Summary

✓ Rosuvastatin (Crestor™) is a new synthetic agent for the treatment and prevention of lipid disorders, a risk factor for coronary heart disease.

✓ Rosuvastatin is undergoing phase III clinical trials. A New Drug Application was submitted to the U.S. Food and Drug Administration in June, 2001. No information on the regulatory status in Canada is currently available.

✓ Limited evidence from small clinical trials suggests that rosuvastatin may produce larger dose-dependent decreases in total cholesterol levels and low-density lipoprotein-cholesterol levels in hypercholesterolemic patients compared to other statins. There is insufficient evidence to draw conclusions about the safety of rosuvastatin.

✓ The impact of rosuvastatin therapy on cardiac morbidity and mortality is not known. More experience is required to determine the effectiveness and relative benefits of this new drug.

The Technology

Rosuvastatin is the latest in a class of lipid-lowering drugs called hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or "statins". Statins competitively inhibit HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonic acid, an early precursor of cholesterol. This process leads to reductions in the total cholesterol and the low-density lipoprotein-cholesterol (LDL-C) in circulation. Elevated serum cholesterol due to elevated LDL-C is related to the development of atherosclerosis, a process in which blood vessels become clogged, leading to heart attacks, strokes and other vascular problems.

As compared to other statins, rosuvastatin has distinct pharmacologic properties, which may cause a stronger inhibition of HMG-CoA reductase, and therefore, a greater reduction of LDL-C levels.

Statins are used to treat hypercholesterolemic conditions with the goal of preventing or treating coronary heart disease (CHD) both in secondary prevention settings (patients with clinically evident complications of atherosclerosis) and primary prevention settings (patients at risk for, but without, clinically evident complications of atherosclerosis).

Regulatory Status

Rosuvastatin is manufactured by AstraZeneca, United Kingdom. AstraZeneca submitted a New Drug Application to the U.S. Food and Drug Administration in June, 2001. Currently, there is no official information regarding the regulatory status of rosuvastatin in Canada.

Patient Group

Risk factors for CHD include unhealthy diet, smoking, obesity, hypertension, diabetes, physical inactivity, psychological and hereditary factors.

Elevated total cholesterol and LDL-C levels, and low high-density lipoprotein-cholesterol (HDL-C) levels are risk factors for the development of CHD, which is the leading cause of death in Canada. According to a 1999 report from the Heart and Stroke Foundation of Canada, 45% of men and 43% of women had a total cholesterol level above the desirable level of 5.2 mmol/L.

Recent studies in the U.S. and Europe showed that two-thirds of patients in primary care settings...
Current Practice

CHD events, such as myocardial infarctions, can be reduced by lowering cholesterol levels and by other types of interventions. Reductions in individual dietary intake of saturated fats and cholesterol produce only small decreases in cholesterol in the general population. Fish oil, garlic, oats, soy proteins and especially plant sterols/stanols have been shown to induce cholesterol-lowering effects but these dietary trials have been of relatively short duration and did not consider clinical endpoints.

Current lipid-lowering drugs include HMG-CoA reductase inhibitors (statins), fibric acid derivatives (e.g., gemfibrozil), nicotinic acid and bile acid sequestrants (e.g., cholestyramine).

Statins currently marketed in Canada are atorvastatin (Lipitor), cerivastatin (Baycol), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol) and simvastatin (Zocor). Pravastatin, lovastatin and simvastatin have been shown to reduce the incidence of myocardial infarction and death from cardiovascular causes in patients with or without a history of myocardial infarction. Adverse effects reported with current statin therapy usually have been mild and transient. The most common effects have been gastrointestinal disturbances, myopathy, hepatic enzyme increases, fatigue, and headache. Rhabdomyolysis is a rare but serious event that can occur with all statins.

Administration and Cost

Rosuvastatin, like the other statins, is administered orally once daily. No cost information for rosuvastatin in Canada is currently available.

Projected Rate of Diffusion

The reduction of total cholesterol and LDL-C levels is one of the steps in the management and prevention of cardiovascular diseases. These diseases are the leading cause of hospital admissions for men and women, excluding childbirth and pregnancy, in Canada. It is not possible at present to estimate the number of patients for whom rosuvastatin might be prescribed. However, given the large number of patients who are eligible for cholesterol-lowering therapy and current problems with achieving target LDL-C levels, the drug could experience wide uptake.

Concurrent Developments

A number of new agents are under development that reduce LDL-C levels by affecting different steps in cholesterol and lipoprotein biosynthesis.

LDL Cholesterol-lowering Agents in Development

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Developmental phase</th>
<th>Results to date</th>
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<tr>
<td>Cholesterol transport inhibitors</td>
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<tr>
<td>- Ezetimibe</td>
<td>Phase III</td>
<td>16% - 20% LDL reduction</td>
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<tr>
<td>Bile acid transport inhibitors</td>
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<tr>
<td>- S-8921</td>
<td>Pre-clinical</td>
<td>Serum cholesterol reduction</td>
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<td>ACAT inhibitors</td>
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<tr>
<td>- Avasimibe</td>
<td>Phase II / III</td>
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<td>- TS-962</td>
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<td>- F-1251</td>
<td>Phase I</td>
<td>Cholesterol reduction</td>
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<tr>
<td>HMG-CoA reductase inhibitors</td>
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<tr>
<td>- Itavastatin (NK-107)</td>
<td>Awaiting approval in Japan</td>
<td>Not available</td>
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<tr>
<td>- NK-104</td>
<td>In early clinical trials</td>
<td>LDL and triglyceride reduction</td>
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* ACAT = acyl coenzyme A cholesterol acyltransferase

The Evidence

No published clinical trials are available at present, but lower quality evidence was found in abstract form. Results from three phase III trials of rosuvastatin involving 1640 subjects were presented as abstracts by AstraZeneca at the 50th conference of the American College of Cardiology in Florida, March, 2001. The results showed that rosuvastatin might be more effective than current statins in reducing LDL-C and in increasing HDL-C levels. It is noteworthy, though, that these studies lack proper blinding methods. No formal statistical analyses or measures of statistical significance were provided in the abstract reports.
The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization funded by the federal, provincial and territorial governments.

Smaller randomised studies comparing rosuvastatin (40 mg) and atorvastatin (80 mg) (currently the most potent statin on the market) showed a similar decrease in LDL-C levels for both drugs, but a greater increase in HDL-C levels with rosuvastatin after six weeks of treatment.24,25 A safety profile for rosuvastatin was assessed in three small, randomized, double blind trials involving a total of 37 healthy volunteers. No evidence of clinically relevant liver function abnormalities or myopathy appeared with repeated doses of up to 80 mg of rosuvastatin on two separate dosing days.26 These trials are obviously very small and of extremely short duration.

### Implementation Issues

The profile of LDL-C reduction in the prevention of CHD is reflected in the formulation of guidelines for treatment based on LDL-C levels and the establishment of target LDL-C levels as goals of therapy.27 However, cholesterol levels are not the only risk factor for cardiac health. Lifestyle modifications and the control of other risk factors are also important in the prevention and treatment of CHD.

The studies to date are insufficient to determine if rosuvastatin offers an advantage over other statins. There are no large and/or long-term investigations examining adverse effects related to the use of rosuvastatin, and a dose-to-dose comparison between the new drug and current statins is not available. Because of the established safety, effectiveness and tolerability of current lipid-lowering agents for the prevention of CHD, an accurate assessment of the relative benefits and risks of rosuvastatin will require more investigation.

### References


25. Olsson AG. Statin therapy and reductions in low-density lipoprotein cholesterol: initial clinical data on the potent new statin rosvastatin. Am J Cardiol 2001;87(5 Suppl A):33B-6B.
