PROPOSAL FOR THE INCLUSION OF A STATIN FOR THE SECONDARY PREVENTION OF CARDIOVASCULAR DISEASES IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

NHS Centre for the Evaluation of Effectiveness of Health Care (CeVEAS)
Local Health Unit Modena - Italy
Viale Muratori 201 41100 Modena.
Tel +39-059-435200
Fax +39-059435222
Web page: http://www.ceveas.it

Universities Allied for Essential Medicines (UAEM)
Weill Cornell Medical College—The Rockefeller University—Sloan-Kettering Cancer Institute Chapter
420 E 70th St, Suite 10M
New York, New York (USA) 10021
Web page: www.essentialmedicine.org

Person to contact:

NHS Centre for the Evaluation of Effectiveness of Health Care (CeVEAS)

Dr. Nicola Magrini, MD
CeVEAS
Viale Muratori 201
41100 Modena - Italy
Tel +39-059-435200
Fax +39-059435.222

Universities Allied for Essential Medicines (UAEM)

Sandeep P. Kishore, MSc
420 E 70th, Suite 10M
New York, New York (USA) 10021
Tel: (917) 733 – 1973
Email: sunny.kishore@gmail.com

NOVEMBER 2006

CONTENTS

WHO Model List Application, November, 2007

Contributors:

CeVEAS, Modena, Italy
NHS Centre for the Evaluation of the Effectiveness of Health Care

Nicola Magrini, MD
Director, Clinical Pharmacologist

Giulio Formoso, MPH, MPharm
Epidemiologist

Massimo Brunetti, MS
Health Economist

Universities Allied for Essential Medicines, New York, USA

Sandeep P. Kishore, M.Sc,
Tri-Institutional Medical Scientist Training Program of Weill Cornell Medical College, the Rockefeller University, and Sloan-Kettering Cancer Institute; Universities Allied for Essential Medicines

Benjamin Herbstman, MHS,
Weill Cornell Medical College
Universities Allied for Essential Medicines

Helen-Ann Brown, MLS, MS, AHIP,
Weill Cornell Medical Library

Patricia Mongelia, MLIS, CHIS,
Weill Cornell Medical Library

Senior Advisor:
Antonio M. Gotto, Jr., MD, DPhil
The Stephen and Suzanne Weiss Dean, Weill Cornell Medical College
Provost for Medical Affairs, Cornell University

Acknowledgements:

Dai Ellis
The Clinton Foundation, New York, USA

Thomas Gaziano, M.D., M.Sc
Associate Physician, Division of Cardiology, Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital.

Mark Hartman
Executive Vice President, Generics Medicines (North America), Dr. Reddy's Pharmaceuticals, South Carolina, USA

Christopher Murray, M.D., D.Phil
Richard Saltonstall Professor of Population Policy and Director of the Harvard Initiative for Global Health, Harvard University; Former Executive Director of the Evidence and Information for Policy, World Health Organization.

Alvin I. Mushlin, MD, ScM
Chairman, Department of Public Health, Weill Cornell Medical College, New York, USA

Jonathan Quick, M.D.
Director, Department of Essential Drugs and Medicines Policy, World Health Organization; President and CEO of Management Sciences for Health

Jim Rankin
Management Sciences for Health (MSH), Drug Management Program

Srinath Reddy MBBS, MDDM,
President, Public Health Foundation India, Chairman of Department of Cardiology, All India-Institute of Medical Sciences (AIMS)

Bruce Schackman, Chief of Division of Health Policy, Department of Public Health, Well Cornell Medical College, New York, USA

Derek Yach, MBChB, MPH.
Director of Program on Global Health, The Rockefeller Foundation, Former Executive Director of Non-Communicable Diseases and Mental Health of WHO

1. Summary statement of the proposal for inclusion, change or deletion

Presently cardiovascular disease (CVD) is the leading cause of mortality in the developed and in most of the developing world. Considering the absolute number of deaths, low-and-middle income countries carry the majority of the burden (Gaziano TA et al, 2006). The WHO Expert Committee has previously considered a lipid-lowering drug (HMG-CoA reductase Inhibitor, statin) to address CVD in 2005, but concluded:

> "…Several of these drugs have been shown to reduce the incidence of fatal and non-fatal myocardial infarction, stroke and mortality (all causes), as well as the need for coronary by-pass surgery. All remain very costly but may be cost-effective for secondary prevention of cardiovascular disease as well as for primary prevention in some very high-risk patients. Since no single drug has been shown to be significantly more effective or less expensive than others in the group, none is included in the Model List; the choice of drug for use in patients at highest risk should be decided at the national level."

WHO Model List of Essential Medicines (EML 14, revised March 2005)
http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf

We alert the Expert Panel to the fact that statins are presently much cheaper than before – driven in part by the fact there are now three statins with United States patent expirations (see FDA press releases) now available in generic form: lovastatin, pravastatin and simvastatin. Treatment costs have dropped from several thousand dollars/ year (in the U.S.) to, based on tender agreements catalogued from *The International Drug Price Indicator Guide* (Management Sciences for Health, MSH) $30 - $300/year, depending on the statin of interest and the country of production. We catalogue multiple, off-patent sources of generic formulations of a statin that are FDA-approved, bioequivalent to innovators' products and made available to international suppliers.

Information contained herein surveys recent effectiveness, efficacy (potency) and safety data on statins, particularly from the past 5 years. As use of a statin was previously considered cost-prohibitive we have summarized recent studies that analyze the cost-effectiveness of statins in the developing world. We adopt WHO recommendations of cost-effectiveness. Based on our assessment and consultations with experts in this field, we conclude that statins are highly cost-effective.

Based on our review of patent status, availability worldwide by global manufacturers and clinical efficacy, we propose that a generic statin (e.g. 20-40 mg/day simvastatin, 20-40 mg/day pravastatin, 20-40 mg/day lovastatin or 40 mg/day fluvastatin) be recommended as example of a therapeutic class for secondary prevention of heart disease for the Core List of Essential Medicines.

2. Name of the focal point in WHO submitting or supporting the application

Dr Shanthi P.B. Mendis, Chronic Diseases Prevention and Management (CPM)

3. Name of the organization(s) consulted and/or supporting the application

CEVEAS, Center for the Evaluation of the Effectiveness of Health Care, Modena, Italy

Office of the Dean, Weill Cornell Medical College, New York, USA

Department of Public Health, Weill Cornell Medical College, New York, USA

Office of the Chairman of Cardiology, All India Institute of Medical Sciences (AIMS)

The Rockefeller Foundation – Global Health Division

World Heart Federation

4. International Nonproprietary Name (INN, generic name) of the medicine

Simvastatin, Pravastatin, Lovastatin (which are off-patent and available as generics), fluvastatin, atorvastatin. The effectiveness of all these statins is currently proved by at least one RCT on long-term clinical outcomes, therefore the inclusion of one of this statins in the Essential Medicines List is supported for the secondary prevention of cardiovascular diseases.

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Simvastatin: tablets containing 5, 10, 20, 40 or 80mg
Pravastatin: tablets containing 10, 20, 40mg
Lovastatin: tablets containing 10, 20, 40mg
Fluvastatin: tablets containing 20, 40mg (capsules); 80 (XL tablets)
Atorvastatin: tablets containing 10, 20, 40, 80 mg

6. International availability - sources, if possible manufacturers (Appendix A)

As an example, a comprehensive listing for one statin, generic simvastatin, is appended to this submission (Appendix A), considering its worldwide availability, its evidence base (number of studies and their sample size), the easier access to provisional prices and the interest of several generic firms in producing it. Generic simvastatin is registered in many countries in the developed and developing world. In the United States, the FDA has approved ANDA on June 23, 2006 for the production of generic simvastatin by Dr. Reddy's Pharmaceuticals (India and USA), Teva Pharmaceuticals (Israel and USA) for the 20 and 40mg formulations and Ranbaxy Pharmaceuticals (India and USA) for the production of the 80mg formulations. Patent expiry for simvastatin several years ago in non-US and non-EU markets has led to the registration and production of generic simvastatin by numerous global

manufacturers. Other generic statins are similarly available worldwide, though documenting all available sources would have been needlessly work-intensive. For simplification, we reference simvastatin as an example of a statin (e.g. national registry text for formulary) but insist that different nations will have varying access and production capabilities of all generic statins.
For other generic statins, their choice will depend on their prices and availability at local (national) level.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested on the Model List of Essential Medicines as an example of the therapeutic group of lipid-lowering agents. Other members of the class may serve as alternatives, depending on quality, price and local availability.
The choice should consider either effectiveness and safety, as well as cost . About clinical profile, no head to head trials are available except those comparing different regimens (high vs low dose), therefore preference should be given to statins supported by at least one long-term RCT with clinical events as the main outcomes but also considering the overall evidence base (number of studies and sample sizes). About the cost issue, it should be considered that prices can have fluctuations at local levels (comparing different areas).

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment on current use, target population)

As stated in the 2003 World Health Organization (WHO) document on prevention of cardiovascular disease, "noncommunicable disease accounts for a large and increasing burden of disease worldwide." (WHO Report on Prevention of Recurrent Heart attacks, 2003). Cardiovascular disease (CVD) is the most important single cause of noncommunicable disease, accounting in 2001 for 29% of all deaths and 10% of the global disease burden. Although the incidence of CVD has been decreasing over the last quarter century in many high-income populations, its incidence in low and middle-income populations has been rising steadily, so that approximately three-quarters of global deaths from CVD now occur in those populations.

The three major manifestations of cardiovascular disease are:

- Coronary heart disease (CHD) including myocardial infarction and angina
- Cerebrovascular disease (transient ischemic attack and stroke)
- Peripheral arterial disease

The average level of blood cholesterol within a population is an important determinant of the CHD risk of the population. However, as stated in the systematic review from the National Institute of Clinical Excellence (NICE, 2005), "although blood cholesterol is an important risk factor for CHD, it is by itself a relatively poor predictor of future CHD events. It has been shown that, in British men aged 40-59, there is considerable overlap between the distribution of blood cholesterol concentrations in those who subsequently go on to suffer from CHD and the distribution in those who do not.

Consequently, other risk factors, such as tobacco smoking, diabetes, physical inactivity, and obesity, need to be taken into account when defining individual risk of CHD. Cholesterol lowering is therefore only one of a number of methods of reducing the risk of coronary heart disease. CHD risk can also be reduced by changes in lifestyle, such as smoking cessation, exercise and the use of cholesterol-lowering diets along with non-cholesterol drug treatments, including aspirin and anti-hypertensives. The cost-effectiveness of statins must be seen in the context of these other interventions.".

Global Disease Burden:

Mortality
As stated previously, CVD is the leading cause of death globally, accounting for nearly 1/3 of all global deaths (see Table 1) nearly 80% of deaths attributed to cardiovascular disease are in the developing world (Beaglehole R, et al., 2004). This trend of developing countries shouldering the burden of CVD is only predicted to worsen. In developing countries between 1990 and 2020, ischemic heart disease mortality has been predicted to increase 120% in women and 137% in men, and cerebrovascular disease mortality has been predicted to increase by 124% in women and 107% in men (Yusuf S 2001).

Table 1. Deaths per Year due to Cardiovascular Disease.
World Health Organization. Shaping the Future. World Health Report, 2003. Geneva: WHO, 2003.

Deaths Per Year		
Total Deaths per Year	57,000,000	0.9% of 6.4 billion population
Cardiovascular Deaths	16,600,000	29% (of all deaths)
Coronary Heart Disease		43% (of cardiovascular deaths)
Stroke		32%
Peripheral Artery		25%
In Developing World		78%

Morbidity
According to the Disease Control Priorities Project (DCCP), ischaemic heart disease and stroke (CVD) are among the top five leading cause of disease burden in lower- and middle-income countries. In high-income countries, they are the leading cause of morbidity (Lopez AD et al., 2006).

Underlying Causes
One reason for this current and future increase in CVD is the process of epidemiological transitions. When a society better meets its basic human needs, there is an increase in chronic diseases like CVD and a decrease in parasitic and infectious diseases under such transitions. Due to improvements in infrastructure and the economy, citizens in developing countries have begun reaching ages when they are most vulnerable to CVD (Pearson TA 1999). The rise in CVD is also due to increasing urbanization and the lifestyle changes that accompany it. In 1970, only 36.6% of the world's population lived in urban settings, and by 1994 the proportion of urban dwellers rose to 44.8%. By 2025, 61.1% of the world's population has been predicted to live in urban areas (Chockalingam A 1999). This projection is relevant as urban dwellers have been shown to have a higher risk of CVD. Studies comparing urban populations in India with rural groups show that the urban dwellers have a substantially higher level of CVD risk. There are many possible reasons for this increase. Individuals in urban settings frequently adopt a westernized diet and patterns of physical inactivity, which lead to

increased blood pressure, BMI, blood sugar, and lipid levels (Reddy KS 1993). These individuals also more frequently use tobacco, which further elevates their risk for CVD.

While elevated blood pressure seems to be the most important single risk factor (being more than 4 millions the number of deaths attributable to it in developing countries) deaths attributable to elevated blood cholesterol are estimated to account for more than 2 millions in developing countries (Rodgers A et al, 2006). In light of these data, treatment of elevated blood cholesterol in secondary prevention of CV disease could have a positive public health impact in developing as well as developed countries.

Age of Onset
The relatively early age of CVD deaths is one of the most concerning differences between CVD in the developed and developing world. In developing countries, people with CVD who were younger than 70 years represented 46.7% of CVD deaths. In developed countries, however, only 26.5% of CVD deaths occurred in individuals younger than 70 years (Murray CJL, et al. 1994). This early age of CVD mortality directly has economic consequences, highlighting the role of preventive measures.

Target Population: age
Ischemic heart disease and cerebrovascular disease are the leading cause of deaths for those aged 60 years and over and the second and fifth leading cause of death for those aged 15-59 across all incomes (WHO World Health Report 2003).

Risk by Race/Ethnicity
South Asia and Africa experience higher mortality due to cardiovascular disease than do China and South America (WHO World Health Report 2003), although it remains unclear if this is due to increased "ethnic risk" for the disease or an artifact. Although blood cholesterol is an important risk factor for CHD, it is by itself a relatively poor predictor of future CHD events. In British men aged 40-59, for example, there is considerable overlap between the distribution of blood cholesterol in those who develop CHD and those who do not.

Available evidence, however, does indicate trends in certain populations. As stated in the review from NICE (2005), "the prevalence of CHD also varies substantially by ethnic group. The prevalence of angina and MI is particularly high in those from the Indian subcontinent, and very low in those of Chinese origin (see Table 2)."

Table 2: "Ethnic Risk" of MI and Angina. Based on Prevalence of Angina and MI in England, 1999 (age standardized percentages).

Ethnic Group	**Angina:**		**MI:**	
	Men	Women	Men	Women
Black Carribean	1.7	4.3	0.6	1.0
Indian	6.8	3.7	4.0	0.6
Pakistani	6.7	4.9	6.0	2.9
Bangladeshi	9.9	4.3	7.1	0.4
Chinese	2.0	0.8	1.3	-
Irish	5.6	3.7	4.1	2.7
General Population	5.3	3.9	4.2	1.8

Interestingly, countries such as China and Japan exhibit consistently high rates of stroke, but not CHD. Hispanics in the United States may also have a higher risk than non-Hispanic whites (Swenson CJ, 2002). Asian Indians have a high incidence of CHD owing to high triglycerides, low HDL cholesterol and increased frequency of diabetes. Predisposition of the Indian cohort to metabolic diseases is pronounced when compared with similar cohorts of Europeans and Chinese (Anand SS et al., 2003).

Cost Savings in Target Population

The cost of treatment is sizeable, but the cost associated with CVD death in the developing world is even greater. For example, in South Africa, 25% of the country's health expenditures (2%-3% of the gross national income [GNI]) was spent on direct treatment of CVD (Pestana S, 1996) In contrast, in 5 countries surveyed in a recent report (Brazil, India, China, South Africa, and Mexico), conservative estimates indicate that at least 21 million years of future productive life are lost because of CVD annually (Leeder S 2004) This enormous figure, with its associated social and economic consequences, is in large part due to the earlier age of CVD death in the developing world compared with that in more developed countries. The use of cost-effective treatments like statins can decrease this mortality and the costs associated with it.

Developing countries, however, are the least able to obtain such treatments because the resources to combat CVD are few. The GNI per capita of developed countries is nearly 25-fold that of developing countries ($27,000 compared with $1100). Developed countries spend twice as much of their GNI on healthcare (10% vs. 6%). The result is that developed countries spend 40 times the amount on health care (Gaziano TA 2005). With the enormous differences in resources and the growing burden of disease, it is essential to find a cost-effective way to manage the increasing prevalence of CVD in developing countries.

9. Treatment details

9.1 Indications for use

The British National Formulary (BNF) states that statins should be considered for all patients, including the elderly, with symptomatic CVD, such as those with coronary heart disease (CHD)

(including history of angina or acute myocardial infarction [MI]) and those with occlusive arterial disease (including peripheral vascular disease, nonhaemorrhagic stroke, or transient ischaemic attacks). In patients with diabetes mellitus, the risk of developing CVD depends on the duration and complications of diabetes, age, and concomitant risk factors. Statin therapy should be considered for *all* patients over 40 years with diabetes mellitus (types 1 and 2). In younger patients with diabetes, treatment with a statin should be considered if there is target-organ damage, poor glycaemic control (HbA_{1c} greater than 9%), a low level of high-density lipoprotein (HDL) cholesterol and a raised triglyceride concentration, hypertension, or a family history of premature CVD.

9.2 Dosage regimens

Active ingredients:

* Lovastatin: tablets containing 10, 20, 40mg
* Simvastatin: tablets containing 5, 10, 20, 40 or 80mg
* Pravastatin: tablets containing 10, 20, 40mg
Fluvastatin: tablets containing 20, 40mg (capsules); 80 (XL tablets)
atorvastatin: tablets containing 10, 20, 40, 80 mg
Rosuvastatin tablets containing 5, 10, 20 or 40 mg

* generic formulation available

9.3 Duration of therapy

Lifelong therapy is recommended once it is started

9.4 Reference to existing WHO and other clinical guidelines

The recommendation of the WHO document on prevention of cardiovascular diseases in low and middle income populations states that “Blood cholesterol reduction with statins is recommended for all patients with established CHD who can tolerate this treatment, which should be continued in the long term, probably life-long. Patients at high baseline risk are particularly likely to benefit. Lowering total and LDL-cholesterol using a moderate, trial-validated dose of statin (e.g. simvastatin 40 mg/day) is likely to be the best approach”. (WHO, 2003)

According to the guidelines from the US National Cholesterol Education Program and its updates, the recommendations for treatment are now rather “aggressive” and focus on reducing cholesterol levels in secondary prevention in most patients. Table 3 summarizes the target cholesterol levels and cut-off levels to start drug treatment.

Table 3. ATP III LDL-C Goals and Cutpoints for Cholesterol Treatment in Different Risk Categories Based on Recent Clinical Trial Evidence (Circulation, July, 2004).

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy
High risk: CHD or CHD risk equivalent options (10 year risk > 20%)	<100 mg/dL optional: <70 mg/dL	> or = 100 mg/dL	> or = 100 mg/dL < 100 mg/dL consider drug

9.5 Need for special diagnostic or treatment facilities and skills

No special diagnostic or treatment facilities are required for the treatment of patients in secondary cardiovascular prevention (primary prevention would also require the measurement of the long term cardiovascular risk, the latter implying the availability of specific population-based models and of professional skills).Where available, the measurement of cholesterol levels would help find the optimal statin dose.

About monitoring issues, the last release of the guideline of the National Cholesterol Education Program (NCEP) affirms that

"With good adherence, maximum LDL lowering, as well as lowering of triglyceride and raising of HDL cholesterol, is achieved within 6 weeks of initiating drug therapy. Thus, the first followup visit should occur 6–8 weeks after initiating drug therapy. If the dose is increased, monitoring should be continued at 6–8 weeks until the final dose is determined. If the initial dose of the drug must be increased or another drug added in an effort to reach the treatment goal(s), the patient should be seen in another 6–8 weeks for followup evaluation of the new drug regimen. This process should be repeated until the patient has reached his/her treatment goal(s). Once the patient has achieved the treatment goal(s), followup intervals may be reduced to every 4–6 months. The primary focus of these visits is encouragement of long-term adherence with therapy. Lipoprotein profiles should be assessed at least annually, and preferably at each clinic visit to promote compliance."
About safety monitoring, the following table summarizes the main recommendations of the NCEP guideline.

Table 4. NCEP recommendations for safety monitoring

Muscle soreness, tenderness or pain	evaluate muscle symptoms and CK initially. Evaluate muscle symptoms at each follow-up visit. Obtain a CK when persons have muscle soreness, tenderness or pain
ALT, AST	Evaluate ALT/AST initially, approximately 12 weeks after starting, then annually or more frequently if indicated

The WHO document on prevention of cardiovascular diseases in low and middle income populations states that "Current guidelines suggest that total or LDL-cholesterol levels should be measured before initiation of treatment and reduced below particular levels, e.g. to a total cholesterol level of less than 5 mmol/L or an LDL-cholesterol level of less than 3 mmol/L. However, the absence of any defined cholesterol threshold for benefit in the recent Heart protection study and PROSPER studies suggests

that taking a moderate trial validated dose of statin is more important that aiming for a particular target cholesterol level. Thus monitoring may not be mandatory in settings in which resources are limited"

In case it is not possible to proceed with drug monitoring (because of lack of instrumentation/facilities) statin treatment should be either reconsidered or suspended in case of development of muscle sore or tenderness

10. Summary of comparative effectiveness in a variety of clinical settings

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Systematic reviews, technology assessment reports, and meta-analyses of statins were searched on the Database of Abstracts of Reviews of Effectiveness (DARE – www.crd.york.ac.uk/crdweb/). This search was restricted to documents evaluating the effect of statins on clinical outcomes in secondary cardiovascular prevention and diabetes, published after 2002 (therefore potentially including relevant randomized controlled trials [RCTs] published after that date, such as the Prospective Study of Pravastatin in the Elderly [PROSPER] and the Heart Protection Study [HPS]). In addition, relevant reviews were searched in Clinical Evidence (CE) (www.clinicalevidence.org). The Central Cochrane files were searched and completed relevant reviews were retrieved.

The Cochrane Central Register of Controlled Trials (Central) and PubMed were also searched for relevant RCTs that might not have been included in systematic reviews (those published from 2003 to 2006, > 1000 pz per study arm, follow-up ≥ 6 months, looking at clinical outcomes in secondary-prevention and/or diabetes patients).

To investigate safety data, these searches were supplemented by searches of reports on the US Food and Drug Administration [FDA].

A summary of the selected secondary studies (systematic reviews, technology assessment reports, meta-analyses) and relevant long-term primary studies assessing clinical outcomes appears in Appendix B.

10.2 Summary of available estimates of comparative effectiveness (appraisal of quality, outcome measures, summary of results)

Benefits in the secondary prevention of cardiovascular disease:

The systematic review carried out by the UK National Institute of Clinical Excellence (NICE) in 2005 provides a wide and thorough analysis of the benefits of statins in secondary cardiovascular prevention. Further reviews are more partial in scope or were carried out earlier and add little information for an overview of this topic.

According to the NICE review, statin therapy is associated with a statistically significant reduction in several endpoints, including the risk for all-cause mortality (RR =0.80; 95% CI 0.71-0.90), fatal MI (RR 0.57; 95% CI 0.45-0.72), nonfatal MI (RR =0.69; 95% CI 0.61-0.78), a composite endpoint of CHD death plus nonfatal MI (RR =0.74; 95% CI 0.69-0.79), cardiovascular mortality (RR =0.75; 95% CI 0.68-0.83), CHD mortality (RR =0.72; 95% CI 0.64-0.80), nonfatal stroke (RR =0.75; 95% CI 0.59-0.95), peripheral artery disease (RR =0.58; 95% CI 0.42-0.80), unstable angina (RR =0.82; 95% CI 0.72-0.94), and coronary revascularisation (RR =0.76; 95% CI 0.66-0.87).

To better understand the absolute effect of statins, the NICE review reported the absolute risk reductions and Numbers Needed to Treat (NNTs) calculated from each of the three largest RCTs of statins in secondary cardiovascular prevention. These results relate to different lengths of time (since the studies were of different duration - see table below).

Table 5: Effectiveness of statins in three RCTs of secondary CHD Prevention, expressed using absolute measures of risk reduction:

Study/Outcome	Risk in Placebo Arm	ARR (95% CI)	NNT (95% CI)
4S (Simvastatin)			
All-cause mortality	11.52	3.32 (1.57 to 5.07)	31 (19.7 to 63.6)
CHD mortality	8.5	3.50 (2.03 to 4.98)	29 (20.1 to 49.2)
Total stroke	n/a		
CHD mortality + nonfatal MI	27.98	8.57 (6.09 to 11.06)	12 (9.0 to 16.4)
CARE (Pravastatin)			
All-cause mortality	9.43	0.78 (-0.96 to 2.53)	ns
CHD mortality	5.73	1.11 (-0.23 to 2.46)	ns
Total stroke	3.66	1.16 (0.11 to 2.21)	87 (45.3 to 915.6)
CHD mortality + nonfatal Mi	13.19	3.00 (1.05 to 4.95)	34 (20.2 to 95.5)
LIPID (Pravastatin)			
All-cause mortality	14.06	3.02 (1.66 to 4.39)	34 (22.8 to 60.4)
CHD mortality	8.29	1.92 (0.85 to 3.00)	52 (33.3 to 117.7)
Total stroke	4.53	0.79 (-0.04 to 1.61)	ns
CHD mortality + nonfatal MI	15.88	3.54 (2.10 to 4.97)	29 (20.1 to 47.6)

Absolute Risk Reduction (ARR) and Numbers Needed to Treat (NNT).
ns = not statistically significant

A metanalysis from the Cholesterol Treatment Trialists' Collaborators (2005) further suggests that statin use lowers the absolute risk of major vascular events of 4,8% (95% CI 3,9-5,7%) per mmol/L LDL cholesterol reduction in people with previous myocardial infarction.

The results presented above are consistent with those reported in Clinical Evidence (CE). One of the reviews identified on CE, based on a systematic review by Amarenco et al, provided further insight on the risk of stroke, finding that "in people with coronary heart disease, raised and normal cholesterol levels, diabetes, prior ischaemic stroke or transient ischaemic attack (TIA), and the elderly, statins significantly reduced stroke compared with placebo or no treatment after a mean of 4.3 years (2.7% *vs* 3.4% with control; OR 0.79, 95% CI 0.73 to 0.85). The review also found that the effect of statins on stroke was closely associated with the reduction in low density lipoprotein (LDL)-cholesterol, such that each 10% reduction in LDL-cholesterol reduced the risk of stroke by about 16%."

The 2003 WHO publication on preventing recurrent heart attacks and strokes also states that "there are strong and continuous relations between total and LDL-cholesterol concentration and CHD risk. Several RCTs with statin treatment have demonstrated reductions in recurrent cardiovascular events, cardiovascular death and all-cause mortality in patients with MI and angina. The relative benefits appeared similar in all patient groups, including patients with angina, MI and coronary revascularization, so that absolute benefits are directly related to the level of vascular risk".

However, after analysing published and unpublished data from RCTs on statins, the systematic review from NICE suggests that it is not clear whether drug reducing LDL-C more are more effective in the reduction of cardiovascular events.

Benefits from earlier treatments

The systematic review from NICE indicates that "after the conclusion of the placebo-controlled phase of the 4S (Scandinavian Simvastatin Survival Study) randomised controlled trial, which lasted for a median of 5.4 years, patients were followed up for a further 5 years. During that 5-year period, when more than 80% of patients in each group were treated with lipid-lowering drugs, the relative risks of mortality were close to unity. However, over the whole 10.4-year period, the original simvastatin group had a reduced risk of all-cause and CHD mortality relative to the original placebo group, suggesting that benefit may be gained from earlier rather than deferred statin therapy."

Benefits at different intensities of treatment

Four RCTs were selected among those published between 2004 and 2006 evaluating the effects of high-dose statins on clinical endpoints in secondary cardiovascular prevention (see Appendix B). Three of these RCTs compare the effects of higher vs lower doses (of these, two compare different statins) and one compares high-dose vs placebo in people with previous stroke but no CHD.

Among the three head-to-head comparisons, two suggest an incremental benefit of higher doses: with atorvastatin 80 mg/day versus atorvastatin 10 mg/day, the absolute risk reduction for major CVD events was 2.2% after 4.9 years in people with previous MI or revascularization, and with atorvastatin 80 mg/day versus pravastatin 40 mg/day, the absolute risk reduction for a composite end point of all-cause mortality and cardiovascular events was 3.9% after 2 years in people hospitalised for an acute coronary syndrome. In the third RCT, no difference in the primary endpoint of major coronary events was demonstrated between atorvastatin 80 mg and simvastatin 20 mg after 4.8 years.

Higher doses increase the incidence of adverse effects (by about 2% overall) and liver enzyme elevations (by about 1-2%).

Dose-response relationship in cholesterol lowering

Statins differ in potency, since their effects on cholesterol lowering occurs at different doses (see table below). The dose-response relationship of all statins seems to be relatively flat, however, with a 15% to 30% further decrease in cholesterol with every doubling of the dose. The table below shows data on potency and cholesterol lowering.

Table 6: Lowering of LDL cholesterol with incremental doses of different statins [modified from Law et al, 2003]

Statin	**5 mg**	**10 mg**	**20 mg**	**40 mg**	**80 mg**
Rosuvastatin	-38%	-43%	-48%	-53%	-58%
Atorvastatin	-31%	-37%	-43%	-49%	-55%
Pravastatin	-15%	-20%	-24%	-29%	-33%
Simvastatin	-23%	-27%	-32%	-37%	-42%
Fluvastatin	-10%	-15%	-21%	-27%	-33%
Lovastatin	-	-21%	-29%	-37%	-45%

As mentioned in the next paragraph, it is not clear whether drugs reducing cholesterol more also reduce clinical events more. In particular, no relevant studies of rosuvastatin were identified which reported clinical outcomes. Thus, although there is RCT evidence to suggest that rosuvastatin is more effective than atorvastatin, pravastatin and simvastatin in reducing both total and LDL cholesterol, it is not possible to prove that these reductions translate into comparable reductions in clinical events.

Comparison between different statins

Different statins show different effects on cholesterol levels (see the paragraph below). However, a recent systematic review of published RCTs of pravastatin, simvastatin, and atorvastatin (Zhou et al, 2006) found that these 3 statins, when used at their standard doses, do not differ significantly in their effects on long-term cardiovascular prevention. Results were based on an adjusted indirect comparison of 8 RCTs. The relatively wide confidence intervals in some pairwise comparisons, however, may suggest that more evidence is needed. In this regard, additional results from ongoing statin trials and properly designed large observational studies will help better address the question of whether statins differ in their effects on CVD risk.

Use of statins in specific subgroups

Women

Meta-analyses using subgroup data from studies carried out in mixed populations (NICE 2005) show that statin therapy in women is associated with a significant reduction in risk for CHD death plus nonfatal MI in secondary prevention (RR 0.75, 95% CI 0.61-0.92). Results from another meta-analysis (Walsh & Pignone, 2004) also show that statins may be effective in lowering the risk for nonfatal MI (RR 0.71, 95% CI 0.58-0.87) and total CHD events (RR 0.80, 95% CI 0.71-0.91).

Failure to achieve significant results in relation to other outcomes is likely due to the small numbers involved. Thus, although the incidence of CHD is lower in women than in men, there is no evidence that the effectiveness of statins differs in women relative to men at the same level of cardiovascular risk

People with diabetes

A meta-analysis published in 2006 (Costa J et al) shows that, in secondary cardiovascular prevention, statin therapy in people with diabetes appears to be associated with a statistically significant reduction in major coronary events (NNT =15; 95% CI 11-24), stroke (NNT =19; 95% CI 11-50), CHD death (NNT =19; 95% CI 10-90), CHD death plus nonfatal MI (NNT =15; 95% CI 19-40) and revascularization (NNT =11; 95% CI 8-21) compared with placebo. Failure to achieve significant results in relation to other outcomes is probably due to the small numbers involved. Diabetic patients appear to benefit more than subjects without diabetes, given their higher baseline risk.

Elderly

One of the available placebo-controlled studies, the PROSPER study (Shepherd J et al, 2002) was specifically carried out in 5804 people aged 70-82, of whom 2565 had had a previous cardiovascular event. In this subpopulation, pravastatin reduced the risk for CHD death plus nonfatal MI plus fatal or nonfatal stroke by 4.3% in 3.2 years. As stated by the NICE review, "the 4S and CARE studies [also] presented subgroup data relating to people aged under 65, and those aged 65 and over. Although the results should again be treated with caution, in people aged 65 and over statin treatment appears to be associated with a statistically significant reduction in the relative risk of CHD mortality, total stroke, nonfatal MI, coronary revascularisation, and CHD death plus nonfatal MI. Failure to achieve significant results in relation to other outcomes is again probably due to the small numbers involved. Again, there is no evidence that statins are more or less effective in older people and in those aged under 65 as, although the point estimates of effect vary, the confidence intervals overlap". It is therefore difficult to compare the effect of statins in people aged under 65 and in those aged 65 and over in terms of absolute risk reduction and numbers needed to treat, considering the different profile of the study populations and the different duration. However, subgroup analysis of the CARE study indicates that, in secondary CHD prevention, the number needed to treat to prevent CHD death or nonfatal MI is substantially lower in patients aged 65 and over than in younger patients.

Different ethnic groups

As stated in the paper by Ong HT (2006), "the major statin trials were performed in the developed world, where ethnic minorities were particularly underrepresented (Bartlett C, 2003). However, there is evidence that the correlation between elevated cholesterol and coronary disease holds true for all ethnic

groups, including Asians and Eastern Europeans (Asia Pacific Cohort Studies, 2003; Verschuren WM, 1995; Cai J, 2004). In particular, the larger the LDL-C reduction, the larger the reduction in vascular disease risk, with a decrease of 1 mmol/L over five years reducing major vascular events by 23% (Cholesterol Treatment Trialists' Collaboration, 2005).
There are specific ethnic differences in response to drug treatment. African Americans, for example, are less affected by agents targeting the renin-angiotensin system than by other drugs for treating heart failure (Taylor JS, 2002). A Japanese study of 51,321 patients found that just 5 mg daily of simvastatin reduced total cholesterol by about 20% and LDL-C by about 25%, and these effects persisted for the 6 years of the trial. (Matsuzawa Y, 2003). For this reason, certain statins (e.g. rosuvastatin) are prescribed at half the dose for Asian patients than for Caucasians."

Studies with cerivastatin and simvastatin indicate that pharmacokinetic differences between different ethnic groups do not require clinical dosage modification (Muck W, 1998 and Tan CE, 2003). Were a statin to be included on the Model List of Essential Medicines, Ong argues the recommended dose should be decided by specific government bodies.

11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to date

Since the nineties, treatment with statins has been of widespread use in high income countries (especially in secondary prevention of cardiovascular diseases). Consequently, several millions people have been using statins in the last fifteen years, although a more precise worldwide estimate would be difficult to provide.

11.2 Description of adverse effects/reactions

Investigating the potential for side effects of statins is particularly relevant because statin therapy does involve a lifelong commitment. The most reliable data on the incidence of side-effects come from RCTs with a maximum duration of 5 years, from observational studies, and from adverse event reporting systems, which can under-represent their actual incidence. Long-term safety over longer time-span remains unproven. However, statins are generally considered to be well tolerated and to have a good safety profile. This view is generally supported both by the evidence of the trials available and by post-marketing surveillance data. Although increases in creatine kinase and myopathy have been reported, rhabdomyolysis and hepatotoxicity are rare.

The systematic review from NICE states that "the most common adverse reactions caused by statins are relatively minor and transient: they include headache, dizziness, rash, diarrhoea, abdominal pain, constipation and flatulence".

Data from another systematic review (Law et al, 2003) can be useful in this regard. Forty eight of 164 trials about the effectiveness of statins in LDL cholesterol reduction "reported the number of participants with one or more symptoms possibly caused by the drug (1063/14197 allocated to statins and 923/10568 allocated to placebo). Meta-analysis of these data showed no excess risk in people allocated to statins. On average 1% fewer treated patients than placebo patients reported symptoms (95% confidence interval 3% fewer to 1% more in treated patients). The prevalence of each of 12 specific symptoms, including muscle pain and various gastrointestinal symptoms, was similar in treated and placebo patients, even for the highest daily dose tested (80 mg for all six statins). The upper confidence limits excluded the possibility that statins caused any symptom in more than 2% of treated patients".

However, as stated in the NICE review, "some of the adverse effects associated with statins are potentially very serious. Rare but clinically important adverse effects are elevations in hepatic transaminases, peripheral neuropathy, and myopathy. If statin therapy is not discontinued, myopathy (defined as creatine kinase increase to >10 times the upper limit of normal accompanied by muscle pain or weakness) may result in rhabdomyolysis (severe muscle damage) and acute renal failure. Although the exact mechanism by which statins cause rhabdomyolysis remains unclear, the risk appears to be dose-related."

A summary of the important adverse effects reported by clinical trials is included in the review from NICE, which reports post-marketing surveillance data as well (see below). Other post-marketing data from the FDA (2005) and a systematic review of the suspected relation between statin use and cancer are also included in the following discussion.

Safety data coming from RCT on atorvastatin, fluvastatin, pravastatin and simvastatin.

Although, the first statin became available in the late 1980s, the effects of lifetime use are still unknown. The best clinical trial evidence of long-term safety comes from large-scale trials of simvastatin and pravastatin. By comparison, the trial evidence for the long-term safety of atorvastatin and fluvastatin is weak, and that for rosuvastatin is nonexistent. Clinical trial results suggest that the incidence of severe muscle problems with statin therapy is low. Aggregation of data from all the RCTs included in the NICE review of clinical effectiveness indicates that there were only 6 nonfatal cases of rhabdomyolysis among 47,637 patients randomly assigned to statin treatment versus 3 cases among 47,180 patients randomised to control (placebo, 'usual care,' or no statin treatment). There were 22 cases of myositis in 43,125 patients randomised to statin treatment and 25 cases in 42,678 patients randomised to the control group. Not all studies reported the number of patients suffering myalgia. However, in the largest study, the HPS, 20,536 patients were randomised to 40 mg of simvastatin per day or placebo, and creatine kinase levels were measured in patients who either reported unexplained muscle symptoms or used a nonstudy statin in addition to study therapy. Over the mean 5 years of the study, similar numbers of patients in each group (3,379 [32.9%] in the simvastatin group and 3,409 [33.2%] in the placebo group) complained of unexplained muscle pain or weakness, and only 49 statin patients (0.48%)and 50 control patients (0.49%) discontinued because of muscle symptoms. Although the RCT results indicate a low incidence of serious muscle problems in study participants who were followed up by researchers, they are likely to underestimate the incidence of such problems if statins are used in unselected populations. In addition to the issues relating to RCT evidence noted above, the generalisability of the statin RCT findings is further limited by the fact that some of the large, long-term studies excluded patients known to be hypersensitive to, or intolerant of, statins.

Post-marketing surveillance on atorvastatin, fluvastatin, pravastatin and simvastatin.

The most recent systematic review available states that "no published post-marketing surveillance data for the UK are available for atorvastatin, fluvastatin, pravastatin or simvastatin. An epidemiological study using data from the UK General Practice Research Database for the years 1991-1997 found that current statin therapy was associated with an eightfold increase in the risk for myopathy. However, this equated to approximately one case per 10,000 person-years of statin therapy. The non-UK data suggest that, between product approval and June 26, 2001, fatal cases of rhabdomyolysis associated with statin therapy were rare, with reporting rates lower than 1 death per million prescriptions, with the exception of cerivastatin, which has been withdrawn from world markets. However, these figures are likely to underestimate the risk both because they are based on voluntary reporting by health care professionals, and because they use as the denominator the number of prescriptions, not the number of individuals using the medication. Rates of fatal and nonfatal rhabdomyolysis voluntarily reported to the US FDA's post-marketing database were also similar, at less than 1 case per million prescriptions, for all statins except cerivastatin (FDA 2005). More than 80% of cases reported for each drug when taken as monotherapy resulted in hospitalization for renal failure and dialysis, and 10% resulted in death. This demonstrates that, although rhabdomyolysis is a rare event, it presents a significant safety issue for statin drugs even when taken as monotherapy"; however, the risk is about 300 times greater when statins are used in combination with gemfibrozil.

Safety of more recent statins: pre- and post-marketing data on rosuvastatin

Concerns have been expressed about the safety of rosuvastatin, based on both pre-marketing and post-marketing data (Wolfe SM, 2004). At this time (October 2006), the use of rosuvastatin is supported by

the results of short-term studies, including RCTs with surrogate end-points. Because no long-term randomised trials evaluating the effect of rosuvastatin on clinical end points have yet been completed, evidence regarding the risk/benefit ratio is currently lacking.

As stated in the NICE review, pre-marketing data indicated that, at 80 mg/day, rosuvastatin was associated with a higher frequency of creatine kinase elevations, and a higher incidence of myopathy and rhabdomyolysis, than other currently approved statins; as a result, the 80-mg dose was discontinued, but the FDA approved rosuvastatin in the belief that doses lower than 80 mg would be safer". Subsequently, other cases of rhabdomyolysis were reported, but data from the FDA indicate that there is no substantial difference between rosuvastatin and other statins in the incidence of rhabdomyolysis, myopathy, and renal failure (2005). However, labelling changes have been made both in the European Union and the USA. "These changes, which take into consideration post-marketing reports suggesting that inappropriate use of the 40-mg dose may have contributed to cases of muscle toxicity, highlight the patient populations who may be at increased risk for myopathy, particularly at the highest approved dose (40 mg). Patients at risk include those aged over 65, those with hypothyroidism and/or renal insufficiency, some Asian populations, and people concomitantly using cyclosporine and gemfibrozil. With respect to renal toxicity, despite data on tubular proteinuria, there is no convincing evidence of a risk for serious renal injury due to the use of rosuvastatin**"**

11.3 Identification of variation in safety due to health systems and patient factors

Statins and cancer

A recent meta-analysis of data from 26 RCTs (Dale KM et al, 2006), which reported a total of 6662 incident cancers and 2407 cancer deaths, indicates that statins did not reduce or increase the incidence of cancer (OR 1.02; 95% CI 0.97-1.07) or cancer deaths (OR 1.01; 95% CI 0.93-1.09). No differences were noted for any individual cancer type or any specific statin.

Drug-drug interactions.

Long term use of statins makes the issue of drug interactions particularly relevant. As noticed in the systematic review from NICE, "different statins may differ both in their potential for interacting with other drugs, and in their rates of adverse events. In August 2001, cerivastatin, a synthetic statin, was withdrawn from the world market after the occurrence of 52 unexpected deaths from drug-related rhabdomyolysis (31 in the USA and a further 21 worldwide). In addition, 385 nonfatal cases were reported among the estimated 700,000 cerivastatin users in the USA, and most of these required hospitalisation. Many of the fatalities had either received the full dose of cerivastatin (0.8 mg/day) or were using the drug concomitantly with gemfibrozil: this drug-drug interaction was implicated in 12 of the 31 US fatalities."

Drug interactions often depend on the pathways of statin metabolism, which involve enzymes such as those in the Cytochrome P450 family. As stated in the NICE review, "concomitant use of potent inhibitors of this enzyme (e.g. 'azole'antifungal agents and HIV protease inhibitors) may increase plasma levels of those statins and thus increase the risk of side effects such as rhabdomyolysis. The risk of serious myopathy is also increased when high doses of simvastatin are combined with less potent CYP3A4 inhibitors, including amiodarone, verapamil, and diltiazem. Moreover, it appears that the consumption of even modest quantities of grapefruit juice can significantly increase exposure to

simvastatin, thus increasing the risk of serious myopathy. Patients taking atorvastatin should also avoid drinking large quantities of grapefruit juice. These concerns do not apply to fluvastatin, which is metabolised by a different cytochrome P450 enzyme, or to pravastatin and rosuvastatin, which are not substantially metabolised by cytochrome P450.

Given the widespread use of many of these drugs, especially antibiotic and antifungal agents, attention should be paid to careful labelling and other information so that potentially harmful interactions can be avoided.

11.4 Summary of comparative safety against comparators

The main clinical practice guidelines recommend statins as the first choice drug for lipid lowering treatment in secondary prevention of cardiovascular diseases, considering their higher effectiveness than other comparator drugs (as also highlighted in Clinical Evidence, 2005) and their overall good safety profile (see previous paragraphs). Their benefit-risk profile is therefore more favourable comparing to drugs of other classes (e.g. fibrates, resins, bile acid sequestrants).

12. Summary of available data on comparative costs and cost-effectiveness

12.1 Range of cost of the proposed medicine

We used the *International Drug Price Indicator Guide*, published by Management Sciences for Health (MSH), to obtain present prices of statins. First, statins are less expensive than in the past. Lovastatin, in one country is priced at just $7/year of treatment, much less than the several thousands dollars per several years ago. The MSH Drug Price Indicator Guide catalogues the prices of medicines achieved through tender agreements between selected national governments and generic firms. MSH cautions, however, that these tender agreements may not represent an "international" price [personal communication, Jim Rankin, MSH, October 2006]. We present these prices as examples of how inexpensive statins currently are, but not as final price. MSH indicates that for Lovastatin, in particular, the cost of $33 to $46.50 is likely a more representative price. Nevertheless, individual high-level purchasers and national governments will have to identify the optimal manufacturing and pricing agreements internally. Appendix C catalogues past, present and projected prices of statins.

Patent status has a clear effect on pricing of medicines internationally. Lovastatin, the first approved statin, lost its patent in the US in 2001 and is currently the most inexpensive statin. It is included on numerous national Essential Drug lists, including those of Thailand (Wiwanitkit V, et al., 2002) and Malaysia (Babar Z, 2005). A similar trend is expected with simvastatin and pravastatin. In particular, simvastatin lost its patent status in the US on June 23, 2006, and that same day the FDA announced that 3 manufacturers received approval to produce generic simvastatin. When these manufacturers submitted Abbreviated New Drug Applications (ANDAs), they received market exclusivity for a period of 6 months until Jan 2007. The 3 manufacturers are: Teva Pharmaceuticals (based in Israel), Ranbaxy Pharmaceuticals (based in India), and Dr. Reddy's Laboratories (also based in India). Dr. Reddy's Laboratories is an authorized generic manufacturer of simvastatin, as designated by the innovator, Merck & Co. The exclusivity helps explain in part, why the price of simvastatin currently remains quite high (~$300 per year). We have evidence, including market intelligence from generic firms, suggesting that the price of simvastatin will fall quickly in January 2007. Several additional firms are predicted to enter production following expiration of the exclusivity agreements (personal communication, Executive Vice President, Generics Division, Dr. Reddy's Laboratories [October 25th, 2006). Although information on international prices is not yet available, Dr. Reddy's Laboratories indicates 20- and 40-mg generic simvastatin will be available for $10 per 90-count bottle (3-month supply), or $40/year of treatment, by January 2007 in the United States. Prices for simvastatin abroad may be as much as one-third of this price. Indeed, the market exclusivity of pravastatin ended the week of October 23 in the United States, and prices are now $10 per 90-count bottle.

12.2 Comparative cost-effectiveness presented as range of cost per routine outcome

The cost-effectiveness of statin treatment has been evaluated in several studies, most conducted in developed countries. Due to the long-term treatment duration of statin RCTs, economic evaluations were based on long-term follow-up; furthermore, most studies (primary and secondary prevention) were designed to include cost-effectiveness modelling.

The cost-effectiveness of statin treatment is strongly related to the absolute risk for CHD. Pooled estimates by Franco et al showed values of US $21,571 per life-year saved (LYS) for an annual CHD risk of 2% and US $ 16,862/LYS for an annual risk of 3%. Most studies agree that statin treatment is

cost-effective for high-risk patients, but les cost-effective for those at a lower risk. A cost-effectiveness analysis conducted by the School of Health and Related Research (ScHARR) of the University of Sheffield, UK, confirmed this favourable trend for secondary prevention (NICE 2005). Furthermore the ScHARR model showed that cost per quality-adjusted life year (QALY), a traditional measure of cost-effectiveness per QALY saved, increased sharply by age, particularly in primary prevention.

In an analysis of effectiveness calculated in economic evaluations, the benefits of statin treatment in primary modelling analyses (using all data directly collected from RCTs) and secondary modelling analyses (mortality in untreated cohort is either predicted [extrapolated] by risk functions or taken from other sources such as prospective cohorts) have been calculated with quite different assumptions about treatment period and treatment effect. All secondary analyses extrapolated the treatment's effects to periods of time far beyond the available evidence. Only five studies of primary modelling presented sufficient data describing the experience of the three main secondary-prevention trials of statin therapy: 4S, Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) and Cholesterol and Recurrent Events (CARE).

Studies funded by pharmaceutical companies generally showed more favourable cost-effectiveness ratios, in particular for low-risk patients.

Only two studies considered the cost-effectiveness of statin therapy in the developing world in combination with other CVD medicines on the Essential Medicines List (EML). A study by Murray CJ studied several interventions across 14 global subepidemiologic regions. The interventions included treatments for hypertension (a beta-blocker [atenolol]), for hypercholesterolemia (a statin), or combination therapy consisting of a beta-blocker, a statin, aspirin, and a diuretic to treat patients at risk for ischaemic heart disease stratified according to absolute risk (5, 15, 25 and 35%). The input data were derived from systematic reviews or meta-analyses, cost of health care, screening and cost of acquisition of the medicine. The report concludes that administering statins for lipid levels above 6.2 mmol/L (240 mg/dL) is very cost-effective; in all regions the cost/DALY was below the Gross National Income per capita (GNII), a measure that is considered highly cost-effective by WHO standards.

A study by Gaziano et al in 2006 evaluates the cost-effectiveness of combination therapy in the developing world for both primary prevention (patients with a 25% risk of CVD) and secondary prevention (patients with a history of heart disease); however, these authors do not report on the cost-effectiveness of using a statin alone. In this study, the authors investigate whether 4 generic drugs (aspirin, a calcium channel blocker or a beta- blocker, and an angiotensin-converting-enzyme [ACE] inhibitor [lisinopril]) and a statin (lovastatin) would be cost-effective in resource-poor settings in 3 scenarios: (1) Secondary prevention using a beta blocker, (2) Primary prevention (using a calcium channel blocker) in populations with varying 10-year risks for CVD (35%, 25%, 15% and 5%) and (3) Primary prevention (using a calcium channel blocker) in those older than 55 years without any additional risk factor assessment. Each strategy was compared with no treatment. The annual cost of generic lovastatin at the time was $14, representing an MSH tender price. Results showed that this combined approach is cost-effective according to WHO recommendations for both primary and secondary prevention.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Please note that we strongly advise individual countries to identify which statins are the most available of the generics (lovastatin, fluvastatin, simvastatin and pravastatin.) As an example, generic simvastatin is registered in the United States and United Kingdom. As the patent for simvastatin expired several years ago in Non-US, Non-EU countries numerous countries including India, Thailand and Malaysia have registered and are producing generic simvastatin. Several Indian generic firms are producing simvastatin for export. Lovastatin is registered in EU, US and India and Malaysia. Summary of regulatory approval in the US is provided below.

In United States:

Statin	**FDA Approval Date**
Lovastatin	8/31/1987
Pravastatin	10/31/1991
Simvastatin	12/23/1991
Fluvastatin	12/31/1993
Atorvastatin	12/17/1996

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopeia)

British Pharmacopoeia: Yes (2005, British National Formulary)
International Pharmacopoeia: Yes (Martindale ExtraPharmacopeia)
United States Pharmacopoeia: Yes (Version 27)

15. Proposed (new/adapted) text for the WHO Model Formulary

Description:

As an example, simvastatin will be quoted as representative of a generic statin available (considering its projected availability and price)

Simvastatin is an HMG-CoA reductase inhibitor useful for the treatment of hyperlipidemia and increased cardiovascular risk. Tablets contain fixed doses of simvastatin which has been shown to lower lipid levels by 25 to 30%.

How Supplied:

Tablets, 5, 10, 20, 40 or 80 mg of simvastatin as active ingredients derived from *Aspergillus terreus.*

Use:

Simvastatin tablets are indicated for the treatment of increased cardiovascular risk in adults and for patients who have experienced a cardiovascular event including an MI or stroke or have diabetes. Use with other medicines that address cardiovascular risk including hypertension is recommended. Simvastatin therapy is lifelong. laboratory testing and treatment history should be used for treatment of experienced patients.

Contraindications:

Active liver disease or elevated liver enzymes, hypersensitivity to simvastatin products, pregnancy and lactation.

Warnings:

Patients with Impaired Liver Function

For liver function, it is advised to monitor liver function at baseline and 12 weeks following initiation of therapy or dose increases and 6 month intervals thereafter.

Precautions (summarized from MICROMEDEX ®)

Complicated medical histories, including renal insufficiency secondary to diabetes; increased risk of myopathy/rhabdomyolysis
increased risk of myopathy/rhabdomyolysis
Heavy alcohol use
History of liver disease
Major surgery; increased risk of myopathy/rhabdomyolysis
Myopathy and renal failure (rhabdomyolysis); discontinue therapy immediately
Reduce doses or discontinue therapy if serum transaminase levels 3 times the upper limit of normal persist
Withhold temporarily or discontinue therapy in any patient who develops a condition suggestive of or predisposing to myopathy or renal failure

Drug Interactions

Concomitant use with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, fibrates, niacin (1 gram or more/day), cyclosporine, telithromycin, danazol, gemfibrozil, amiodarone, verapamil, or large quantities of grapefruit juice (greater than 1 quart/day);

Paediatric Use

Safety and efficacy have not been studied in paediatric patients under ten years age.

Geriatric Use

Meta-analyses of this population are not available, but available evidence indicates statin use can reduce the risk of death to CHD by 4.3% in over 3 years of treatment.

Pregnancy Use

Simvastatin is not indicated for Pregnancy.

Adverse Effects
Clinical Trials: The most common adverse reactions caused by statins are headaches, dizziness, rash, diarrhoea, abdominal pain, constipation and flatulence.

Elevations in hepatic transaminases, peripheral neuropathy and myopathy may result from long-term clinical use. Myopathy, defined as >10 times the upper limit of normal levels of creatine kinase accompanied by muscle pain or weakness which may result in rhabdomyolysis and acute renal failure.

Dosage and Administration
Oral administration in the evening by tablets in 5, 10, 20, 40 and 80 doses.

Patient advice
Take simvastatin as your healthcare provider prescribed it. It is usually taken in the evening after a meal. Do not take 2 doses at the same time. Contact your healthcare provider if you are not sure what to do.

Information for Patients (DRUGDEX ®)

Patients should be advised that simvastatin:

Lowers cholesterol levels to prevent heart attack or other problems. Used in combination with a diet program to lower cholesterol.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to simvastatin, or if you are pregnant, breast-feeding, or have liver disease.

How to Use This Medicine:
Tablet
Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
Take the medicine in the evening, unless your doctor tells you otherwise.
Carefully follow your doctor's instructions about diet and exercise.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are also using digoxin (Lanoxin®), gemfibrozil (Lopid®), nefazodone (Serzone®), niacin, or an antibiotic such as clarithromycin, erythromycin, fluconazole, itraconazole, ketoconazole, telithromycin, Diflucan®, Nizoral®, or Sporanox®. Tell your doctor if you are using cyclosporine (Neoral®, Sandimmune®), danazol, or a blood thinner such as warfarin (Coumadin®).
Make sure your doctor knows if you are using a heart medicine such as amiodarone, verapamil, Cordarone®, or Inderal®. Tell your doctor if you use medicines to treat HIV/AIDS, such as Agenerase®, Crixivan®, Invirase®, Norvir®, Sustiva®, or Viracept®.
Do not drink alcohol while you are using this medicine.
Do not eat grapefruit or drink grapefruit juice while you are using this medicine.

Warnings While Using This Medicine:
Using this medicine while you are pregnant can harm your unborn baby. Use an effective form of birth control to keep from getting pregnant. If you think you have become pregnant while using the medicine, tell your doctor right away.
Make sure your doctor knows if you have diabetes, kidney disease, or a muscle disorder. Make sure your doctor knows if you have a history of liver disease, heart problems, or stroke.
If your doctor tells you to increase the amount of medicine you are taking or if you are just starting this medicine, make sure you tell the doctor right away if you get muscle pain, tenderness, or weakness.
Make sure any doctor or dentist who treats you knows that you are using this medicine.
Your doctor will need to check your blood or urine at regular visits while you are using this medicine. Be sure to keep all appointments.
Do not stop using this medicine without asking your doctor. You may need a special diet to keep your cholesterol levels from going up after you stop using the medicine.
Tell your doctor if you drink alcohol regularly.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Blistering, peeling, red skin rash.
Chest pain.
Dark-colored urine or pale stools.
Fever, chills, and body aches.
Muscle pain, tenderness, or weakness.
Stomach pain, nausea, vomiting, loss of appetite.
Unusual bleeding, bruising, or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Constipation or diarrhoea.
Mild gas or indigestion.
Mild muscle or joint pain.
Trouble sleeping.
If you notice other side effects that you think are caused by this medicine, tell your doctor.

References (arranged alphabetically)

Anand SS, Yi Q, Gerstein H, et al. "Relationship of metabolic syndrome and fibrinolytic dysfunction to cardiovascular disease." *Circulation*. 2003. 108: 420-425.

Asia Pacific Cohort Studies Collaboration. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. Int J Epidemiol. 2003. 32: 563-572.

Babar, Z, Ibrahim M, Singh H and Bukhari NI. "A survey of Medicines Availability, Affordability, and Price Components in Malaysia using the WHO/HAI Methodology." Malaysia, 2005. Health Action International (HAI)/WHO.
[http://www.haiweb.org/medicineprices/surveys/200410MY/survey_report.pdf]

Ballantyne CM, *Am J Cardiol* 2000; 86:759-763

Ballantyne CM et al. *Am J Cardiol* 2004; 93:1487-1494

Bartlett C, Dave P, Dieppe P, Doyal L, Ebrahim S et al. "Women, older persons and ethnic minorities: Factors associated with their inclusion in randomized trials of statins 1990 to 2001. Heart. 2003. 89: 327-328.

Beaglehole R and Mensah G. "The Atlas of Heart Disease and Stroke." World Health Organization).[http://www.who.int/cardiovascular_diseases/resources/atlas/en/print.html]

Cai J, Pajak A, Li Y, Shestov D, Davis C, et al. Total cholesterol and mortality in China, Poland, Russia, and the US. *Ann Epidemiol*. 2004. 14: 399-408.

Chockalingam A, Balaguer-Vinto I, eds. Impending Global Pandemic of Cardiovascular Diseases: Challenges and Opportunities for the Prevention and Control of Cardiovascular Diseases in Developing Countries and Economies in Transition. World Heart Federation. Barcelona: Prous Science; 1999.

Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90056 participants in 14 randomized trials of statins. 2005. *Lancet*: 366: 1267-1278.

Costa J, Borges M, David C, Vaz Carneiro A. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. BMJ 2006;332:1115-24

Dale KM, Coleman CI, Henyan NN, et al. Statins and cancer risk: a meta-analysis. JAMA 2006;295:74-80

Edwards JE, Moore RA, BMC Family Practice 2003;4:18 http://www.biomedcentral.com/1471-2296/4/18

FDA Press Release. "FDA Approves First Generic Pravastatin." April 24, 2006. [http://www.fda.gov/bbs/topics/NEWS/2006/NEW01363.html]

FDA Press Release. “FDA Approves Generic Simvastatin”. June 23, 2006. [http://www.fda.gov/bbs/topics/NEWS/2006/NEW01394.html]

FDA. Re: Docket No. 2004P-0113/CP1. Available at: http://www.fda.gov/cder/drug/infopage/rosuvastatin/crestor_CP.pdf. Accessed Nov 15, 2006

Forouhi NG, Sattar N. “CVD risk factors and ethnicity – a homogenous relationship?” *Atheroscler Suppl*. 2006. 7(1): 11-9.

Franco OH, Steyerberg EW, Peeters A et al Effectiveness calculation in economic analysis: the case of statins for cardiovascular disease prevention *J Epidemiol Community Health*. 2006; 60: 839-845

Gaziano TA. Cardiovascular Disease in the Developing World and Its Cost-Effective Management. *Circulation*. 2005, 112; 3547-3553.

Gaziano TA. Opie LH and Weinstein MC. Cardiovascular Disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. *The Lancet. 2006;* 368: 679 – 686.

Gaziano TA, Reddy KS, Paccaud F, Horton S, Chaturvedi V. Cardiovascular Disease. In: Disease Control Priorities in Developing Countries (2nd ed). © The World Bank Group, 2006. Available at: http://www.dcp2.org/pubs/DCP. Accessed October 5, 2006.

Inclen Multicentre Collaborative Group. “Risk Factors for Cardiovascular Disease in the Developing World: A Multicentre collaborative study in the International Clinical Epidemiology Network (INCLEN).” *Journal of Clinical Epidemiology*. 1992. 45 (8): 841-847

Jones PH, et al. *Am J Cardiol*. 2003;92:152-160.

Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density, lipoprotein cholesterol, ischaemic heart disease and stroke: systematic review and meta-analysis. BMJ 2003;326;1423-32

Leeder S et al. A Race Against Time: The Challenge of Cardiovascular Diseases in Developing Countries. New York, NY: Trustees of Columbia University, 2004.

Lopez AD, Mather CD, Ezzati M, Jamison DT, Murray CJL. “Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data.” *The Lancet*. 2006. 367: 1747-1757.

Matsuzawa Y, Kita T, Mabuchi H, Matsuzako M, Nakaya N, et al., for the J-LIT Study Group. Sustained reduction of serum cholesterol in low dose 6-year simvastatin treatment with minimum side effects in 51,321 Japanese hypercholesterolemic patients. *Circulation*. 2003. 67: 287-294.

Muck W, Unger S, Kawano K, Ahr G. Inter-ethnic comparisons of the pharmacokinetics of the HMG-CoA reductase inhibitor cerivastatin. 1998. *Br J Clin Pharmacol*. 45: 583-590.

Murray CJL et al. Effectiveness and cost of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *The Lancet*. 2003; 361: 717 – 725

Murray CJL, et al. Global Comparative Assessments in the Health Sector. Geneva, Switzerland: World Health Organization; 1994.

NICE. Statins for the prevention of coronary events - Technology assessment report commissioned to ScHARR by the NICE HTA Programme–2005

Ong HT. Evidence-based prescribing of statins: A developing world perspective. PLoS Med 2006; 3(3): e50.

Pasternak RC, et al. and American College of Cardiology; American Heart Association; National Heart, Lung and Blood Institute (ACC, AHA, NHLBI). "Clinical Advisory on the Use and Safety of Statins." *Circulation*. 2002. 106:1024-1028.

Pestana JA, et al. The directed and indirect costs of cardiovascular diseases in South Arica in 1991. S Afr Med. The indirect costs of cardiovascular disease in South Africa in 1991. *S Afr Med J*. 1996;86;679-684.

Reddy KS. Cardiovascular diseases in India. World Health Stat Q. 46 (1993); 101-107.

Rodgers A, Lawes CMM, Gaziano T, and Vos T. The growing burden of risk from high blood pressure, cholesterol, and bodyweight. In Disease control priorities in developing countries, 2nd edition, 2006. Available at http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dcp2.chapter.4715

Shepherd J, Blauw GJ, Murphy MB, et al Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623–30

Swenson CJ, Trepka MJ, Rewers MJ, et al. "Cardiovascular mortality in Hispanics and non-Hispanic whites. *Am J Epidemiol*. 2002. 156: 919-928.

Tan CD, Loh LM, Tai ES. Do Singapore patients require lower doses of statins? The SGH Lipid Clinic Experience. *Singapore Med J*. 2003. 44: 635-638.

Taylor JS, Ellis GR. "Racial differences in responses to drug treatment: Implications for pharmacotherapy of heart failure." *Am J Cardiovasc Drugs*. 2: 389-399.

Verschuren WM, Jacobs DR, Bloemberg BP, Krumhout D, Menotti A, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures: Twenty-five-year follow up of the seven countries study. *JAMA*. 1995. 274: 131-136.

Walsh JME, Pignone M. Drug treatment of hyperlipidemia in women. JAMA 2004;291:2243-52

Wiwanitkit V, Wangsaturaka D and Tangphao O. LDL-cholesterol lowering effect of a generic project of simvastatin compared with simvastatin (Zocor™) in Thai hypercholesterolemic subjects – a

randomized crossover study, the first report from Thailand. BMC Clinical Pharmacology. 2002 : 2 :1 [http://www.biomedcentral.com/1472-6904/2/1]

World Health Organization. Shaping the Future. World Health Report, 2003. Geneva: WHO, 2003.

World Health Organization. Prevention of recurrent heart attacks and strokes in low and middle incomes populations 2003 Geneva, WHO