CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366/S-016

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	January 27, 2010
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	21-366
Applicant Name	Astra Zeneca
Date of Submission	8 April 2009
PDUFA Goal Date	8 February 2010
Proprietary Name / Established (USAN) Name	Crestor/rosuvastatin calcium
Dosage Forms/Strength	Tablet: 5 mg, 10 mg, 20 mg, and 40 mg
Proposed Indication(s)	Prevention of cardiovascular events
Recommended Action:	Approve

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Mary Roberts, MD
Statistical Review	David Hoberman, PhD
Pharmacology Toxicology Review	Not Applicable
CMC Review/OBP Review	Janice Brown, PhD
Microbiology Review	Not Applicable
Clinical Pharmacology Review	Not Applicable
DDMAC	Not Applicable
DSI	Susan Leibenhaut, MD
CDTL Review	Amy Egan, MD
OSE/DMEPA	Not Applicable
OSE/DDRE	Not Applicable
OSE/DSRCS	Not Applicable
Thorough QT Consult	Not Applicable

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Introduction

This memorandum summarizes the Agency review team's assessment of an efficacy supplement submitted by AstraZeneca requesting approval of rosuvastatin for the prevention of cardiovascular events. Data from the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial provide the basis for approval.

1. Background

Rosuvastatin, a member of the statin class of medications, was approved in the United States in 2003. Rosuvastatin is currently indicated for:

1. Patients with primary hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia (Fredrickson Type IIa and IIb) as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C
2. Patients with hypertriglyceridemia (Fredrickson Type IV) as an adjunct to diet
3. Patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) as an adjunct to diet
4. Patients with homozygous familial hypercholesterolemia to reduce LDL-C, total-C, and ApoB
5. Slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet
6. Pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated total-C, LDL-C, and Apo B after failing an adequate trial of diet therapy

Two years prior to the initial approval of rosuvastatin, a retrospective analysis of a clinical trial was published raising the hypothesis that statin therapy may reduce the risk for cardiovascular disease in subjects with "normal" levels of LDL-C but elevated levels of hsCRP, a biomarker of inflammation. Inflammation is believed to play a causal role in atherosclerosis and thrombosis.

The JUPITER trial prospectively tested the hypothesis that treatment with 20 mg once-daily rosuvastatin would reduce the risk for cardiovascular events in asymptomatic subjects with elevated levels of hsCRP not considered appropriate for statin therapy because of "normal" levels of LDL-C. It was also hypothesized that treatment with rosuvastatin would reduce the incidence of type 2 diabetes.

2. CMC

Dr. Brown granted the company their request for a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR, part 25, 25.31 (b). The basis for

granting the request is the fact that the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

3. Nonclinical Pharmacology/Toxicology

Not applicable, as no new nonclinical data were required or submitted for this supplement. Reference is made to the nonclinical and toxicology assessments provided in the original rosuvastatin NDA.

4. Clinical Pharmacology

Not applicable, as no new clinical pharmacology data were required or submitted for this supplement. Reference is made to the nonclinical and toxicology assessments provided in the original rosuvastatin NDA.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

JUPITER was a randomized, double-blind, placebo-controlled trial of approximately 18,000 individuals without clinically-evidence cardiovascular disease (CVD) allocated 1:1 to 20 mg rosuvastatin or placebo. Inclusion criteria included men aged 50 years or over, women aged 60 years and over, fasting LDL-C < 130 mg/dl, hsCRP ≥ 2.0 mg/L, and TG < 500 mg/dl. Subjects with a history of cardiovascular events such as myocardial infarction, stroke, unstable angina, and arterial revascularization or having a CHD risk equivalent were excluded from the study. The primary efficacy variable was first occurrence of a major cardiovascular event (MACE): CVD death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, and arterial revascularization procedures. Secondary efficacy variables included total mortality, noncardiovascular mortality, investigator-reported diabetes mellitus, venous thromboembolic events, and bone fractures. Subjects were to be followed for approximately 3.5 years to accrue approximately 520 clinical endpoints.

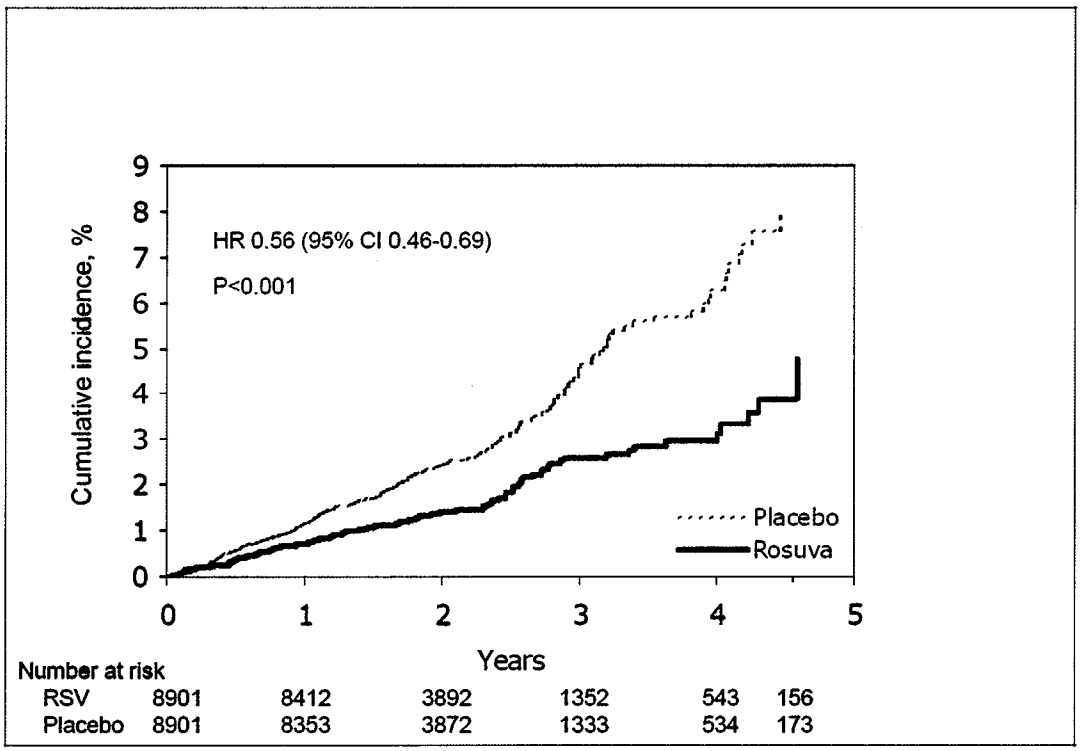
The two groups were well-matched for baseline demographic characteristics. The mean age was 66 years (range 49 to 97 years), approximately 60% of the subjects were male, 70% were Caucasian and 12% Black. The average BMI was 29 kg/m^2, 16% were current smokers, 57% had a history of hypertension, and 11% had a family history of CVD. Baseline blood pressure was 135/80 mmHg. Twenty-five percent of subjects had an HDL-C level ≥ 60 mg/dl. The mean baseline LDL-C level was 104 mg/dl and the median hsCRP level was 4.3 mg/L. The average Framingham risk score was 11.6 with 40% categorized as low-risk, 50% as intermediate-risk, and 8.8% as high-risk. The latter group was inadvertently randomized into the trial.

A total of 89,846 subjects were screened for participation in JUPITER. Of these, 72,044 subjects were screening failures, primarily because their LDL-C or hsCRP values were too high or low, respectively. Approximately 18,000 subjects were therefore randomized to rosuvastatin 20 mg (n=8901) or placebo (n=8901). A total of 92% of the subjects randomized completed the study.

The trial was stopped early due to meeting predefined stopping criteria for benefit. Although one concern related to premature termination of clinical trials is overestimation of the treatment effect, as pointed out in Dr. Hoberman's statistical review, in the case of JUPITER, any bias secondary to early termination is expected to be very modest.

In the primary efficacy analysis, 2.8% of placebo subjects vs. 1.6% of rosuvastatin subjects had a major cardiovascular event ($p<0.001$). These results are shown below graphically.

Cumulative Incidence Major Cardiovascular Events



The table below, taken from Dr. Robert's review, provides the number of events for each component of the primary endpoint. Although all of the individual endpoints lean in favor of rosuvastatin, only non-fatal myocardial infarction, non-fatal stroke, and arterial revascularization were of nominal statistical significance.

Number of Events by Individual Endpoint

Endpoint	Rosuvastatin 20 mg N=8901	Placebo N=8901	p-value[b]
First MCE	142	252	<0.001
Cardiovascular death	29	37	0.33
Non-fatal MI	21	61	<0.01
Non-fatal stroke	30	57	<0.01
Hospitalized unstable angina	15	27	0.069
Arterial revascularization	47	70	0.036

Source: Applicant's Table 18, Pg 62, CSR JUPITER
[a] Event occurrence counts only 1 MCE for each subject. If subject had more than 1 MCE on the same day, only 1 event is shown in above table, according to the following hierarchy: 1)unstable angina, 2) MI, 3) arterial revascularization, 4) non-fatal stroke, 5) cardiovascular death
[b]p-values except for First MCE calculated by FDA statistician, Dr. David Hoberman

In an analysis of noncardiovascular death, 1.4% of placebo subjects vs. 1.2% of rosuvastatin subjects died due to noncardiovascular causes (nominal p=0.17).

In an analysis of investigator-reported diabetes, 2.3% of placebo subjects vs. 2.8% of rosuvastatin subjects developed diabetes during the trial (nominal p=0.015).

In an analysis of venous thromboembolic events, 0.5% of placebo subjects vs. 0.3% of rosuvastatin subjects developed a deep vein thrombosis or a pulmonary embolism (nominal p=0.018).

In an analysis of bone fractures, 2.4% of placebo subjects vs. 2.5% of rosuvastatin subjects experienced one or more fractures (nominal p=0.55).

The changes in major lipoprotein lipid and hsCRP levels are shown in the following table taken from Dr. Robert's review. As expected, 20 mg daily rosuvastatin significantly lowered levels of TC, LDL-C, TG, Apo B, and hsCRP and significantly increased levels of HDL-C and Apo A-I.

Changes in Major Lipoprotein Lipids and hsCRP

Parameter	Baseline		After 12 months	
	Rosuvastatin 20 mg	Placebo	Rosuvastatin 20 mg	Placebo
TC (mg/dL)				
N	8899	8901	7962	7928
Mean (SD)	183.23 (24.71)	183.39 (24.16)	139.15 (33.31)	188.85 (30.02)
Median	186.00	185.00	133.00	188.00
Range	76.0-291.0	71.0-340.0	62.0-297.0	76.0-352.0
HDL-C (mg/dL)				
N	8899	8901	7960	7927
Mean (SD)	51.36 (15.34)	51.26 (15.20)	54.66 (16.33)	52.22 (15.60)
Median	49.00	49.00	52.00	50.00
Range	11.0-145.0	13.0-145.0	12.0-164.0	10.0-149.0
LDL-C (mg/dL)				
N	8899	8899	7949	7909
Mean (SD)	104.34 (18.91)	104.57 (18.51)	61.64 (27.57)	109.10 (25.02)
Median	108.00	108.00	55.00	110.00
Range	12.0-148.0	6.0-170.00	0.0-205.0	6.0-254.0

Parameter	Baseline		After 12 months	
	Rosuvastatin 20 mg	Placebo	Rosuvastatin 20 mg	Placebo
TG (mg/dL)				
N	8899	8901	7962	7928
Mean (SD)	137.76 (73.42)	137.80 (73.46)	114.91 (64.90)	138.39 (75.71)
Median	118.00	118.0	99.00	119.00
Range	19.0-499.0	24.0-496.0	18.0-1385.0	25.0-796.0)
Apo B-100 (mg/dL)				
N	8861	8856	7873	7858
Mean (SD)	108.73 (21.71)	108.72 (21.02)	70.91 (22.17)	105.41 (21.80)
Median	109.00	109.00	66.00	105.00
Range	28.0-234.0	28.0-222.0	26.0-196.0	27.0-218.0
Apo A-1 (mg/dL)				
N	8863	8857	7887	7859
Mean (SD)	165.90 (30.95)	164.96 (30.47)	168.01 (32.41)	163.95 (31.01)
Median	162.00	162.00	165.00	161.00
Range	64.0-331.0	56.0-378.0	42.0-357.0	16.0-325.0
Apo B-100/Apo A-1 ratio				
N	8861	8856	7873	7857
Mean (SD)	0.68 (0.193)	0.68 (0.190)	0.44 (0.170)	0.67 (0.221)
Median	0.66	0.67	0.40	0.65
Range	0.1-1.6	0.1-2.4	0.1-1.7	0.2-10.3
hsCRP (mg/L)				
N	8901	8901	7950	7923
Mean (SD)	6.629 (8.59)	6.923 (9.17)	4.535 (9.86)	6.010 (10.26)
Median	4.200	4.300	2.200	3.500
Range	1.10-192.0	0.55-174.50	0.10-294.60	0.07-213.00

The favorable effect of rosuvastatin treatment on the risk for major cardiovascular events was observed in subgroups defined by age, gender, race, smoking status, BMI, baseline lipid levels, and presence or absence of hypertension.

As described in Dr. Hoberman's statistical review, results from the analyses of subgroups defined by number of traditional cardiovascular risk factors at baseline suggest that there may be little-to-no benefit of rosuvastatin treatment in subjects with no traditional cardiovascular risk factors (elevated HDL negates age) or with only age as a risk factor. However, these results should be viewed with a degree of skepticism appropriate for post-hoc analyses of relatively small subgroups.

In an analysis of total mortality, 2.8% of placebo subjects vs. 2.2% of rosuvastatin subjects died from any cause (nominal p=0.02). Although there were numerically fewer deaths due to cardiovascular disease and cancer (common causes of death in a population of this age) in the rosuvastatin vs. placebo groups, the differences were not statistically significant. The company makes the argument that the total mortality findings are of importance and believe that they should be included in the product labeling. While one might reasonably expect that treatment of middle and older-aged individuals at risk for heart disease with 20 mg rosuvastatin would reduce deaths due to cardiovascular disease, there is no biological plausibility to support the assertion that rosuvastatin would decrease the risk of death due to cancer or other noncardiovascular-related causes of death. I agree with Dr. Hoberman that the total mortality

findings should not be included in the labeling, as they could be misconstrued as suggesting that rosuvastatin reduces the risk of death due to all causes.

7. Safety

As a class, statins are associated with muscle toxicity (i.e., myalgia, myopathy, and rhabdomyolysis) and hepatic transaminitis. Myalgia was reported by 8% of rosuvastatin-treated subjects vs. 7% of placebo-treated subjects. A 90-year-old man in the rosuvastatin group developed rhabdomyolysis. A greater percentage of subjects in the rosuvastatin group developed ALT >3x ULN compared with the placebo group. There were no reported cases of Hy's Law. The data from the JUPITER trial do not raise concern about rosuvastatin's skeletal muscle or liver safety profiles.

In contrast to the *a priori* hypothesis that treatment with rosuvastatin would decrease the incidence of type 2 diabetes, there were more subjects randomized to rosuvastatin compared with placebo who developed investigator-reported type 2 diabetes (2.8% vs. 2.3%, nominal p=0.015). While the company provided data from other rosuvastatin trials which do not raise concern regarding diabetes, impaired glucose tolerance has been reported with other statins. The absolute risk for investigator-reported diabetes with rosuvastatin treatment in JUPITER was small. Moreover, diabetics benefit in terms of cardiovascular risk reduction from statin treatment to the same extent as nondiabetics. The imbalance in investigator-reported diabetes will be included in the labeling.

Two safety findings discussed in detail in Dr. Roberts' review are deaths due to gastrointestinal disorders and confusional state.

There were 13 deaths in the rosuvastatin group vs. 1 death in the placebo group coded as being due to disorders from the gastrointestinal tract. This imbalance was of nominal statistical significance. Upon review of the case narratives, Dr. Roberts noted that two of the deaths in the rosuvastatin group were miscoded. Of the remaining subjects, two subjects had pancreatitis, two subjects experienced peritonitis, and four subjects experienced a fatal gastrointestinal hemorrhage, two of which were associated with either a post-surgical complication or history of alcoholic cirrhosis and esophageal varices. Two subjects died of complications associated with cancer. The placebo-treated subject died of peritonitis following gastric bypass surgery. In three additional long-term placebo-controlled trials of rosuvastatin, there were no imbalances in deaths due to a gastrointestinal disorder between rosuvastatin and placebo-treated subjects. Dr. Roberts and Dr. Egan concluded that the imbalance in deaths due to a gastrointestinal disorder noted in JUPITER likely represents a chance finding. I agree and support the decision not to include these data in the labeling.

Case reports and anecdotal evidence raise the possibility that statins may impair cognition or memory. There were 18 rosuvastatin-treated subjects compared with 4 placebo-treated subjects who were coded as having developed "confusional state". The difference was of nominal statistical significance. The company argues that most of the cases in the rosuvastatin-treated subjects had confounding factors that suggest alternative explanations for the confusional state. This may be true, but given that JUPITER was a very large randomized trial, potential

confounding factors would likely be equally distributed between the treatment groups. Although there were no significant imbalances in other adverse reactions related to memory or cognition between treatment groups in JUPITER, it is possible that the imbalance in "confusional state" represents a true rosuvastatin-induced adverse reaction.

The Division, in collaboration with colleagues from the Office of Surveillance and Epidemiology (OSE), is examining in detail the issue of statins and memory impairment. It should be noted that statin labels currently include memory loss/amnesia as possible adverse reactions. Additional changes to all the statin labels may be forthcoming depending on the outcome of the Division and OSE's ongoing evaluation.

8. Advisory Committee Meeting

On December 15, 2009, members of the Endocrinologic and Metabolic Drugs Advisory Committee, along with guest experts, publicly discussed the data from the JUPITER trial. In response to the question of whether the available data supported approval of rosuvastatin for the primary prevention of cardiovascular disease in men aged 50 years or more or women aged 60 years or more with a LDL-C < 130 mg/dl and an hsCRP $\geq$ 2 mg/L, 12 panelists voted yes and 4 no. One member abstained.

9. Pediatrics

A full waiver of the pediatric study requirement under PREA was requested by the company. This request was granted by the Division with the consent of PeRC because the necessary study (cardiovascular outcomes trial) in pediatric patients is impossible or highly impractical.

10. Other Relevant Regulatory Issues

None

11. Labeling

There are no outstanding labeling issues.

12. Decision/Risk-Benefit Assessment

I agree with Drs. Roberts and Egan that the submitted data support approval of this supplemental NDA.

The JUPITER trial extends the population who may benefit from treatment with a statin (in this case rosuvastatin) to older men and women with at least one additional traditional cardiovascular risk factor, an hsCRP value $\geq$ 2 mg/L, and "normal" (< 130 mg/dl) LDL-C levels.

The reduction in risk for major cardiovascular events associated with rosuvastatin therapy in JUPITER appears to far outweigh potential safety concerns – i.e., increased incidence of investigator-reported type 2 diabetes, myalgias, and hepatic transaminitis.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21366	SUPPL-16	IPR PHARMACEUTICALS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC C COLMAN
02/08/2010