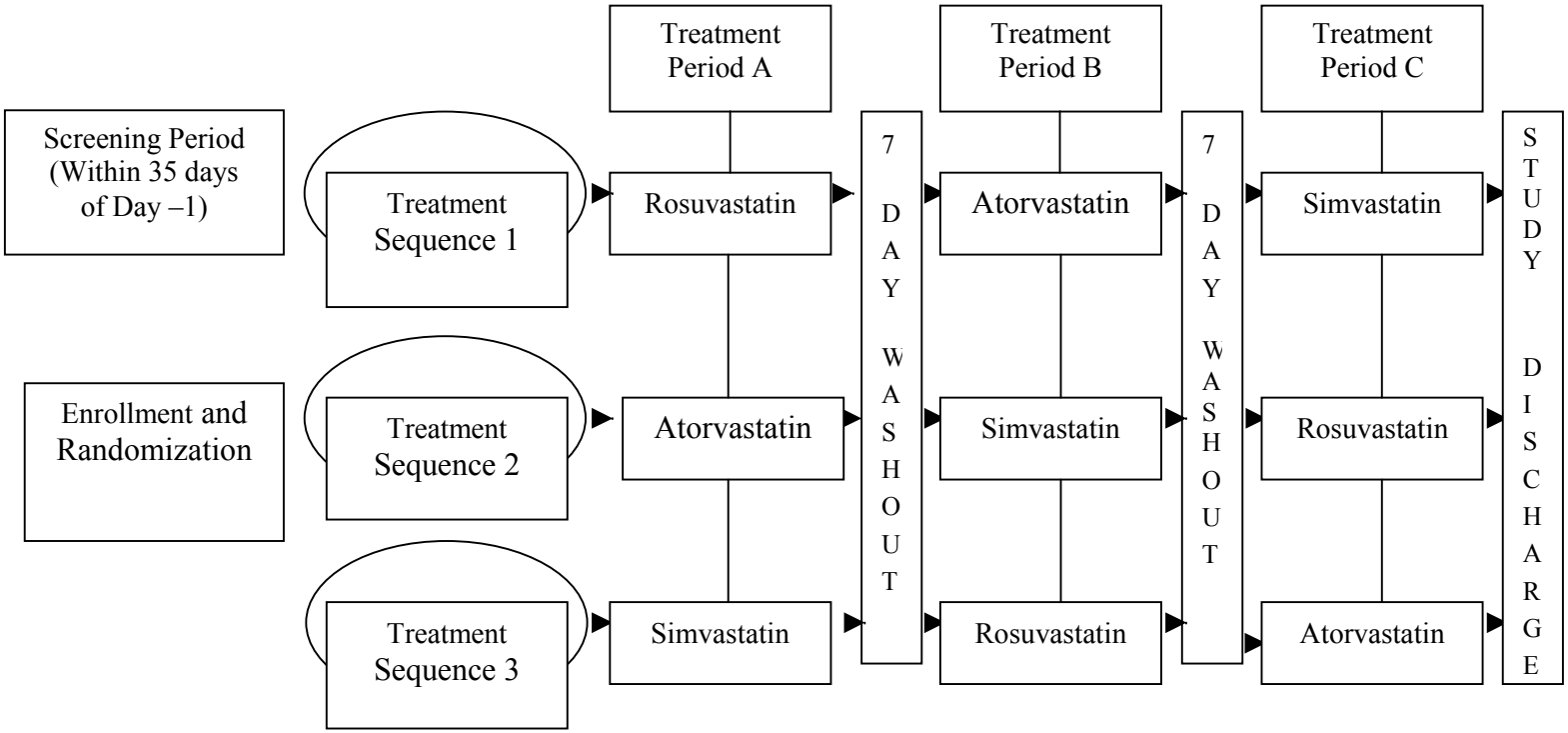


Table 1 Study Plan

Activity	Screening Period	Treatment Period A					Treatment Period B					Treatment Period C			
		Day –1A	Day 1A	Day 2A 3A	Day 4A		Day –1B	Day 1B	Day 2B 3B	Day 4B		Day –1C	Day 1C	Day 2C 3C	Day 4C
Informed Consent	√					7 DAY WASH OUT					7 DAY WASH OUT				
Genetic Consent[a]	√														
Inclusion / Exclusion	√	√					√					√			
Demographics	√														
Medical / Drug History	√														
Urine Drug Screen	√	√					√					√			
Complete Physical Exam	√														√
Brief Physical Exam[b]		√					√					√			
Dietary Assessment[c]	√														
Electrocardiogram	√														
Chemistry/Hematology[b]	√	√					√					√			√
Fasting Lipid Profile[d]			√												
Serology	√														
Urinalysis[b]	√	√					√					√			√
Serum Pregnancy[b]	√	√					√					√			√
Vital Signs[b,e]	√	√	√	√	√		√	√	√	√		√	√	√	√
Genetic Blood Sample[a]			√												
Administration of Study Drug			√					√					√		

Activity	Screening Period	Treatment Period A					Treatment Period B					Treatment Period C			
		Day –1A	Day 1A	Day 2A 3A	Day 4A		Day –1B	Day 1B	Day 2B 3B	Day 4B		Day –1C	Day 1C	Day 2C 3C	Day 4C
Blood Sampling[f]			√	√	√			√	√	√			√	√	√
Adverse Events Concomitant Meds[g]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Discharge[h]					√					√					√

a. Volunteers declining to participate in the genetic portion of the study may not participate in the main pharmacokinetic study
b. Clinical assessments scheduled for Day 4 will be on Day 3 for volunteers receiving simvastatin
c. A 3-day diet diary will be completed and returned to the clinical research center (CRC) for analysis during the screening period
d. Fasting (10 hours) lipid profile to measure total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C)
e. Vital signs will be taken at screening, Day –1, before dosing on Day 1 and in the mornings on Days 2-4
f. Serial blood sampling for rosuvastatin and atorvastatin will be done pre-dose (within 30 minutes), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48, 54, 60, and 72 hours post-dose. Serial blood sampling for simvastatin will be done pre-dose (within 30 minutes), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, and 48 hours post-dose.
g. Volunteers will continue with study restrictions during the washout periods. Concomitant meds should be cleared by the principal investigator if at all possible and recorded on the case report form (CRF). Adverse events and concomitant medication use should be solicited upon return to the CRC after washout or reported by the volunteer during the washout period and recorded on the appropriate CRF.
h. Volunteers receiving simvastatin will be discharged after the final blood sample (48 hours post-dose) on Day 3

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

The design of this study is standard for determining pharmacokinetics of a single dose of rosuvastatin calcium, atorvastatin calcium, and simvastatin.

The 20 mg rosuvastatin calcium, 40 mg atorvastatin calcium, and 40 mg simvastatin are clinically relevant doses, which are sufficient to allow complete characterization of their plasma concentration-time profiles.

The 3 way-crossover design is chosen to strengthen internal validity. The volunteers will serve as their own control for pharmacokinetic plasma profiles on all three study drugs.

3.2.2 Risk/benefit and ethical assessment

Rosuvastatin, atorvastatin, and simvastatin are marketed drugs and in general, are safe and well-tolerated when used according to prescribing information. While there is always a risk in taking any type of pharmaceutical product, the risk to healthy normal volunteers participating in this study is minimal.

There is no health benefit for healthy normal volunteers.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of volunteers who were considered for enrollment but never enrolled e.g., subject screening log, according to local procedures. This information is necessary to establish that the volunteer population was selected without bias.

3.3.2 Inclusion criteria

For inclusion in the study volunteers must fulfill all of the following criteria:

1. Provision of signed written informed consent, ability to communicate with the investigator, and to understand and comply with the requirements of the study

2. Males and females aged 18-65, inclusive

3. Body Mass Index (BMI) 18-29 inclusive. BMI will be calculated as weight in kilogram (kg)/height in meters^2 (m^2).

4. Women who are surgically sterilized, post-menopausal for at least one year, or not pregnant and/or lactating. Women of childbearing potential must be willing to abstain from sexual activity or use an effective double barrier method of contraception during the study period (e.g., condom and diaphragm, condom and foam, condom and sponge, etc.), or intrauterine devices

5. Chinese and Japanese volunteers must have parents of the same reported race. (See Section 4.1.1.1)

6. Residence in the United States for at least 12 months.

For inclusion in the genetic component of the study, volunteers must fulfill the following criterion:

1. Provision of signed written informed consent for genetic research

3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Use of prescription medication for a chronic medical condition

2. Acute illness or use of prescription medication for an acute medical condition within 2 weeks of Day –1A

3. History within the last 3 months of extreme or therapeutic diet programs including but not limited to: weight reduction, weight augmentation, high protein, high carbohydrate, low carbohydrate, or low fat

4. Any contraindication determined by review of a detailed medical and drug history, complete physical examination, vital signs, blood chemistry, hematology, and electrocardiogram (ECG).

5. Medical history or psychological conditions which, in the opinion of the investigator, would compromise the volunteer's safety or successful participation in the study

6. History of severe allergies

7. History of adverse drug reaction or hypersensitivity to statins or drugs with a similar chemical structure.

8. History or presence of gastrointestinal, hepatic, or renal disease or other conditions known to interfere with the ADME of drugs

9. History of alcohol or substance abuse within the past year

10. Positive test results for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAG), or hepatitis C antibody

11. Positive urine drug screen

12. Participation in another study within 30 days of Day –1A, apart from non-invasive methodology studies in which no drugs were given.

13. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study site)

14. Blood donation within 3 months of Day –1A.

3.3.4 Restrictions

Volunteers will be required to:

1. Refrain from alcohol, grapefruit containing products, and apple juice from CRC admission through completion of the study including the washout periods.

2. Refrain from using over-the-counter (OTC) medications, and herbal supplements 1 week prior to CRC admission through the final study assessments including the washout periods. (See Section 3.4.4)

3. Refrain from strenuous exercise during the screening period, washout periods and through final study assessments and discharge from the study.

4. Refrain from eating or drinking starting 10 hours before study drug administration and continuing through 4 hours post study drug administration (with the exception of water which will be allowed ad libatum until 2 hours prior to study drug administration and 2 hours post study drug administration). Lunch will be served approximately 4 hours after dosing. At all other times during the in-patient periods, volunteers will be served standard meals on a regular basis.

3.3.5 Discontinuation of volunteers from treatment or assessment

3.3.5.1 Criteria for discontinuation

Volunteers may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a volunteer from this study are:

- Discontinuation by the volunteer, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca.
- Incorrect enrollment i.e., the volunteer does not to meet the required inclusion/exclusion criteria for the study
- Volunteer lost to follow-up
- At the investigator’s discretion

Specific reasons for discontinuing a volunteer from the genetic research when genetics is a secondary objective of the study are:

- Withdrawal of consent for genetic research. A volunteer may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the volunteer will not prejudice further treatment

3.3.5.2 Procedures for discontinuation

Volunteers who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s) and any adverse events followed up.

3.3.5.3 Procedures for handling incorrectly enrolled volunteers

Volunteers not meeting the inclusion/exclusion criteria for this study should, under no circumstances, be enrolled. Volunteers not meeting the study criteria that are enrolled in error, incorrectly randomized, or if volunteers subsequently fail to meet the criteria for the study post enrollment, will be discontinued from the study. Volunteers discontinued due to these factors will undergo safety assessments before discontinuation and any adverse events will be recorded. These volunteers, if any, will be included for the safety analysis, but will not be included as evaluable volunteers in the analysis of the study.

3.3.5.4 Procedures for discontinuation from genetic aspects of the study

Volunteers who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for the linked genetic research. It must be established whether the volunteer:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic analyses in the future.

- Withdraws consent for the sample to be kept for genetic analysis in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The principal investigator is responsible for providing written notification to AstraZeneca of any volunteer who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca will notify the Clinical Genotyping Group (CGG), which will take the appropriate steps for the sample in question. The CGG will provide a written confirmation of the actions taken. A written confirmation of the actions taken with the sample will then be sent to the investigator, which must be filed in the investigator study file.

3.4 Treatment(s)

3.4.1 Investigational product(s)

Rosuvastatin calcium 20 mg, atorvastatin 40 mg, and simvastatin 40 mg will be supplied as tablets for oral use.

Table 2 Identity of investigational product and comparators

Investigational product	Dosage form and strength	Manufacturer	Formulation number
Rosuvastatin calcium	20 mg tablets	AstraZeneca Pharmaceuticals, LP	F12673
Atorvastatin calcium	40 mg tablets	Pfizer Ireland Pharmaceuticals	F12598
Simvastatin	40 mg tablets	Merck and Company, Inc.	F12835

3.4.1.1 Labeling

Rosuvastatin will be supplied in bottles of 100 tablets. Each bottle will be affixed with a two-panel label with tear off. At least the study number, storage conditions, dosing instructions, and bottle contents will appear on both portions of the label.

Before dispensing the first dose, the volunteer's enrollment number, randomization/subject number, treatment sequence and treatment period must be written on both the permanent and tear off labels. The tear off portion will be removed from the bottle and affixed to the appropriate case report form (CRF). The documentation on the permanent and tear off portion of the label and the removal and placement of the tear-off portion of the label will be done during the corresponding Treatment Period in which it will be given. IT SHOULD NOT BE DOCUMENTED OR TORN OFF PRIOR TO THIS TIME this will help to ensure proper dosing during each Treatment Sequence and Treatment Period.

Atorvastatin and simvastatin will be commercially labeled bottles of 90 tablets and 30 tablets respectively. Each bottle will be packaged in a carton with a two-panel label with tear off. At least the study number, storage conditions, dosing instructions, and carton contents will appear on both portions of the label.

Before dispensing the first dose, the volunteers enrollment number, randomization/subject number, treatment sequence and treatment period must be written on both the permanent and tear off labels. The tear off portion will be removed from the carton and affixed to the appropriate CRF. The documentation on the permanent and tear off portion of the label and the removal and placement of the tear-off portion of the label will be done during the corresponding Treatment Period in which it will be given. IT SHOULD NOT BE DOCUMENTED OR TORN OFF PRIOR TO THIS TIME this will help to ensure proper dosing during each Treatment Sequence and Treatment Period.

3.4.1.2 Storage

All investigational products must be kept in a secure place (e.g. locked cabinet or drug storage area) and under appropriate storage conditions. Investigational study drug will be accessible only to authorized study personnel. A description of the appropriate storage and shipment conditions are specified on the investigational product carton and bottle label and investigator brochure.

3.4.1.3 Accountability

The drug provided for this study is for use only as directed in the protocol. The AstraZeneca monitor will return all unused drugs to Strericycle C/O Universal Solutions, Inc., 2084-900 Lake Industrial Court, Conyers, Georgia 30013. The study site personnel will account for all drugs dispensed and returned. Certificates of delivery and return must be signed.

3.4.2 Doses and treatment regimens

On the morning of Day 1 of each Treatment Period (A, B, C) all volunteers will receive a single dose of rosuvastatin calcium, atorvastatin calcium or simvastatin according to their assigned Treatment Sequence under fasting conditions. (See Restrictions Section 3.3.4). Tablets will be taken orally with 240 mLs of distilled, room temperature water. Tablets are not to be crushed or chewed. Volunteers must remain in an upright position (sitting or standing) for 4 hours after dosing.

3.4.3 Method of assigning volunteers to treatment groups

Written informed consent will be obtained before enrollment. Each volunteer will be assigned a unique enrollment number that will begin with E0001101 for Chinese volunteers, E0001201 for Japanese volunteers, and E0001301 for Caucasian volunteers.

Volunteers fulfilling the eligibility criteria and continuing in the study will be assigned unique randomization codes (subject numbers) that will begin with 1101 for Chinese volunteers, 1201 for Japanese volunteers, and 1301 for Caucasian volunteers.

Volunteers will be assigned enrollment/randomization codes strictly sequentially as they enroll/are eligible for randomization. If a volunteer discontinues from the study the randomization/subject number will not be re-used and the volunteer will not be allowed to re-enter the study. It is important to note that enrollment numbers and subject numbers may not match and careful observation must be made when documenting study information and identifying treatment sequences.

Volunteers will be randomized within each ethnic group according to a randomization scheme that will be generated by the biostatistics group at AstraZeneca.

3.4.4 Concomitant medication

During the screening, in-patient, and washout periods, volunteers will be instructed that no additional medication will be allowed without the prior consent of the investigator. Prescription medicines are not allowed during this study at any time. All medications (OTC

products, dietary supplements, and herbal remedies) will be discontinued 1 week prior to entry into the CRC.

Study personnel will inquire if any concomitant medications were used during the washout periods upon readmission to subsequent Treatment Periods. Use of prescription medication is an exclusion criterion and volunteers will be discontinued if use of prescription medication has occurred during any restricted timeframe (1 week prior to CRC entry, in-patient periods, and washout periods). Any concomitant medications must be recorded on the appropriate CRF.

Any medication, which is considered necessary for the volunteer's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the case report form (CRF).

3.4.5 Treatment compliance

Compliance will be assured by the supervised administration of the study drug by site personnel.

4. MEASUREMENT OF STUDY VARIABLES

The following study measurements will be obtained. The timing of these measurements is detailed in the study plan (Table 1)

4.1 Medical examination and demographic measurements

4.1.1 Enrollment medical examination and demographic measurements

Each volunteer will undergo an enrollment medical examination and screening in the 35 days prior to Day –1A (screening period). This will consist of:

- Recording of demographic data - date of birth, sex, race (See Section 4.1.1.1)
- A standard medical history and a physical examination including the cardiovascular and respiratory systems
- A blood sample for standard clinical chemistry and hematology assessments a mid-stream urine sample for urinalysis and drugs of abuse screen
- A blood sample for serology (HIV, HbsAg, Hepatitis C)
- A resting blood pressure and heart rate measurement.
- A serum pregnancy test (for women of child-bearing potential)
- A 3-day dietary assessment (See Section 4.1.1.4)

- An electrocardiogram (ECG)

4.1.1.1 Demographics

Volunteers entering this study will self-report race by checking a tick box offered during the screening process. The following tick boxes will be offered: Caucasian, Asian, and Other. A choice of "Other" will not be considered eligible for this study.

Additional tick boxes will be provided for Asian volunteers indicating to which Asian sub-group the volunteer belongs. These tick boxes will include Chinese, Japanese, and Other. Volunteers reporting mixed ethnicity or choosing "Other" will not be included in the study.

In addition, The Chinese and Japanese volunteers will be asked to identify the race of each parent. Only those volunteers with both parents matching the self-reported race of the volunteer will be eligible for the study.

4.1.1.2 Medical History and Complete Physical Exam

A complete medical and drug history will be recorded for each volunteer at the initial screening visit and reviewed for any additions or omissions on admission to the CRC (Day –1A). Significant medical conditions that have occurred within the past 2 years, or conditions that are ongoing (i.e., headache, backache, indigestion) are to be recorded in the CRF. The drug history must identify any known drug allergies, presence or history of drug abuse, and use of chronic medications.

The complete physical examination will include an assessment of the following:

- General appearance,
- Skin, head, neck, and lymph nodes
- Musculoskeletal/extremities (including spine)
- Cardiovascular
- Lungs
- Abdomen
- Neurological (reflexes)

Physical examination data to be recorded on the CRF will include: 1) normal/abnormal and 2) a description of any abnormalities.

Height in centimeters (cm) and weight in kg will be measured at screening only and will be recorded on the CRF.

4.1.1.3 HIV and hepatitis testing

A 10 mL blood sample to test for HIV antibody, HbsAG, and hepatitis C antibody will be performed on all volunteers at screening. If a test result is positive, the volunteer will not be allowed to proceed in the study. Although the results of the HIV and hepatitis screens have to be documented in the volunteer's file, they will not be collected on the CRFs and will therefore not be recorded in the study database.

4.1.1.4 Dietary Assessment

During the screening period each prospective volunteer will participate in a 3-day diet diary assessment and analysis.

A trained investigative staff member will instruct volunteers on how to complete a 3-day food diary. In addition, volunteers will be taught how to estimate food quantities and how to record information regarding food brands and varieties in the diary. Volunteers will be instructed not to change their personal eating habits during the 3-day diet assessment, but to eat normally and record all foods and quantities in the diary.

Each volunteer will record his or her food intake in a diary over 3 days during the screening period (ideally, 2 days during the week and 1 day during the weekend). Volunteers will return to the CRC with their record for analysis prior to Day –1A.

A commercially available nutrition analysis software program will be used to analyze the dietary records. The results of the analysis will include the following:

- The contents of each meal and all snacks including all liquids consumed
- The total daily caloric intake for each day
- Total (in grams) carbohydrates, protein, fiber, and fat, (monounsaturated, polyunsaturated and saturated) for each day
- Percent of total caloric intake for each component (carbohydrates, protein, fiber, and fat)
- Dietary cholesterol (mg)
- Minerals (mg)
  - Sodium
  - Potassium
  - Calcium
  - Magnesium

  - Phosphorus
  - Iron
  - Zinc
- Vitamins (mg)
  - Total retinol
  - Thiamine
  - Riboflavin
  - Niacin
  - Vitamin B6
  - Vitamin B12
  - Vitamin C
  - Vitamin D
  - Vitamin E

Additionally, the analysis will provide an average of the same components for the 3 days.

4.1.1.5 Electrocardiographic measurements

A standard resting 12-lead ECG will be obtained at screening only and will be recorded after the volunteer has been lying down for 10 minutes.

4.1.2 Post-study medical examination

A complete physical exam will be given at the time of discharge for all volunteers

4.2 Pharmacokinetic measurements

Serial blood sampling for rosuvastatin and atorvastatin will be done pre-dose (within 30 minutes), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48, 54, 60, and 72 hours post-dose.

Serial blood sampling for simvastatin will be done pre-dose (within 30 minutes), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, and 48 hours post-dose.

4.2.1 Determination of drug concentration in biological samples

Samples for measurement of drug concentration will be analyzed by liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS). Full details of the methodology will be included in the clinical study report.

4.2.2 Collection of biological samples

Blood samples (4 mL) for determination of rosuvastatin in plasma will be taken at the times presented in Table 3.

Blood samples (7mL) for determination of atorvastatin in plasma will be taken at the times presented in Table 3.

Blood samples (7mL) for determination of simvastatin in plasma will be taken at the times presented in Table 4.

Blood samples are expected to be collected at the precise time indicated and must be recorded in real time on the source documents immediately at time of collection.

4.2.2.1 Blood sampling for determination of rosuvastatin, n-desmethyl rosuvastatin, and rosuvastatin lactone in plasma

Venous blood samples (4mL) will be collected into tubes containing lithium heparin anticoagulant at the times indicated in Table 3 below.

Blood samples must be protected from light, cooled to 4 degrees Celsius (°C), and centrifuged at 1500 G (relative centrifugal force) for 10 minutes at 4 °C within 30 minutes of blood sampling. Following centrifugation, a 1.5 mL aliquot of plasma will be transferred to a clean polypropylene tube and an equal volume (1.5 mL) of 0.1 M acetate buffer, pH 4.0 will be added and mixed thoroughly with a vortex mixer to provide plasma for analysis of rosuvastatin. See Appendix C for preparation of the buffer solution for plasma samples.

After ensuring that the 4 mL buffered plasma sample (1.5 mL plasma, 1.5 mL buffer solution) has been thoroughly mixed by vortexing, the sample will be divided into 2 aliquots. These 2 aliquots of 1.5 mL each will be transferred to clean 2 mL polypropylene tubes. The samples will be protected from light, frozen, and stored at -70°C until analysis.

One sample will be used for analysis of rosuvastatin, N-desmthyl rosuvastatin, and rosuvastain lactone and the second sample will be kept at the CRC as a spare in the event of loss or damage of the other sample.

4.2.2.2 Blood sampling for determination of atorvastatin, ortho-hydroxy atorvastatin, and para-hydroxy atorvastatin

Venous blood samples (7mL) will be collected into tubes containing sodium heparin anticoagulant at the times indicated in Table 3. Each blood sample should be gently inverted immediately after collection to thoroughly mix.

Blood samples must be protected from light, cooled to 4 °C, and centrifuged at 1500 G for 10 minutes at 4 °C within 30 minutes of collection. The resultant plasma will be divided into 2 aliquots of 1.5mL each and transferred to clean polypropylene tubes. The samples will be protected from light, frozen, and stored at -70°C until analysis.

One sample will be used for analysis of atorvastatin and the second sample will be kept at the CRC as a spare in the event of loss or damage of the other sample.

4.2.2.3 Blood sampling for determination of simvastatin and simvastatin acid

Venous blood samples (7mL) will be collected into tubes containing potassium ethylenediaminetetraacetic acid (EDTA K2) at the times indicated in Table 4. Each blood sample should be gently inverted immediately after collection to thoroughly mix.

Blood samples must be protected from light, cooled to 4 °C, and centrifuged at 1500 G for 10 minutes at 4 °C within 30 minutes of collection. The resultant plasma will be divided into 2 aliquots of 1.5mL each and transferred to clean polypropylene tubes. The samples will be protected from light, frozen, and stored at -70°C until analysis.

One sample will be used for analysis of simvastatin and the second sample will be kept at the CRC as a spare in the event of loss or damage of the other sample.

Table 3 Schedule of blood sampling and tube numbers for rosuvastatin and atorvastatin

Treatment Periods A B and C Day	Scheduled time	Tube number
1	0.5 hour pre-dose	1
1	0.5 hour post-dose	2
1	1 hour post-dose	3
1	2 hours post-dose	4
1	3 hours post-dose	5
1	4 hours post-dose	6
1	5 hours post-dose	7
1	6 hours post-dose	8
1	8 hours post-dose	9
1	10 hours post-dose	10
1	12 hours post-dose	11
2	18 hours post-dose	12
2	24 hours post-dose	13
2	30 hours post-dose	14
2	36 hours post-dose	15
3	48 hours post-dose	16
3	54 hours post-dose	17
3	60 hours post-dose	18
4	72 hours post-dose	19

Table 4 Schedule of blood sampling and tube numbers for simvastatin

Treatment Periods A B and C Day	Scheduled time	Tube number
1	0.5 hour pre-dose	1
1	0.5 hour post-dose	2
1	1 hour post-dose	3
1	2 hours post-dose	4
1	3 hours post-dose	5
1	4 hours post-dose	6
1	5 hours post-dose	7
1	6 hours post-dose	8
1	8 hours post-dose	9
1	10 hours post-dose	10
1	12 hours post-dose	11
2	18 hours post-dose	12
2	24 hours post-dose	13
2	30 hours post-dose	14
2	36 hours post-dose	15
3	48 hours post-dose	16

4.2.2.4 Labeling of biological samples

AstraZeneca will supply labels for transfer tubes (rosuvastatin samples only) and plasma sample tubes. The labels **must** be applied to the transfer tube and to the plasma sample tubes prior to the start of collection of blood samples on Day 1 of each Treatment Period. The plasma sample labels will include at least the following information:

- Study number: (D3560C00004)
- Randomization/Subject number
- Treatment Period (to be completed by site)
- Treatment Sequence (to be completed by site)
- Assay: (rosuvastatin, atorvastatin, or simvastatin)

- Scheduled time
- Matrix: (Plasma-rosuva,atorva,simva or Plasma-rosuva, atorva, simva spare)

The transfer tube (tube used to vortex buffer and plasma before splitting sample, rosuvastatin only) will include at least the following information:

- Study number: (D3560C00004)
- Randomization/Subject number
- Treatment Period (to be completed by site)
- Treatment Sequence (to be completed by site)
- Scheduled time
- Matrix: (buffered plasma for vortex mixer)

4.2.2.5 Shipping of biological samples

All plasma samples for rosuvastatin, atorvastatin, and simvastatin assays will be shipped to . The samples must be shipped frozen in dry ice via expedited overnight delivery. The samples must be packed securely to avoid damage during transit, should be double bagged to contain leaks, and should be packed with a sufficient quantity of dry ice to ensure they remain frozen for a minimum of 72 hours. Allowance should be made for possible delay of shipment. All applicable shipping regulations must be followed. Documentation sufficient to identify each sample must be included in the shipment. The contact (see below) must be notified by phone or fax when the samples are shipped and all shipping details must be provided.

Ship samples on Mondays-Wednesdays. Do not ship on or the day before a legal holiday.

Samples should be shipped to:

Any questions regarding shipping instructions may be directed to

4.3 Pharmacodynamic measurements

Not applicable

4.4 Safety measurements

4.4.1 Laboratory safety measurements

Blood and urine samples for determination of drugs of abuse, clinical chemistry, hematology, urinalysis, and pregnancy will be taken at the times give in the study plan (Table 1). The date and time of collection will be recorded on the appropriate CRF.

4.4.1.1 Urine drug screen

The following drugs of abuse will be screened: cannabinoids, cocaine, opiates, amphetamines, benzodiazepines, barbiturates, methaqualone, propoxyphene, and methadone. If a test result is positive for drugs of abuse, the volunteer will not participate or continue to participate in the study.

4.4.1.2 Clinical chemistry, hematology, urinalysis

Samples will be collected in the following volumes specified:

- Clinical chemistry/serum pregnancy - 10 mL
- Hematology - 10 mL;
- Urinalysis - 10 mL

The following laboratory variables will be measured:

Clinical chemistry

- Calcium
- Phosphate
- Blood glucose
- Total bilirubin
- Alkaline phosphatase
- Urea nitrogen (BUN)
- Uric acid
- Chloride
- Carbon dioxide
- Creatinine
- Albumin
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Sodium
- Potassium
- Creatine kinase (CK)
- Lactic dehydrogenase (LDH)

Hematology

- Hemoglobin
- Hematocrit
- Platelet count
- Red blood cell count (RBC)
- White blood cell count (WBC) with differential

Urinalysis

- PH
- Glucose
- Blood
- Ketones
- Protein
- Bilirubin
- Specific gravity

Microscopic analysis (if applicable)

- WBC
- RBC
- Casts
- Crystals
- Epithelial cells
- Bacteria

4.4.1.3 Urinalysis

Urine positive for protein or blood will have a microscopic examination performed. Further investigation may be undertaken at the discretion of the investigator. Blood in urine due to

menses may be marked as such and notated as 'not clinically significant' (NCS) without further microscopic examination.

4.4.1.4 Serum pregnancy test

Female volunteers of childbearing potential will have a serum pregnancy test. The serum pregnancy test can be collected with the same sample as the blood chemistry. If the result is positive, the volunteer will not be allowed to proceed in the trial.

4.4.2 Brief physical exam

The brief physical examination will be conducted at the times specified in the study plan (Table 1) and will include an assessment of the following:

- General appearance
- Cardiovascular
- Lungs
- Abdomen

Brief physical examination data to be recorded on the CRF will include: 1) normal/abnormal and 2) a description of any abnormalities

4.4.3 Vital signs

For timing of individual measurements refer to the study plan (Table 1).

Vital signs consist of a sitting heart rate, sitting blood pressure, and oral temperature.

Oral temperature will be measured in °C at screening and Days –1A, -1B, and -1C only.

AstraZeneca will provide the investigator reference range values for each vital sign measurement required by the protocol

4.4.3.1 Blood pressure and heart rate

Heart rate and blood pressure will be measured after the volunteer has been seated for at least 5 minutes. Heart rate will be determined by palpation of the radial pulse for a period of 30 seconds and then multiplied by two, or as measured by an automatic device (e.g. Dinamap®). Blood pressure will be measured using a blood pressure device with an appropriate cuff size. The same device and same arm will be used for each measurement.

4.5 Genetic measurements and co-variables

Consent for genetic research will be obtained on a separate consent form. Refusal to provide such consent is an exclusion criterion and will preclude participation in the main pharmacokinetic study if not provided. The blood samples obtained under this consent will be

used to study the genes implicated in the ADME of statins. DNA samples will not be used in other types of genetic or non-genetic research either as test or control specimens.

4.5.1 Collection of samples for genetic research

Blood samples will be obtained from each volunteer and used to prepare DNA samples. A record of the date of the volunteer consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the CRF.

4.5.1.1 Processing of genetic samples

Approximately 9 mL of blood will be collected from consenting volunteers into ethylenediaminetetraacetic acid (EDTA) coated polypropylene tubes at the time indicated in the protocol study plan (Table 1). The blood should be mixed by gentle inversion of the tube.

Glass tubes must not be used as they may break during transport.

Heparin must not be used as an anticoagulant as it may interfere with downstream genotyping methodology.

After collection, blood samples must be stored appropriately at the site of collection and transported to the AstraZeneca Clinical Genotyping Laboratory as soon as possible.

The samples will be frozen immediately after collection and may be stored at –20°C or –70°C. The samples should be kept frozen until analyzed.

If blood samples are to be stored at –20°C, non-frost free freezers must be used to prevent repeated freeze-thaw of blood, which may reduce yield and quality of the DNA, obtained.

Samples must not be thawed and then re-frozen at any point.

4.5.1.2 Labeling of genetic samples

Collection tubes will be labeled with the following information:

- Genetic sample
- Date of sample
- Study number
- Randomization/Subject number

4.5.1.3 Shipping of genetic samples

For safety reasons, all blood samples must be contained. Standard procedures for transporting biological samples as defined by the courier and in compliance with local regulations will be followed.

Blood samples for genetic analysis collected from each consenting volunteer will be shipped to AstraZeneca Clinical Genotyping Laboratory. The samples must be shipped frozen in dry ice via expedited overnight delivery. The samples must be packed securely to avoid damage during transit, must be double bagged to contain leaks, and will be packed with a sufficient quantity of dry ice to ensure they remain frozen for a minimum of 72 hours. Allowance should be made for possible delay of shipment.

All applicable shipping regulations must be followed. Documentation sufficient to identify each sample (i.e., list of subject identification numbers) must be included in the shipment. The AstraZeneca contact must be notified by telephone or fax when the samples are shipped. All shipping details, including study ID, number of samples, list of sample ID's, courier name, airway bill number, and date of shipment must be provided.

Samples must be shipped on Mondays or Tuesdays only to ensure delivery before the weekend. Do not ship on or the day before a legal holiday.

Samples will be sent o the following address:

4.5.1.4 Storage and coding of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain volunteer confidentiality.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal

details identifying the individual will be available to any AstraZeneca employee working with the DNA.

The blood samples and data for genetic analysis in this study will be coded. Each blood sample will be labeled with the study number and subject number. Only the investigator will be able to link the blood sample to the individual volunteer. The sample and data will not be labeled with a personal identifier. The link between the subject enrollment/randomization code and the DNA number will be maintained.

This link file and any corresponding genetic data will be stored in a secure environment, with restricted access within the . The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent. Access to the link file will require written authorization from the Project Team Leader.

All DNA samples will be stored under secure conditions with restricted access at AstraZeneca. The blood, DNA samples or data derived from the samples may be made available to groups or organizations working with AstraZeneca on this study or as part of the development drug project. However, the samples and any results will remain the property of AstraZeneca at all times. AstraZeneca will not give blood, DNA samples or data derived from the samples to any other parties, except as required by law.

Samples will be stored for a maximum of 15 years, from the date of completion of the study, after which they will be destroyed.

DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible. Further samples will not be acquired from volunteers.

4.5.1.5 Summary of genetic assessments and analysis

The purpose of the genetic research is to generate data for use in future retrospective analyses. Future analyses will explore genetic factors that may influence the disposition, efficacy, safety and tolerability to rosuvastatin. The results of the genetic research will not form part of the clinical study report for this study, but will be recorded and reported separately.

4.6 Volume of blood sampling

The total volume of blood that will be drawn from each volunteer in this study is as follows:

Table 5 Volume of blood to be drawn from each volunteer

Assessment		Sample volume (mL)	n of samples	Total volume (mL)
Blood sampling for rosuvastatin		4 mL	19	95 mL
Blood sampling for atorvastatin		7 mL	19	133 mL
Blood sampling for simvastatin		7 mL	16	112 mL
Lipid profile		10 mL	1	10 mL
Genetic sample		9 mL	1	9 mL
Safety	Serology	10 mL	1	10 mL
	Clinical chemistry/serum pregnancy	10 mL	5	50 mL
	Hematology	10 mL	5	50 mL
Total			**67**	**469 mL**

4.7 Adverse Events

The methods for collecting adverse events are described below.

4.7.1 Adverse Events

4.7.1.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the volunteer or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (i.e., their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?" For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Pharmacology Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

Other Significant Adverse Events (OAE)

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the volunteer from study treatment, will be classified as OAEs. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

4.7.1.2 Recording of adverse events

Adverse events will be collected beginning Day –1A through the final assessment of the final treatment period. SAEs will be collected from the time the informed consent is signed through final assessment of the final treatment period.

The following will be recorded for each AE:

- Start date
- Stop date
- Maximum intensity

- Action taken
- Outcome
- Causality (yes or no)
- Whether conditions constitute and SAE

The intensity rating is defined as:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.7.1.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 8.3. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

4.7.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (i.e., immediately but no later than the end of the next business day) of when he or she becomes aware of it.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day one for all fatal and life-threatening cases and by day five for all other SAEs.

Follow-up information from the investigator on SAEs must also be reported within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. . For a non-serious AE that become serious but which is not fatal or life threatening a report should be received within 5 days.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the case report form. The investigator and/or Sponsor are responsible for informing the Institutional Review Board (IRB) and/or the Regulatory Authority of the SAE as per local requirements.

5. STUDY MANAGEMENT

5.1 Monitoring

5.1.1 Study monitoring

The monitoring of this study will be performed in accordance with the principles of Good Clinical Practice (GCP) as laid out in the International Conference on Harmonization (ICH) document "Good Clinical Practice: Consolidated Guideline".

The specific requirements of the genetic part of the study will be discussed with the investigator(s) and other personnel involved with the study.

5.1.2 Data verification

It is a prerequisite of this study that the study monitor has direct access to source data for data verification. This will be done by comparing data from the CRFs with those in the volunteer's medical notes (permission from the volunteer will be sought as part of the consent process). Such verification is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

Monitoring including source data verification should routinely be performed prior to the transfer of data to Data Management.

Source verification of the genetic consent of participating volunteers will be performed.

5.2 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, an IRB may visit the center to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her center.

5.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to

the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Before the first volunteer is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic testing with AstraZeneca personnel. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the volunteers' samples will also be made clear.

5.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the principal investigator and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol must be notified to or approved by the IRB. Local requirements must be followed.

If an administrative change is required, such a change must be notified to or approved by each IRB according to local requirements.

If a protocol amendment requires a change to the Informed Consent Form, then AstraZeneca and the IRB must be notified. Approval of the revised Master Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to the principal investigator who in turn is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

5.5 Study agreements

The principal investigator must comply with all the terms, conditions, and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this protocol shall prevail.

5.6 Study timetable and end of study

5.7 Data management

5.7.1 Case report forms

Paper CRFs (pCRFs) will be used to record data. Data should be recorded legibly onto the pCRFs in blue or black ballpoint pen. Correction fluid or covering labels must not be used.

The AstraZeneca monitor will check data at the monitoring visits to the study site. The investigator will ensure that the data in the pCRFs are accurate, complete and legible.

Data from the completed pCRFs will be entered onto AstraZeneca's clinical study database and validated under the direction of the Data Manager. Any missing, impossible or inconsistent recordings in the pCRFs will be referred back to the investigator using a data query form and be documented for each individual volunteer before clean file status is declared.

5.7.2 Genetic data

In the case of genotypic data, only the date the volunteer gave consent to participation in the genetic research and the date the blood sample was taken from the volunteer will be recorded in the pCRF and database.

The genotypic data generated from the study will be stored in the AstraZeneca LIMS database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the datasets from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis.

However, some or all of the clinical study dataset may be duplicated within the AstraZeneca LIMS database or other appropriate system for exploratory analysis.

5.8 Reporting of genotypic results

Results from any genetic research performed will be reported separately from the clinical study report. AstraZeneca will not provide individual genotype results to volunteers, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The volunteer's DNA will not be used for any purpose other than those described in the study protocol.

Individual volunteers will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the volunteer's name nor any other personal identifiers will appear in any publication or report.

6. PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY, GENETIC AND STATISTICAL METHODOLOGY

6.1 Pharmacokinetic / pharmacodynamic evaluation

6.1.1 Calculation or derivation of pharmacokinetic variables

The , will carry out the pharmacokinetic analyses.

The pharmacokinetic variables of rosuvastatin, atorvastatin, simvastatin and the relevant metabolites of each defined below will be calculated by non-compartmental methods using WinNonlin Enterprise version 4.1, Pharsight Corp., Mountain View, CA. The actual sampling times will be used in the pharmacokinetic calculations. The following parameters will be derived:

C_{max}	the observed maximum plasma concentration following a single dose
AUC	area under the plasma concentration time curve; calculated by $AUC_{(0-t)}$ and then extrapolated to infinity by the addition of (C_{last} / λ_z)
$AUC_{(0-t)}$	area under the plasma concentration time curve from time zero to the last quantifiable plasma concentration (C_{last}); calculated using the linear trapezoidal rule
$t_{1/2,\lambda z}$	half-life associated with the terminal slope (λ_z) of a semi logarithmic plasma concentration-time curve; calculated as ln(2)/λ_z
t_{max}	the time to reach the observed maximum plasma concentration following a single dose
λ_z	terminal elimination rate constant, calculated by log-linear regression of the terminal portion of the concentration time profile where there are sufficient data (a minimum of 3 plasma concentration values in the terminal log-linear phase, spanning an interval of at least 2 half-lives)
CL/F	apparent oral clearance, calculated as Dose/AUC; (parent compounds only)

6.1.2 Calculation or derivation of pharmacodynamic variables

Not applicable

6.1.3 Calculation or derivation of pharmacokinetics

C_{max} and t_{max} for each volunteer will be determined by inspection of the plasma concentration-time profile. The λ_z will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data (a minimum of 3 plasma concentration values in the terminal log-linear phase, spanning an interval of at least 2 half-lives.) Terminal elimination half-life ($t_{½\lambda z}$) will be calculated as 0.693/λ_z. The $AUC_{(0-t)}$ will be calculated by the linear trapezoidal rule ($AUC = AUC_{(0-t)} + C_{last}/\lambda_z$). $AUC_{(0-t)}$ will be extrapolated to infinity using λ_z to obtain AUC where there are sufficient data. Following the single dose administration of rosuvastatin, atorvastatin and simvastatin, the CL/F will be calculated as Dose/AUC.

6.2 Safety evaluation

6.2.1 Calculation or derivation of safety variables

Safety and tolerability will be assessed by the incidence and severity of AEs, clinical laboratory parameters (hematology, clinical chemistry, urinalysis), vital signs measurements, and physical examination findings.

Where standard summary statistics are referenced below, this will include the mean, standard deviation, median, minimum and maximum for continuous variables, and counts and percentages for discrete variables.

6.2.1.1 Adverse events

Adverse events will be summarized by System Organ Class and Preferred Term, using medical dictionary for regulatory activities (MedDRA). All adverse event data will be listed for all volunteers. Separate listings of all serious adverse events, deaths or other significant adverse events will be presented.

Safety data will be summarized and listed by study medications and ethnic groups.

6.2.1.2 Laboratory data

All laboratory safety data, incorporating hematology, clinical chemistry, and urinalysis data will be listed, with deviations from the normal range explicitly noted on the listings.

Continuous laboratory data will be summarized using standard summary statistics. Both absolute values and change from pre-dose baseline will be summarized.

Discrete laboratory data will be summarized using standard summary statistics.

6.2.1.3 Vital signs

Vital signs data will summarized and listed using standard summary statistics. Both absolute values and change from pre-dose baseline will be summarized. In addition, mean plots showing change within treatment group across time will be produced for absolute values.

6.2.1.4 Physical examination

Physical examination abnormalities will be listed.

6.3 Genetics as a co-variate

Not applicable

6.4 Statistical methods and determination of sample size

6.4.1 Statistical evaluation

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized before database lock.

6.4.2 Description of variables in relation to hypotheses

The primary question is whether the magnitude of the ethnic effect (Chinese or Japanese vs Caucasian) is equivalent when atorvastatin is compared to rosuvastatin or when simvastatin is compared to rosuvastatin. The test statistics are the ratios of the primary parameter rations. For AUC, for example, the ratios are:

- [AUC(Chinese)/AUC(Caucasian)]Atorvastatin / [AUC(Chinese) / AUC(Caucasian)]Rosuvastatin
- [AUC(Japanese)/AUC(Caucasian)]Atorvastatin / [AUC(Japanese) / AUC(Caucasian)]Rosuvastatin
- [AUC(Chinese)/AUC(Caucasian)]Simvastatin / [AUC(Chinese) / AUC(Caucasian)]Rosuvastatin
- [AUC(Japanese)/AUC(Caucasian)] Simvastatin / [AUC(Japanese) / AUC(Caucasian)]Rosuvastatin

Ratios of C_{max} ratios and $AUC_{(0-t)}$ ratios will also be examined.

6.4.3 Description of analysis sets

Statistical analyses for pharmacokinetic parameters will be performed on the evaluable population. A volunteer is considered evaluable if the volunteer satisfied the inclusion and exclusion criteria, completed the study, and had no major protocol deviation or violation.

All volunteers who received at least one dose of study medication will be included in the safety analysis.

6.4.4 Methods of statistical analyses

All demographic and baseline data, including medications, will be listed and summarized using standard summary statistics for continuous variables and frequency counts and percentages for categorical variables.

Pharmacokinetic data, C_{max}, $AUC_{(0-t)}$, and AUC, $t_{½\lambda z,}$ λ_z and CL/F, of each study medication will be summarized for each ethnic group using descriptive statistics, including geometric means and coefficient of variation, and listed. In addition, 95% confidence intervals (CI) for the mean pharmacokinetic parameters will also be presented. Time to peak plasma concentration, $t_{max,}$ will be summarized using the median value and range for each ethnic group.

Log-transformed C_{max}, $AUC_{(0-t),}$ and AUC will be analyzed using a mixed model with the fixed effect of ethnicity, sequence, treatment, and period and random effect subject. Appropriate contrasts and their 90% CIs will be produced from the model, these estimates will then be anti-log transformed to obtain the geometric means and their 90% CIs for the

quantities of interest. In addition, 95% confidence intervals (CI) for the mean pharmacokinetic parameters will also be presented.

6.4.5 Determination of sample size

For AUC, using the equivalence margin of 30% (0.7 to 1.43), an expected ratio of 1, and 90% power to conclude equivalence, the sample size for each group is 27. Approximately 30 volunteers will be recruited to each ethnic group.

6.5 Interim analyses

Not applicable

6.6 Data monitoring committee

Not applicable

7. ETHICS

7.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enroll any volunteer into the study.

The principal investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit volunteers for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

The principal investigator is also responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the principal investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

For the genetic aspect of this study, approval must be obtained for this genetic research and the associated genetic informed consent from the IRB. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any volunteer participates in this genetic research.

7.2 Ethical conduct of the study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

7.3 Informed Consent

The principal investigator will ensure that the volunteer is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Volunteers must also be notified that they are free to discontinue from the study at any time. The volunteer should be given the opportunity to ask questions and allowed time to consider the information provided.

The volunteer's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator must store the original, signed Informed Consent Form. A copy of the Informed Consent Form must be given to the volunteer.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

To participate in the genetic component of the study the volunteer must sign and date both the consent form for the main study (non-genetic components of the study) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the volunteer and the original filed at the study center. The principal investigator(s) is responsible for ensuring that consent is given freely and that the volunteer understands that they may freely discontinue the genetic aspect of the study at any time.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

7.4 Subject data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, volunteers will authorize the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All computer processed data by AstraZeneca may be identified by study code, enrollment codes, randomization codes, and/or initials.

The Master Informed Consent Form will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, or an IRB/Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including volunteers' medical history.

All data protection and confidentiality principles, described in the main study protocol, are applicable to this genetic research.

Reference to participation in this genetic research should not be recorded into the volunteers' general medical records. All notes should be kept within the clinical study records.

Due to the exploratory nature of this genetic research, there will be no routine communication of results to volunteers. AstraZeneca will not provide individual genotype results to volunteers, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the volunteer, however, it must be recognized that there are exceptional circumstances where individuals may see both genetic data and a volunteer's personal identifier, for example in the case of a medical emergency, when AstraZeneca physicians and investigators might know the volunteers' identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

8. PROCEDURES IN CASE OF EMERGENCY OR PREGNANCY

8.1 AstraZeneca emergency contact procedure

In the case of a medical emergency, contact AstraZeneca personnel shown below.

•

For Serious Adverse event reporting

- Drug Safety Fax

8.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.3.**

8.3 Procedures in case of pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the volunteer was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

9. REFERENCES

None

Appendix A
Signatures

Appendix A
Drug Substance Rosuvastatin calcium
Study Code D3560C00004
Appendix Edition Number 1

ASTRAZENECA SIGNATURE(S)

A phase I, randomized, open label, single dose, 3-way crossover pharmacokinetic study comparing plasma exposure of rosuvastatin calcium, atorvastatin calcium, and simvastatin in healthy Chinese, Japanese, and Caucasian volunteers.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

ASTRAZENECA SIGNATURE(S)

A phase I, randomized, open label, single dose, 3-way crossover pharmacokinetic study comparing plasma exposure of rosuvastatin calcium, atorvastatin calcium, and simvastatin in healthy Chinese, Japanese, and Caucasian volunteers.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development
site representative

SIGNATURE OF PRINCIPAL INVESTIGATOR

A phase I, randomized, open label, single dose, 3-way crossover pharmacokinetic study comparing plasma exposure of rosuvastatin calcium, atorvastatin calcium, and simvastatin in healthy Chinese, Japanese, and Caucasian volunteers.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Centre No.: 001

Signature:

Clinical Pharmacology Study Protocol: Appendix B

Drug Substance	Rosuvastatin calcium
Study Code	D3560C00004
Appendix Edition Number	1
Appendix Date	

Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Pharmacology	Study Protocol Appendix C
Drug Substance	Rosuvastatin calcium
Study Code	D3560C00004
Appendix Edition Number	1
Appendix Date	

Appendix C
Preparation of buffer solution for rosuvastatin plasma samples

1. STEP 1 – PREPARE 0.1 M ACETIC ACID

To a 1 liter volumetric flask containing approximately 500 mLs of HPLC water, add 5.75 mLs of concentrated glacial acetic acid. Mix thoroughly and fill to volume with HPLC water.

2. STEP 2 – PREPARE 0.1 M SODIUM ACETATE

To a 500 mL volumetric flask containing approximately 200 mLs of HPLC water, add 6.8 grams of sodium acetate trihydrate. Mix to dissolve and fill to volume with HPLC water

3. STEP 3 – PREPARE BUFFER

In a large beaker, combine 820 mLs of 0.1 M acetic acid and 180 mLs of 0.1 M sodium acetate. Adjust to pH 4.0 with 0.1 M sodium acetate.

Store final buffers in a 1-liter plastic screw cap container. Label with a 1-month expiration, store at 4°C.

Clinical Pharmacology Study Protocol: Appendix D	
Drug Substance	Rosuvastatin calcium
Study Code	D3560C00004
Appendix Edition Number	1
Appendix Date	

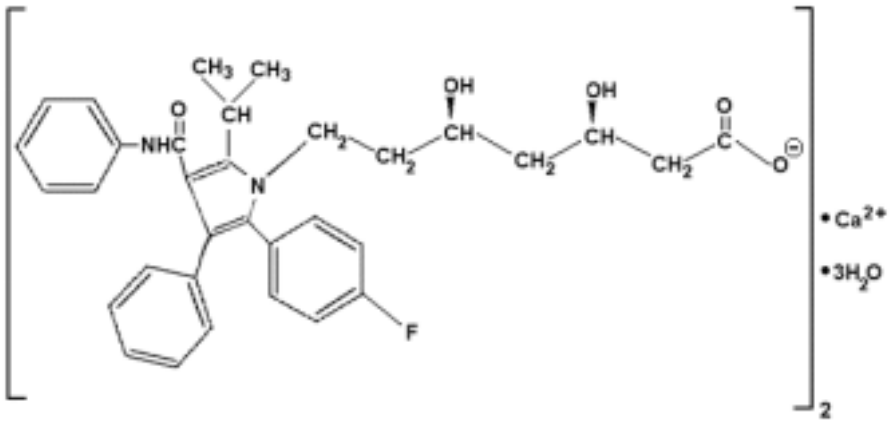
Appendix D
Atorvastatin Professional Information Brochure

Lipitor®
(Atorvastatin Calcium)
Tablets

DESCRIPTION

LIPITOR® (atorvastatin calcium) is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, ι-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \bullet 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

LIPITOR tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

CLINICAL PHARMACOLOGY

Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; LIPITOR also reduces LDL production and the number of LDL particles. LIPITOR reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

LIPITOR reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. LIPITOR also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. LIPITOR reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. LIPITOR reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for

coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Pharmacodynamics

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response (see DOSAGE AND ADMINISTRATION).

Pharmacokinetics and Drug Metabolism

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see DOSAGE AND ADMINISTRATION).

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is Ó98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk (see CONTRAINDICATIONS, Pregnancy and Lactation, and PRECAUTIONS, Nursing Mothers).

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme (see PRECAUTIONS, Drug Interactions). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo

enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age Ó65 years) than in young adults.Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults (see PRECAUTIONS section; Geriatric Use subsection).

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with LIPITOR between men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Insufficiency: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease (see CONTRAINDICATIONS).

Clinical Studies

Prevention of Cardiovascular Disease

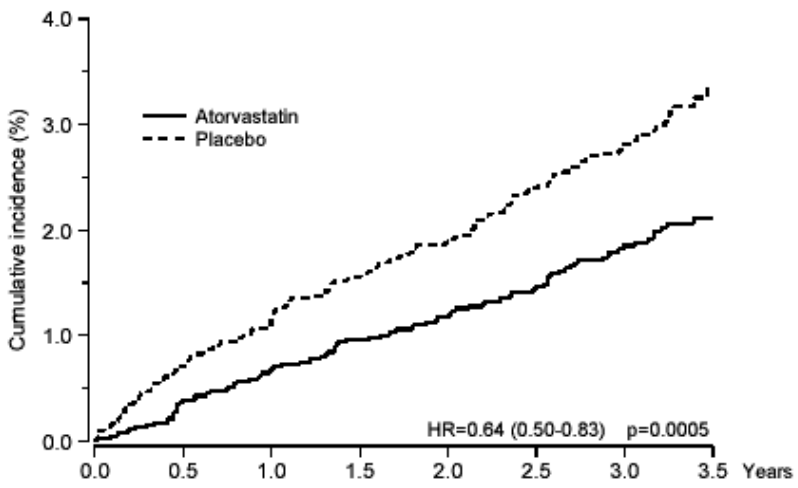
In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of LIPITOR (atorvastatin calcium) on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels Ò251 mg/dl (6.5 mmol/l). Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG

abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either LIPITOR 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of LIPITOR on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs 40 events in the LIPITOR group) or nonfatal MI (108 events in the placebo group vs 60 events in the LIPITOR group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for LIPITOR vs 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity or presence of renal dysfunction. The effect of LIPITOR was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 1: Effect of LIPITOR 10 mg/day on Cumulative Incidence of Nonfatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



LIPITOR also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for LIPITOR and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

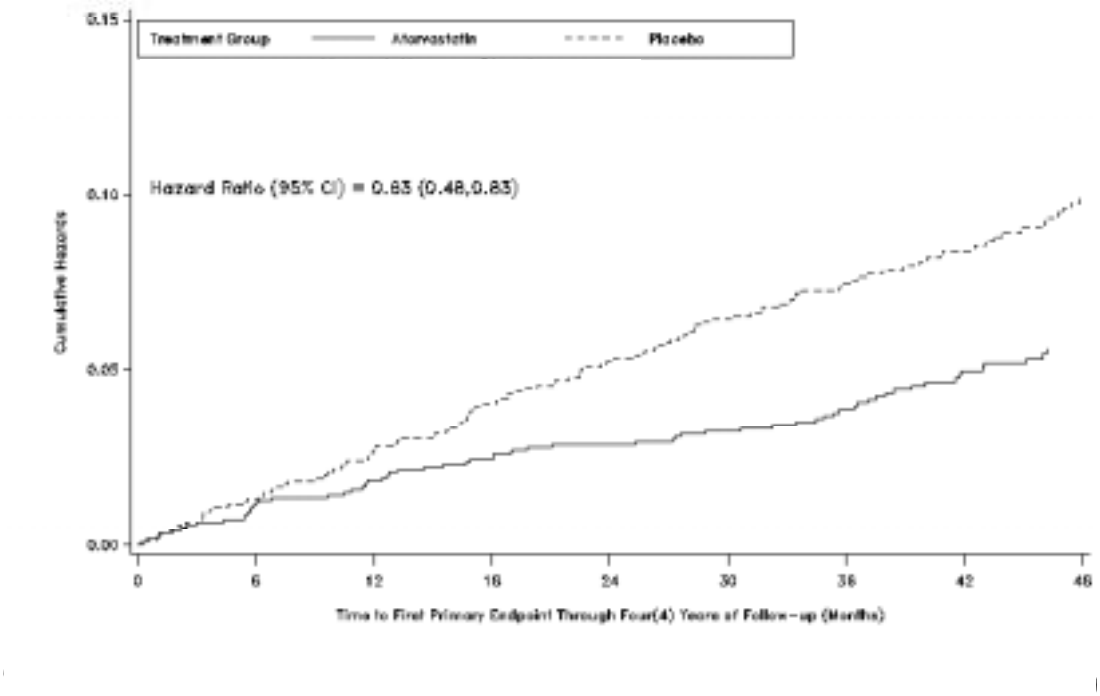
In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of LIPITOR (atorvastatin calcium) on cardiovascular disease (CVD) endpoints was assessed in 2838

subjects (94% White, 68% male), ages 40-75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDLΩ160 mg/dL and TG Ω600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either LIPITOR 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA_{1c} 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52mg/dL.
The effect of LIPITOR 10 mg/ day on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the LIPITOR group vs 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48,0.83) (p=0.001) (see Figure 2). An effect of LIPITOR was seen regardless of age, sex, or baseline lipid levels.

Figure 2. Effect of LIPITOR 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS.



LIPITOR significantly reduced the risk of stroke by 48% (21 events in the LIPITOR group vs 39 events in the placebo group), HR 0.52, 95% CI (0.31,0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the LIPITOR group vs 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86) (p=0.007). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the LIPITOR group vs 82 deaths in the placebo group, (HR 0.73, p=0.059).

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

LIPITOR reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

LIPITOR is effective in a wide variety of patient populations with hypercholesterolemia, with and without hypertriglyceridemia, in men and women, and in the elderly. Experience in pediatric patients has been limited to patients with homozygous FH. In two multicenter, placebo-controlled, dose-response studies in patients with hypercholesterolemia, LIPITOR given as a single dose over 6 weeks significantly reduced total-C, LDL-C, apo B, and TG (Pooled results are provided in Table 1).

TABLE 1. Dose-Response in Patients With Primary Hypercholesterolemia (Adjusted Mean % Change From Baseline)[a]

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

[a] Results are pooled from 2 dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25^{th} and 75^{th} percentile) percent changes from baseline in HDL-C for atorvastatin 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7(0, 17), 7.8(0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hypercholesterolemia, LIPITOR was compared to other HMG-CoA reductase inhibitors. After randomization, patients were treated for 16 weeks with either LIPITOR 10 mg per day or a fixed dose of the comparative agent (Table 2).

TABLE 2. Mean Percent Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	- 6	+7	-28
95% CI for Diff[1]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	- 9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[1] A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.

[a] Significantly different from lovastatin, ANCOVA, p Ω0.05

[b] Significantly different from pravastatin, ANCOVA, p Ω0.05

[c] Significantly different from simvastatin, ANCOVA, p Ω0.05

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 2 is not known. Table 2 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

Hypertriglyceridemia *(Fredrickson* Type IV)

The response to LIPITOR in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below. For the atorvastatin-treated patients, median (min, max) baseline TG level was 565 (267-1502).

TABLE 3. Combined Patients With Isolated Elevated TG: Median (min, max) Percent Changes From Baseline

	Placebo (N=12)	Atorvastatin 10 mg (N=37)	Atorvastatin 20 mg (N=13)	Atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

Dysbetalipoproteinemia *(Fredrickson* Type III)

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia *(Fredrickson* Type III) are shown in the table below.

TABLE 4. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

		Median % Change (min, max)	
	Median (min, max) at Baseline (mg/dL)	Atorvastatin 10 mg	Atorvastatin 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of LIPITOR. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia were randomized to LIPITOR (n=140) or placebo (n=47) for 26 weeks and then all received LIPITOR for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ∅190 mg/dL or 2) a baseline LDL-C ∅160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5-385.0 mg/dL) in the LIPITOR group compared to 230.0 mg/dL (range: 160.0-324.5 mg/dL) in the placebo group. The dosage of LIPITOR (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of LIPITOR-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

LIPITOR significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see Table 5).

TABLE 5
Lipid-altering Effects of LIPITOR in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia
(Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
LIPITOR	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the LIPITOR group compared to 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26 week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of LIPITOR therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

INDICATIONS AND USAGE

Prevention of Cardiovascular Disease
In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

Hypercholesterolemia
LIPITOR is indicated:

1. as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia *(Fredrickson* Types IIa and IIb);

2. as an adjunct to diet for the treatment of patients with elevated serum TG levels*(Fredrickson* Type IV);

3. for the treatment of patients with primary dysbetalipoproteinemia *(Fredrickson* Type III) who do not respond adequately to diet;

4. to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable;

5. as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

   a. LDL-C remains ∅190 mg/dL or
   b. LDL-C remains ∅160 mg/dL and:
      ∉# there is a positive family history of premature cardiovascular disease or
      ∉# two or more other CVD risk factors are present in the pediatric patient

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate (see *National Cholesterol Education Program (NCEP) Guidelines,* summarized in Table 6).

TABLE 6. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL-C Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD [a] or CHD risk equivalents (10-year risk >20%)	<100	∅100	∅130 (100-129: drug optional) [b]
2+ Risk Factors (10-year risk Ω20%)	<130	∅130	10-year risk 10%-20%: ∅130 10-year risk <10%: ∅160
0-1 Risk factor [c]	<160	∅160	∅190 (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease

[b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of < 100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ∅200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Prior to initiating therapy with LIPITOR, secondary causes for hypercholesterolemia (eg, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 x [TG] + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

LIPITOR has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons *(Fredrickson* Types I and V).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	∅200	∅130

CONTRAINDICATIONS

Active liver disease or unexplained persistent elevations of serum transaminases.

Hypersensitivity to any component of this medication.

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Dysfunction

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS).

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and

should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions

The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle).

Antacid: When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine.

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle).

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli,* the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS

Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100

mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2).

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. LIPITOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking LIPITOR, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers

Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with LIPITOR had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls (see CLINICAL PHARMACOLOGY, Clinical Studies section; ADVERSE REACTIONS, Pediatric Patients (ages 10-17 years); and DOSAGE AND ADMINISTRATION, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on LIPITOR therapy (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). **LIPITOR has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients (see

CLINICAL PHARMACOLOGY, Clinical Studies: Homozygous Familial Hypercholesterolemia).

Geriatric Use

The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1,958 patients initiated therapy with atorvastatin 10 mg. Of these, 835 were elderly (≥65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was –38.2% in the elderly patients versus –34.6% in the non-elderly group.

The rates of discontinuation due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain.

Clinical Adverse Experiences

Adverse experiences reported in Ó2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 7.

TABLE 7. Adverse Events in Placebo-Controlled Studies
(% of Patients)

BODY SYSTEM/ Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
In ASCOT (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 10,305 participants treated with LIPITOR 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with LIPITOR was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)
In CARDS (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 2838 subjects with type 2 diabetes treated with LIPITOR 10 mg daily (n=1428) or placebo (n=1410), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in italics occurred in Ó2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: *Chest pain,* face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

Digestive System: *Nausea,* gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System: *Bronchitis, rhinitis,* pneumonia, dyspnea, asthma, epistaxis.

Nervous System: *Insomnia, dizziness,* paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

Musculoskeletal System: *Arthritis,* leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System: *Urinary tract infection, hematuria, albuminuria,* urinary frequency, cystitis, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: *Peripheral edema,* hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

Postintroduction Reports

Adverse events associated with LIPITOR therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following:

anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, and fatigue.

Pediatric Patients (ages 10-17 years)
In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of LIPITOR 10 to 20 mg daily was generally similar to that of placebo (see CLINICAL PHARMACOLOGY, Clinical Studies section and PRECAUTIONS, Pediatric Use).

OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving LIPITOR and should continue on this diet during treatment with LIPITOR.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

The recommended starting dose of LIPITOR is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of LIPITOR is 10 to 80 mg once daily. LIPITOR can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of LIPITOR should be individualized according to patient characteristics such as goal of therapy and response (see *NCEP Guidelines*, summarized in Table 5). After initiation and/or upon titration of LIPITOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)
The recommended starting dose of LIPITOR is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[1], CLINICAL PHARMACOLOGY, and

[1] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children Adolescents, *Pediatrics.* 89(3):495-501. 1992.

INDICATIONS AND USAGE). Adjustments should be made at intervals of 4 weeks or more.

Homozygous Familial Hypercholesterolemia

The dosage of LIPITOR in patients with homozygous FH is 10 to 80 mg daily. LIPITOR should be used as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) in these patients or if such treatments are unavailable.

Concomitant Therapy

Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS, Skeletal Muscle, and PRECAUTIONS, Drug Interactions for other drug-drug interactions).

Dosage in Patients With Renal Insufficiency

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HOW SUPPLIED

LIPITOR® (atorvastatin calcium) is supplied as white, elliptical, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin.

10 mg tablets: coded “PD 155” on one side and “10” on the other.
NDC 0071-0155-23 bottles of 90
NDC 0071-0155-34 bottles of 5000
NDC 0071-0155-40 10 x 10 unit dose blisters

20 mg tablets: coded “PD 156” on one side and “20” on the other.
NDC 0071-0156-23 bottles of 90
NDC 0071-0156-40 10 x 10 unit dose blisters
NDC 0071-0156-94 bottles of 5000

40 mg tablets: coded “PD 157” on one side and “40” on the other.
NDC 0071-0157-23 bottles of 90
NDC 0071-0157-73 bottles of 500

80 mg tablets: coded “PD 158” on one side and “80” on the other.
NDC 0071-0158-23 bottles of 90
NDC 0071-0158-73 bottles of 500

Storage
Store at controlled room temperature 20 - 25°C (68 - 77°F) [see USP].

Rx Only

Manufactured by:
Pfizer Ireland Pharmaceuticals
Dublin, Ireland

LAB-0021-9.0 Revised September 2005

Clinical Pharmacology Study Protocol: Appendix E	
Drug Substance	Rosuvastatin calcium
Study Code	D3560C00004
Appendix Edition Number	1
Appendix Date	

Appendix E
Simvastatin Professional Information Brochure

TABLETS

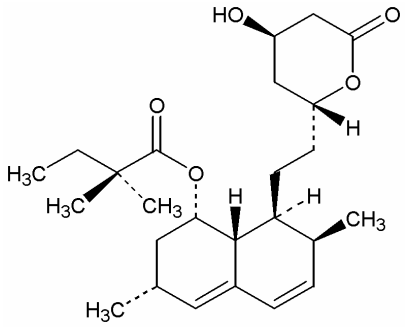
ZOCOR®

(SIMVASTATIN)

DESCRIPTION

ZOCOR[1] (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding η-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1ζ,3ζ,7η,8η(2*S**,4*S**),-8aη]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:



Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and other ingredients. Butylated hydroxyanisole is added as a preservative.

CLINICAL PHARMACOLOGY

Epidemiological studies have demonstrated that elevated levels of total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), as well as decreased levels of high-density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis and increased cardiovascular risk. Lowering LDL-C decreases this risk. However, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding η-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the η-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. Plasma concentrations of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Since simvastatin undergoes extensive first-pass extraction in the liver, the availability of the drug to the general circulation is low (<5%).

[1] Registered trademark of MERCK & CO., Inc.

Both simvastatin and its η-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Rat studies indicate that when radiolabeled simvastatin was administered, simvastatin-derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the η-hydroxyacid of simvastatin and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. While the recommended therapeutic dose range is 5 to 80 mg/day, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

In a study including 16 elderly patients between 70 and 78 years of age who received ZOCOR 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age. Clinical study experience in the elderly (n=1522), suggests that there were no overall differences in safety between elderly and younger patients (see PRECAUTIONS, *Geriatric Use*).

Kinetic studies with another reductase inhibitor, having a similar principal route of elimination, have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

In a study of 12 healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Gemfibrozil: Coadministration of gemfibrozil (600 mg twice daily for 3 days) with simvastatin (40 mg daily) resulted in clinically significant increases in simvastatin acid AUC (185%) and C_{max} (112%), possibly due to inhibition of simvastatin acid glucuronidation by gemfibrozil (see WARNINGS, *Myopathy/Rhabdomyolysis*, PRECAUTIONS, *Drug Interactions*, DOSAGE AND ADMINISTRATION).

Fenofibrate: Coadministration of fenofibrate (160 mg daily) with ZOCOR (80 mg daily) for 7 days had no effect on plasma AUC (and C_{max}) of either total HMG-CoA reductase inhibitory activity or fenofibric acid; there was a modest reduction (approximately 35%) of simvastatin acid which was not considered clinically significant (see WARNINGS, *Myopathy/Rhabdomyolysis*, PRECAUTIONS, *Drug Interactions*).

Simvastatin is a substrate for CYP3A4 (see PRECAUTIONS, *Drug Interactions*). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study[2], 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with, and 30 and 90 minutes following, a single dose of 60 mg simvastatin on the third day. This regimen of grapefruit juice resulted in mean increases in the concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [measured using a radioenzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 2.4-fold and 3.6-fold, respectively, and of simvastatin and its η-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 16-fold and 7-fold, respectively. In a second study, 16 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 20 mg simvastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using a validated enzyme inhibition assay different from that used in the first[2] study, both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.13-fold and 1.18-fold, respectively, and of simvastatin and its η-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of

[2] Lilja JJ, Kivisto KT, Neuvonen PJ. Clin Pharmacol Ther 1998;64(5):477-83.

1.88-fold and 1.31-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.

Clinical Studies in Adults

Reductions in Risk of CHD Mortality and Cardiovascular Events

In 4S, the effect of therapy with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with standard care, including diet, and either ZOCOR 20-40 mg/day (n=2,221) or placebo (n=2,223) for a median duration of 5.4 years. After six weeks of treatment with ZOCOR the median (25^{th} and 75^{th} percentile) changes in LDL-C, TG, and HDL-C were -39% (-46, -31%), -19% (-31, 0%), and 6% (-3, 17%). Over the course of the study, treatment with ZOCOR led to mean reductions in total-C, LDL-C and TG of 25%, 35%, and 10%, respectively, and a mean increase in HDL-C of 8%. ZOCOR significantly reduced the risk of mortality by 30% (p=0.0003, 182 deaths in the ZOCOR group vs 256 deaths in the placebo group). The risk of CHD mortality was significantly reduced by 42% (p=0.00001, 111 vs 189 deaths). There was no statistically significant difference between groups in non-cardiovascular mortality. ZOCOR also significantly decreased the risk of having major coronary events (CHD mortality plus hospital-verified and silent non-fatal myocardial infarction [MI]) by 34% (p<0.00001, 431 vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (p<0.00001, 252 vs 383 patients). Furthermore, ZOCOR significantly reduced the risk of fatal plus non-fatal cerebrovascular events (combined stroke and transient ischemic attacks) by 28% (p=0.033, 75 vs 102 patients). ZOCOR reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels. Because there were only 53 female deaths, the effect of ZOCOR on mortality in women could not be adequately assessed. However, ZOCOR significantly lessened the risk of having major coronary events by 34% (60 vs 91 women with one or more event). The randomization was stratified by angina alone (21% of each treatment group) or a previous MI. Because there were only 57 deaths among the patients with angina alone at baseline, the effect of ZOCOR on mortality in this subgroup could not be adequately assessed. However, trends in reduced coronary mortality, major coronary events and revascularization procedures were consistent between this group and the total study cohort. Additionally, in this study, 1,021 of the patients were 65 and older. Cholesterol reduction with simvastatin resulted in similar decreases in relative risk for total mortality, CHD mortality, and major coronary events in these elderly patients, compared with younger patients.

The Heart Protection Study (HPS) was a large, multi-center, placebo-controlled, double-blind study with a mean duration of 5 years conducted in 20,536 patients (10,269 on ZOCOR 40 mg and 10,267 on placebo). Patients were allocated to treatment using a covariate adaptive method[3] which took into account the distribution of 10 important baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients had a mean age of 64 years (range 40-80 years), were 97% Caucasian and were at high risk of developing a major coronary event because of existing coronary heart disease (65%), diabetes (Type 2, 26%; Type 1, 3%), history of stroke or other cerebrovascular disease (16%), peripheral vessel disease (33%), or hypertension in males 65 years of age and older (6%). At baseline, 3,421 patients (17%) had LDL-C levels below 100 mg/dL, of whom 953 (5%) had LDL-C levels below 80 mg/dL; 7,068 patients (34%) had levels between 100 and 130 mg/dL; and 10,047 patients (49%) had levels greater than 130 mg/dL.

The HPS results showed that ZOCOR 40 mg/day significantly reduced: total and CHD mortality; non-fatal myocardial infarctions, stroke, and revascularization procedures (coronary and non-coronary) (see Table 1).

[3] D.R. Taves, Minimization: a new method of assigning patients to treatment and control groups. Clin. Pharmacol. Ther. **15** (1974), pp. 443-453

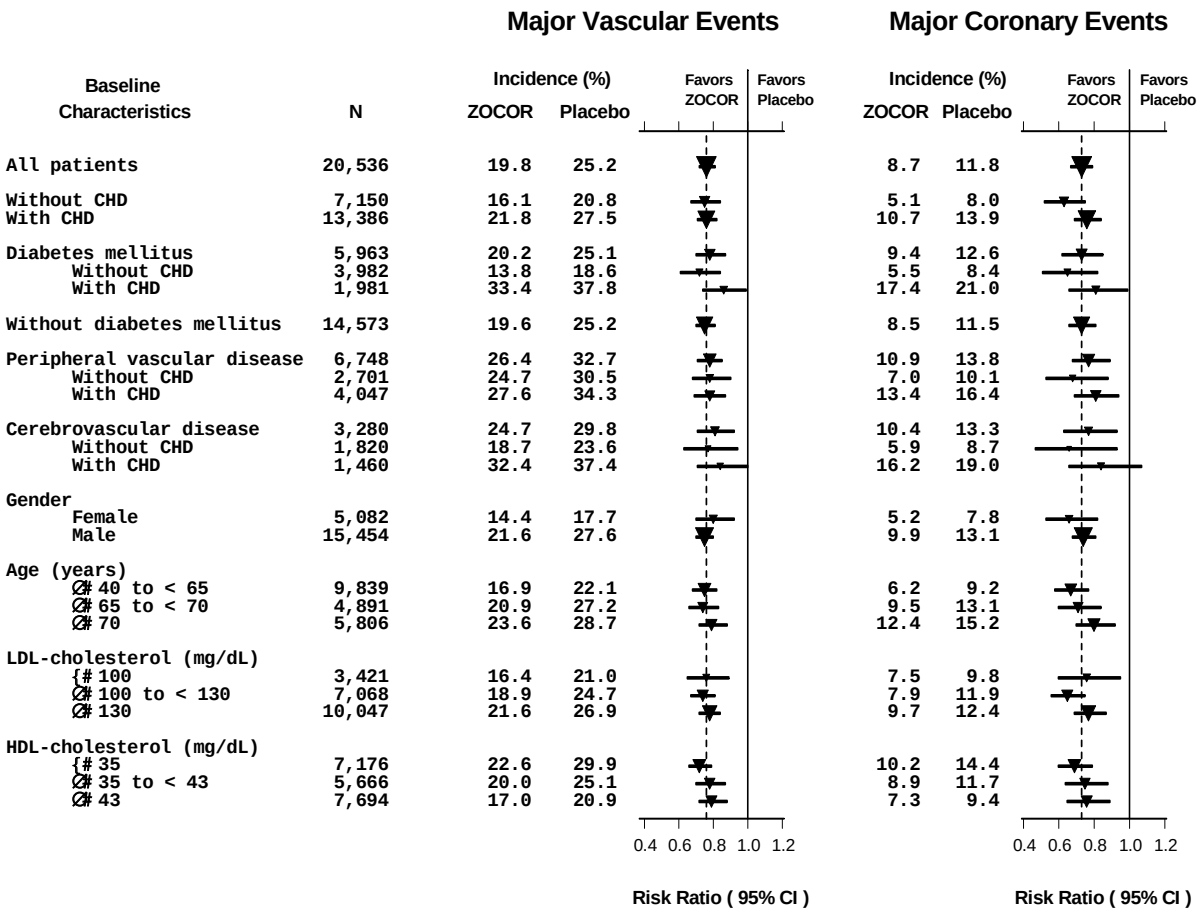
TABLE 1
Summary of Heart Protection Study Results

Endpoint	ZOCOR (N=10,269) n (%)†	Placebo (N=10,267) n (%)†	Risk Reduction (%) (95% CI)	p-Value
Primary				
Mortality	1,328 (12.9)	1,507 (14.7)	13 (6-19)	p=0.0003
CHD mortality	587 (5.7)	707 (6.9)	18 (8-26)	p=0.0005
Secondary				
Non-fatal MI	357 (3.5)	574 (5.6)	38 (30-46)	p<0.0001
Stroke	444 (4.3)	585 (5.7)	25 (15-34)	p<0.0001
Tertiary				
Coronary revascularization	513 (5)	725 (7.1)	30 (22-38)	p<0.0001
Peripheral and other non-coronary revascularization	450 (4.4)	532 (5.2)	16 (5-26)	p=0.006

† n = number of patients with indicated event

Two composite endpoints were defined in order to have sufficient events to assess relative risk reductions across a range of baseline characteristics (see Figure 1). A composite of major coronary events (MCE) was comprised of CHD mortality and non-fatal MI (analyzed by time-to-first event; 898 patients treated with ZOCOR had events and 1,212 patients on placebo had events). A composite of major vascular events (MVE) was comprised of MCE, stroke and revascularization procedures including coronary, peripheral and other non-coronary procedures (analyzed by time-to-first event; 2,033 patients treated with ZOCOR had events and 2,585 patients on placebo had events). Significant relative risk reductions were observed for both composite endpoints (27% for MCE and 24% for MVE, p<0.0001). Furthermore, treatment with ZOCOR produced significant relative risk reductions for all components of the composite endpoints. The risk reductions produced by ZOCOR in both MCE and MVE were evident and consistent regardless of cardiovascular disease related medical history at study entry (i.e., CHD alone; or peripheral vascular disease, cerebrovascular disease, diabetes or treated hypertension, with or without CHD), gender, age, creatinine levels up to the entry limit of 2.3 mg/dL, baseline levels of LDL-C, HDL-C, apolipoprotein B and A-1, baseline concomitant cardiovascular medications (i.e., aspirin, beta blockers, or calcium channel blockers), smoking status, alcohol intake, or obesity. Diabetics showed risk reductions for MCE and MVE due to ZOCOR treatment regardless of baseline HbA1c levels or obesity with the greatest effects seen for diabetics without CHD.

Figure 1
The Effects of Treatment with ZOCOR on Major Vascular Events and Major Coronary Events in HPS



N= number of patients in each subgroup. The inverted triangles are point estimates of the relative risk, with their 95% confidence intervals represented as a line. The area of a triangle is proportional to the number of patients with MVE or MCE in the subgroup relative to the number with MVE or MCE, respectively, in the entire study population. The vertical solid line represents a relative risk of one. The vertical dashed line represents the point estimate of relative risk in the entire study population.

Angiographic Studies

In the Multicenter Anti-Atheroma Study, the effect of simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic patients with coronary heart disease. In this randomized, double-blind, controlled study, patients were treated with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. The co-primary study endpoints were mean change per-patient in minimum and mean lumen diameters, indicating focal and diffuse disease, respectively. Simvastatin significantly slowed the progression of lesions as measured in the Year 4 angiogram by both parameters, as well as by change in percent diameter stenosis. In addition, simvastatin significantly decreased the proportion of patients with new lesions and with new total occlusions.

Modifications of Lipid Profiles

Primary Hypercholesterolemia (Fredrickson type IIa and IIb)

ZOCOR has been shown to be highly effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during chronic therapy. ZOCOR consistently and significantly decreased total-C, LDL-C, total-C/HDL-C ratio, and LDL-C/HDL-C ratio; ZOCOR also decreased TG and increased HDL-C (see Table 2).

TABLE 2
Mean Response in Patients with Primary Hypercholesterolemia and Combined (mixed) Hyperlipidemia
(Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG[†]
Lower Dose Comparative Study [‡] (Mean % Change at Week 6)					
ZOCOR 5 mg q.p.m.	109	-19	-26	10	-12
ZOCOR 10 mg q.p.m.	110	-23	-30	12	-15
Scandinavian Simvastatin Survival Study [§] (Mean % Change at Week 6)					
Placebo	2223	-1	-1	0	-2
ZOCOR 20 mg q.p.m.	2221	-28	-38	8	-19
Upper Dose Comparative Study [‖] (Mean % Change Averaged at Weeks 18 and 24)					
ZOCOR 40 mg q.p.m.	433	-31	-41	9	-18
ZOCOR 80 mg q.p.m.	664	-36	-47	8	-24
Multi-Center Combined Hyperlipidemia Study [¶] (Mean % Change at Week 6)					
Placebo	125	1	2	3	-4
ZOCOR 40 mg q.p.m.	123	-25	-29	13	-28
ZOCOR 80 mg q.p.m.	124	-31	-36	16	-33

[†] median percent change
[‡] mean baseline LDL-C 244 mg/dL and median baseline TG 168 mg/dL
[§] mean baseline LDL-C 188 mg/dL and median baseline TG 128 mg/dL
[‖] mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL
[¶] mean baseline LDL-C 156 mg/dL and median baseline TG 391 mg/dL.

In the Upper Dose Comparative Study, the mean reduction in LDL-C was 47% at the 80-mg dose. Of the 664 patients randomized to 80 mg, 475 patients with plasma TG Ω200 mg/dL had a median reduction in TG of 21%, while in 189 patients with TG > 200 mg/dL, the median reduction in TG was 36%. In these studies, patients with TG > 350 mg/dL were excluded.

Hypertriglyceridemia (Fredrickson type lV)

The results of a subgroup analysis in 74 patients with type lV hyperlipidemia from a 130-patient, double-blind, placebo-controlled, 3-period crossover study are presented in Table 3.

TABLE 3
Six-week, Lipid-lowering Effects of Simvastatin in Type lV Hyperlipidemia
Median Percent Change (25th and 75th percentile) from Baseline[†]

TREATMENT	N	Total-C	LDL-C	HDL-C	TG	VLDL-C	Non-HDL-C
Placebo	74	+2 (-7, +7)	+1 (-8, +14)	+3 (-3, +10)	-9 (-25, +13)	-7 (-25, +11)	+1 (-9, +8)
ZOCOR 40 mg/day	74	-25 (-34, -19)	-28 (-40, -17)	+11 (+5, +23)	-29 (-43, -16)	-37 (-54, -23)	-32 (-42, -23)
ZOCOR 80 mg/day	74	-32 (-38, -24)	-37 (-46, -26)	+15 (+5, +23)	-34 (-45, -18)	-41 (-57, -28)	-38 (-49, -32)

[†] The median baseline values (mg/dL) for the patients in this study were: total-C = 254, LDL-C = 135, HDL-C = 36, TG = 404, VLDL-C = 83, and non-HDL-C = 215.

Dysbetalipoproteinemia (Fredrickson type lll)

The results of a subgroup analysis in 7 patients with type lll hyperlipidemia (dysbetalipoproteinemia) (apo E2/2) (VLDL-C/TG>0.25) from a 130-patient, double-blind, placebo-controlled, 3-period crossover study are presented in Table 4. In this study the median baseline values (mg/dL) were: total-C = 324, LDL-C = 121, HDL-C = 31, TG = 411, VLDL-C = 170, and non-HDL-C = 291.

TABLE 4
Six-week, Lipid-lowering Effects of Simvastatin in Type lll Hyperlipidemia
Median Percent Change (min,max) from Baseline

TREATMENT	N	Total-C	LDL-C + IDL	HDL-C	TG	VLDL-C+IDL	Non-HDL-C
Placebo	7	-8 (-24, +34)	-8 (-27, +23)	-2 (-21, +16)	+4 (-22, +90)	-4 (-28, +78)	-8 (-26, -39)
ZOCOR 40 mg/day	7	-50 (-66, -39)	-50 (-60, -31)	+7 (-8, +23)	-41 (-74, -16)	-58 (-90, -37)	-57 (-72, -44)
ZOCOR 80 mg/day	7	-52 (-55, -41)	-51 (-57, -28)	+7 (-5, +29)	-38 (-58, +2)	-60 (-72, -39)	-59 (-61, -46)

Homozygous Familial Hypercholesterolemia

In a controlled clinical study, 12 patients 15-39 years of age with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 divided doses. Eleven of the 12 patients had reductions in LDL-C. In those patients with reductions, the mean LDL-C changes for the 40- and 80-mg doses were 14% (range 8% to 23%, median 12%) and 30% (range 14% to 46%, median 29%), respectively. One patient had an increase of 15% in LDL-C. Another patient with absent LDL-C receptor function had an LDL-C reduction of 41% with the 80-mg dose.

Endocrine Function

In clinical studies, simvastatin did not impair adrenal reserve or significantly reduce basal plasma cortisol concentration. Small reductions from baseline in basal plasma testosterone in men were observed in clinical studies with simvastatin, an effect also observed with other inhibitors of HMG-CoA reductase and the bile acid sequestrant cholestyramine. There was no effect on plasma gonadotropin levels. In a placebo-controlled, 12-week study there was no significant effect of simvastatin 80 mg on the plasma testosterone response to human chorionic gonadotropin (hCG). In another 24-week study, simvastatin 20-40 mg had no detectable effect on spermatogenesis. In 4S, in which 4,444 patients were randomized to simvastatin 20-40 mg/day or placebo for a median duration of 5.4 years, the incidence of male sexual adverse events in the two treatment groups was not significantly different. Because of these factors, the small changes in plasma testosterone are unlikely to be clinically significant. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown.

Clinical Studies in Adolescents

In a double-blind, placebo-controlled study, 175 patients (99 adolescent boys and 76 post-menarchal girls) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (heFH) were randomized to simvastatin (n=106) or placebo (n=67) for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

ZOCOR significantly decreased plasma levels of total-C, LDL-C, and Apo B (see Table 5). Results from the extension at 48 weeks were comparable to those observed in the base study.

TABLE 5
Lipid-lowering Effects of Simvastatin in Adolescent Patients with Heterozygous Familial Hypercholesterolemia
(Mean Percent Change from Baseline)

Dosage	Duration	N		Total-C	LDL-C	HDL-C	TG†	Apo B
Placebo	24 Weeks	67	% Change from Baseline (95% CI)	1.6 (-2.2, 5.3)	1.1 (-3.4, 5.5)	3.6 (-0.7, 8.0)	-3.2 (-11.8, 5.4)	-0.5 (-4.7, 3.6)
			Mean baseline, mg/dL (SD)	278.6 (51.8)	211.9 (49.0)	46.9 (11.9)	90.0 (50.7)	186.3 (38.1)
ZOCOR	24 Weeks	106	% Change from Baseline (95% CI)	-26.5 (-29.6, -23.3)	-36.8 (-40.5, -33.0)	8.3 (4.6, 11.9)	-7.9 (-15.8, 0.0)	-32.4 (-35.9, -29.0)
			Mean baseline, mg/dL (SD)	270.2 (44.0)	203.8 (41.5)	47.7 (9.0)	78.3 (46.0)	179.9 (33.8)

† median percent change

After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the ZOCOR 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

INDICATIONS AND USAGE

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet.

Reductions in Risk of CHD Mortality and Cardiovascular Events

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles

ZOCOR is indicated to:

- Reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb[4]).
- Treat patients with hypertriglyceridemia (Fredrickson type lV hyperlipidemia).
- Treat patients with primary dysbetalipoproteinemia (Fredrickson type lll hyperlipidemia).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH)

ZOCOR is indicated as an adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolemia, if after an adequate trial of diet therapy the following findings are present:

1. LDL cholesterol remains ∅190 mg/dL; or
2. LDL cholesterol remains ∅160 mg/dL and
   - There is a positive family history of premature cardiovascular disease (CVD) or
   - Two or more other CVD risk factors are present in the adolescent patient.

The minimum goal of treatment in pediatric and adolescent patients is to achieve a mean LDL-C <130 mg/dL. The optimal age at which to initiate lipid-lowering therapy to decrease the risk of symptomatic adulthood CAD has not been determined.

General Recommendations

Prior to initiating therapy with simvastatin, secondary causes for hypercholesterolemia (e.g., hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dL (< 4.5 mmol/L), LDL-C can be estimated using the following equation:

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[4] Classification of Hyperlipoproteinemias

		Lipid Elevations	
	Lipoproteins		
Type	elevated	major	minor
I (rare)	chylomicrons	TG	⇒⇓ C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	⇒⇓ C
V (rare)	chylomicrons, VLDL	TG	⇒⇓ C

C = cholesterol, TG = triglycerides,
LDL = low-density lipoprotein,
VLDL = very-low-density lipoprotein,
IDL = intermediate-density lipoprotein.

LDL-C = total-C – [(0.20 x TG) + HDL-C]

For TG levels > 400 mg/dL (> 4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, ZOCOR is not indicated.

Lipid determinations should be performed at intervals of no less than four weeks and dosage adjusted according to the patient's response to therapy.

The NCEP Treatment Guidelines are summarized in Table 6:

TABLE 6
NCEP Treatment Guidelines:
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes
and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	∅100	∅130 (100-129: drug optional)‡
2+ Risk factors (10-year risk Ω20%)	<130	∅130	10-year risk 10-20%: ∅130 10-year risk { 10%: ∅160
0-1 Risk factor§	<160	∅160	∅190 (160-189: LDL-lowering drug optional)

† CHD, coronary heart disease
‡ Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
§ Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ∅200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge.

The NCEP classification of cholesterol levels in pediatric patients with a familial history of either hypercholesterolemia or premature cardiovascular disease is summarized in Table 7.

TABLE 7
NCEP Classification of Cholesterol Levels in Pediatric Patients
with a Familial History of Either HeFH or Premature CVD

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	∅200	∅130

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy.

ZOCOR is indicated to reduce elevated LDL-C and TG levels in patients with Type IIb hyperlipidemia (where hypercholesterolemia is the major abnormality). However, it has not been studied in conditions where the major abnormality is elevation of chylomicrons (i.e., hyperlipidemia Fredrickson types I and V).[4]

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as ZOCOR to decrease the synthesis of

cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZOCOR is contraindicated during pregnancy and in nursing mothers. **ZOCOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, ZOCOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, *Pregnancy*).

WARNINGS

Myopathy/Rhabdomyolysis

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,050 patients were treated with ZOCOR with 24,747 (approximately 60%) treated for at least 4 years, the incidence of myopathy was approximately 0.02%, 0.08% and 0.53% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

All patients starting therapy with simvastatin or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

The risk of myopathy/rhabdomyolysis is increased by concomitant use of simvastatin with the following:

Potent inhibitors of CYP3A4: Simvastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). When simvastatin is used with a potent inhibitor of CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of simvastatin.

The use of simvastatin concomitantly with the potent CYP3A4 inhibitors itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided. Concomitant use of other medicines labeled as having a potent inhibitory effect on CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin should be suspended during the course of treatment.

Gemfibrozil, particularly with higher doses of simvastatin: The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with gemfibrozil. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination.

Other lipid-lowering drugs (other fibrates or ∅1 g/day of niacin): Caution should be used when prescribing other fibrates or lipid-lowering doses (∅1 g/day) of niacin with simvastatin, as these agents can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of simvastatin with other fibrates or niacin should be carefully weighed against the potential risks of these combinations.**

Cyclosporine or danazol, with higher doses of simvastatin: The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine or danazol. The benefits of the use of simvastatin in patients receiving cyclosporine or danazol should be carefully weighed against the risks of these combinations.

Amiodarone or verapamil, with higher doses of simvastatin: The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of simvastatin at doses higher than 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone. In an analysis of clinical trials involving 25,248 patients treated with simvastatin 20 to 80 mg, the incidence of myopathy was higher in patients receiving verapamil and simvastatin (4/635; 0.63%) than in patients taking simvastatin without a calcium channel blocker (13/21,224; 0.061%).

Prescribing recommendations for interacting agents are summarized in Table 8 (see also CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions*; DOSAGE AND ADMINISTRATION).

TABLE 8
Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone	Avoid simvastatin
Gemfibrozil Cyclosporine Danazol	Do not exceed 10 mg simvastatin daily
Amiodarone Verapamil	Do not exceed 20 mg simvastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

Liver Dysfunction

Persistent increases (to more than 3X the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In 4S (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the number of patients with more than one transaminase elevation to > 3X ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to > 3X ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1,105 patients, the 12-month incidence of persistent hepatic transaminase elevation without regard to drug relationship was 0.9% and 2.1% at the 40- and 80-mg dose, respectively. No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.

It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated. Patients titrated to the 80-mg dose should receive an additional test prior to titration, 3 months after titration to the 80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding

and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3X ULN or greater persist, withdrawal of therapy with ZOCOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

PRECAUTIONS

General

Simvastatin may cause elevation of CK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Information for Patients

Patients should be advised about substances they should not take concomitantly with simvastatin and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, *Myopathy/Rhabdomyolysis*). Patients should also be advised to inform other physicians prescribing a new medication that they are taking ZOCOR.

Drug Interactions

CYP3A4 Interactions

Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of simvastatin.

See WARNINGS, *Myopathy/Rhabdomyolysis*, and CLINICAL PHARMACOLOGY, *Pharmacokinetics.*

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
Telithromycin
HIV protease inhibitors
Nefazodone
Large quantities of grapefruit juice (>1 quart daily)

Interactions with lipid-lowering drugs that can cause myopathy when given alone

See WARNINGS, *Myopathy/Rhabdomyolysis.*

The risk of myopathy is increased by gemfibrozil **(see DOSAGE AND ADMINISTRATION)** and to a lesser extent by other fibrates and niacin (nicotinic acid) (≥1 g/day).

Other drug interactions

Cyclosporine or Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol particularly with higher doses of simvastatin (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*; WARNINGS, *Myopathy/Rhabdomyolysis*).

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Propranolol: In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as

measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in

an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[5] of approximately 100 prospectively followed pregnancies in women exposed to ZOCOR or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with ZOCOR during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. ZOCOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Nursing Mothers

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population**. In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. See CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescents;* ADVERSE REACTIONS, *Adolescent Patients*; and DOSAGE AND ADMINISTRATION, *Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia*. Adolescent females should be counseled on appropriate contraceptive methods while on simvastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

Geriatric Use

A pharmacokinetic study with simvastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age. In 4S, 1,021 (23%) of 4,444 patients were 65 or older. In 4S, lipid-lowering efficacy was at least as great in elderly patients compared with younger patients. In this study, ZOCOR significantly reduced total mortality and CHD mortality in elderly patients

[5] Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology*, 10(6):439-446, 1996.

with a history of CHD. In HPS, 52% of patients were elderly (4,891 patients 65-69 years and 5,806 patients 70 years or older). The relative risk reductions of CHD death, non-fatal MI, coronary and non-coronary revascularization procedures, and stroke were similar in older and younger patients (see CLINICAL PHARMACOLOGY). In HPS, among 32,145 patients entering the active run-in period, there were 2 cases of myopathy/rhabdomyolysis; these patients were aged 67 and 73. Of the 7 cases of myopathy/rhabdomyolysis among 10,269 patients allocated to simvastatin, 4 were aged 65 or more (at baseline), of whom one was over 75. There were no overall differences in safety between older and younger patients in either 4S or HPS.

ADVERSE REACTIONS

In the pre-marketing controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR. Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

Clinical Adverse Experiences

In Adults

Adverse experiences occurring in adults at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in Table 9.

TABLE 9
Adverse Experiences in Clinical Studies
Incidence 1 Percent or Greater, Regardless of Causality

	ZOCOR (N = 1,583) %	Placebo (N = 157) %	Cholestyramine (N = 179) %
Body as a Whole			
Abdominal pain	3.2	3.2	8.9
Asthenia	1.6	2.5	1.1
Gastrointestinal			
Constipation	2.3	1.3	29.1
Diarrhea	1.9	2.5	7.8
Dyspepsia	1.1	—	4.5
Flatulence	1.9	1.3	14.5
Nausea	1.3	1.9	10.1
Nervous System/ Psychiatric			
Headache	3.5	5.1	4.5
Respiratory			
Upper respiratory infection	2.1	1.9	3.4

Scandinavian Simvastatin Survival Study

Clinical Adverse Experiences

In 4S (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 4,444 patients treated with 20-40 mg/day of ZOCOR (n=2,221) or placebo (n=2,223), the safety and tolerability profiles were comparable between groups over the median 5.4 years of the study. The clinical adverse experiences reported as possibly, probably, or definitely drug-related in ∅0.5% in either treatment group are shown in Table 10.

TABLE 10
Drug-Related Clinical Adverse Experiences in 4S
Incidence 0.5 Percent or Greater

	ZOCOR (N = 2,221) %	Placebo (N = 2,223) %
Body as a Whole		
Abdominal pain	0.9	0.9
Gastrointestinal		
Diarrhea	0.5	0.3
Dyspepsia	0.6	0.5
Flatulence	0.9	0.7
Nausea	0.4	0.6
Musculoskeletal		
Myalgia	1.2	1.3
Skin		
Eczema	0.8	0.8
Pruritus	0.5	0.4
Rash	0.6	0.6
Special Senses		
Cataract	0.5	0.8

Heart Protection Study

Clinical Adverse Experiences

In HPS (see CLINICAL PHARMACOLOGY, *Clinical Studies*), involving 20,536 patients treated with ZOCOR 40 mg/day (n=10,269) or placebo (n=10,267), the safety profiles were comparable between patients treated with ZOCOR and patients treated with placebo over the mean 5 years of the study. In this large trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse experiences were comparable (4.8% in patients treated with ZOCOR compared with 5.1% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was <0.1% in patients treated with ZOCOR.

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with simvastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, ν-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Concomitant Lipid-Lowering Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin at doses exceeding 10 mg/day with gemfibrozil should be avoided (see WARNINGS, *Myopathy/Rhabdomyolysis*).

Adolescent Patients (ages 10-17 years)

In a 48-week, controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with ZOCOR (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescents*, and PRECAUTIONS, *Pediatric Use*).

OVERDOSAGE

Significant lethality was observed in mice after a single oral dose of 9 g/m^2. No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m^2, respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

A few cases of overdosage with ZOCOR have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

The dialyzability of simvastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet. In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet. The dosage should be individualized according to the goals of therapy and the patient's response. (For the treatment of adult dyslipidemia, see NCEP Treatment Guidelines. For the reduction in risks of major coronary events, see CLINICAL PHARMACOLOGY, *Clinical Studies in Adults.*) The dosage range is 5-80 mg/day (see below).

The recommended usual starting dose is 20 to 40 mg once a day in the evening. For patients at high risk for a CHD event due to existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter. See below for dosage recommendations in special populations (i.e., homozygous familial hypercholesterolemia, adolescents and renal insufficiency) or for patients receiving concomitant therapy (i.e., cyclosporine, danazol, amiodarone, verapamil, or gemfibrozil).

Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage for patients with homozygous familial hypercholesterolemia is ZOCOR 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. ZOCOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia

The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[6] and CLINICAL PHARMACOLOGY). Adjustments should be made at intervals of 4 weeks or more.

Concomitant Lipid-Lowering Therapy

ZOCOR is effective alone or when used concomitantly with bile-acid sequestrants. If ZOCOR is used in combination with gemfibrozil, the dose of ZOCOR should not exceed 10 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Patients taking Cyclosporine or Danazol

In patients taking cyclosporine or danazol concomitantly with ZOCOR (see WARNINGS, *Myopathy/Rhabdomyolysis*), therapy should begin with 5 mg/day and should not exceed 10 mg/day.

Patients taking Amiodarone or Verapamil

In patients taking amiodarone or verapamil concomitantly with ZOCOR, the dose should not exceed 20 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*, *Other drug interactions*).

[6] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 89(3):495-501. 1992.

Patients with Renal Insufficiency

Because ZOCOR does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However, caution should be exercised when ZOCOR is administered to patients with severe renal insufficiency; such patients should be started at 5 mg/day and be closely monitored (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Myopathy/Rhabdomyolysis*).

HOW SUPPLIED

No. 3588 — Tablets ZOCOR 5 mg are buff, shield-shaped, film-coated tablets, coded MSD 726 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0726-31 unit of use bottles of 30
NDC 0006-0726-61 unit of use bottles of 60
NDC 0006-0726-54 unit of use bottles of 90
NDC 0006-0726-28 unit dose packages of 100
NDC 0006-0726-82 bottles of 1000.

No. 3589 — Tablets ZOCOR 10 mg are peach, shield-shaped, film-coated tablets, coded MSD 735 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0735-31 unit of use bottles of 30
NDC 0006-0735-54 unit of use bottles of 90
NDC 0006-0735-28 unit dose packages of 100
NDC 0006-0735-82 bottles of 1000
NDC 0006-0735-87 bottles of 10,000.

No. 3590 — Tablets ZOCOR 20 mg are tan, shield-shaped, film-coated tablets, coded MSD 740 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0740-31 unit of use bottles of 30
NDC 0006-0740-61 unit of use bottles of 60
NDC 0006-0740-54 unit of use bottles of 90
NDC 0006-0740-28 unit dose packages of 100
NDC 0006-0740-82 bottles of 1000
NDC 0006-0740-87 bottles of 10,000.

No. 3591 — Tablets ZOCOR 40 mg are brick red, shield-shaped, film-coated tablets, coded MSD 749 on one side and ZOCOR on the other. They are supplied as follows:

NDC 0006-0749-31 unit of use bottles of 30
NDC 0006-0749-61 unit of use bottles of 60
NDC 0006-0749-54 unit of use bottles of 90
NDC 0006-0749-28 unit dose packages of 100
NDC 0006-0749-82 bottles of 1000.

No. 6577 — Tablets ZOCOR 80 mg are brick red, capsule-shaped, film-coated tablets, coded 543 on one side and 80 on the other. They are supplied as follows:

NDC 0006-0543-31 unit of use bottles of 30
NDC 0006-0543-61 unit of use bottles of 60
NDC 0006-0543-54 unit of use bottles of 90
NDC 0006-0543-28 unit dose packages of 100
NDC 0006-0543-82 bottles of 1000.

Storage

Store between 5-30°C (41-86°F).

Tablets ZOCOR (simvastatin) 5 mg, 10 mg, 20 mg, and 40 mg are manufactured by:

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

Tablets ZOCOR (simvastatin) 80 mg are manufactured for:

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

By:
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