FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
July 9, 2003

Questions to the Committee

I. Efficacy

1. Has the sponsor provided sufficient evidence to support the efficacy of Crestor in the proposed target populations?
2. Do the efficacy data support a dose-response with respect to LDL-C lowering sufficient to justify use of the 40 mg dose?

II. Safety

A. *Myotoxicity*

1. Has the sponsor provided sufficient evidence that the myotoxic potential per LDL-lowering efficacy of rosuvastatin is similar to that of currently marketed statins?

2. Has the risk of muscle toxicity associated with rosuvastatin therapy been adequately evaluated in the clinical development program, with respect to, among others:
   a. number of patients studied and duration of treatment over the proposed dosage range
   b. special populations (e.g., elderly, renal impairment, co-morbid medical conditions)
   c. drug-drug interactions

B. *Renal Effects*

1. Clinical laboratory monitoring in the Crestor development program exposed a heretofore unknown effect of a statin to cause mild proteinuria, sometimes associated with microscopic hematuria and mild renal impairment (increased creatinine). This effect appears dose related in frequency (and perhaps severity), and reversible on discontinuation of therapy or on lowering the dose of drug.
   a. Has the risk of adverse renal effects of rosuvastatin been adequately evaluated over the proposed dosage range?
   b. What further investigations are needed, if any, of this novel drug effect?
   c. Comment on the data presented suggesting this may be a statin class effect.
   d. Is monitoring of renal function recommended for this drug or potentially for all statins?

III. Dosing Recommendations

1. Are the data adequate to support the 5, 10, or 20 mg doses as safe start doses?
2. Are the safety data adequate to support a maximum dose of 40 mg daily?
3. Does the committee recommend a range of start doses (e.g., 5 to 20 mg) in which an individual may be initiated on therapy based on CHD risks, baseline LDL-C levels, and target LDL-C?
4. Alternatively, should there be a fixed start dose of 10 mg recommended for the general population with 5 and 20 mg reserved for special circumstances, as proposed by the sponsor?

IV. Overall recommendation

1. Do you recommend that Crestor 5-40 mg be approved by FDA as an adjunct to diet for the treatment of patients with primary hypercholesterolemia and mixed dyslipidemia and isolated hypertriglyceridemia and for the treatment of patients with homozygous familial hypercholesterolemia as an adjunct to LDL apheresis or if apheresis is not available?