

had a dose reduction to 40 mg at which time the lab results improved. One patient had renal laboratory abnormalities observed while on fenofibrate and was initiated on rosuvastatin 40 mg during the OLE phase without any change in renal urine tests. The serum creatinine increased from 2.1 to 2.3; however, an initial increase of 1.5 to 1.7 to 2.1 occurred while on fenofibrate.

Clinical Renal Adverse Events

Renal failure cases have been summarized by the sponsor and FDA reviewer in their briefing documents. Two cases of acute renal failure of unknown etiology were observed at the 80 mg dose. Five cases (2 at 10 mg; 1 at 20 mg; 2 at 40 mg) were reported in doses lower than 80 mg but none was attributed to drug.

Conclusions on Renal Safety

Proteinuria with or without hematuria and in some cases associated with an increase in serum creatinine levels at the 80 mg dose is observed at a higher frequency than observed at lower doses. From the largest safety datapool, there appears to be a slight increase in frequency of proteinuria with or without hematuria at the 40 mg dose compared to lower doses; however, these rates are low without evidence of clinical deterioration. The rate of proteinuria at the 40 mg dose varies between 3 to 5% depending on the method of analysis (last visit analysis or any visit analysis). Combined proteinuria and hematuria varies between 0.2 and 1.5%. In the FDA analysis, a very small subgroup of patients (n=9) treated with 40 mg who had combined proteinuria/hematuria and increased serum creatinine demonstrated either stable or improved laboratory values while continuing on 40 mg therapy or reducing the dose. In a larger subgroup of patients treated with 40 mg for ≥ 96 weeks (n=98 or 100), 4 patients had proteinuria at any time (2 at last visit) and one had combined proteinuria/hematuria at the last visit. None of these cases was reported with a $>30\%$ increase in serum creatinine.

It is evident that there is marked variability in the renal laboratory tests. This database is further complicated by the presence of other co-morbid medical conditions (hypertension in $\sim 50\%$, renal impairment in $\sim 40\%$, and diabetes in $\sim 17\%$ of the study cohort) which may also contribute to renal laboratory abnormalities if not functional deterioration. In the absence of an adequate control group, it is not possible to attribute all these findings to rosuvastatin. Furthermore, it is important to bear in mind that these renal signals are derived from a minute proportion of a clinical development program containing over 12,000 patients.

In conclusion, one cannot confirm nor exclude the possibility that these renal laboratory abnormalities are entirely due to rosuvastatin 40 mg based on these data. The sponsor has several ongoing studies which may provide further information on these renal findings. These studies include a 2-year, placebo-controlled study at the 40 mg dose in approximately 840 patients to evaluate effects of rosuvastatin therapy on carotid intima media thickness (METEOR) and a 2-year comparative efficacy study of the 5 and 40 mg doses in patients with asymptomatic carotid artery stenosis. Complete urinalysis and serum chemistries will be performed at baseline and several times post-baseline in these studies. These controlled studies will allow for a better determination of whether the renal laboratory abnormalities are due to rosuvastatin independent of other medical conditions. Until those studies are completed and reviewed by the FDA, the labeling for rosuvastatin should contain information on these laboratory findings and the recommendation for monitoring.

CLINICAL PHARMACOLOGY

Rosuvastatin is administered orally in the active form, has an elimination half-life of approximately 19 hours, and is excreted primarily in the feces (90%). Intravenous studies reveal a 28% renal clearance rate and 72% hepatic clearance rate. The absolute bioavailability is approximately 20%. The drug is not extensively metabolized by the cytochrome P450 system. Its major metabolite, N-desmethyl rosuvastatin, is formed primarily via CYP2C9. Drug-drug interaction studies with potent CYP3A4 inhibitors (ketoconazole, erythromycin, and itraconazole) reveal little dependence of rosuvastatin on CYP3A4 for metabolism. Coadministration of rosuvastatin with fluconazole (CYP2C9 inhibitor) resulted in a 14% increase in rosuvastatin AUC, which is not considered to be clinically significant.

Drug-Drug Interactions of Clinical Interest

Drug interactions of clinical relevance include cyclosporine and gemfibrozil. Co-administration of rosuvastatin with cyclosporine resulted in an increase in C_{max} and AUC of rosuvastatin of 11- and 7-fold, respectively. Co-administration of rosuvastatin with gemfibrozil resulted in an approximate 2-fold increase in both C_{max} and AUC of rosuvastatin. No clinically relevant changes in rosuvastatin pharmacokinetics were noted with fenofibrate co-administration. Since cyclosporine and gemfibrozil are each associated with a risk of myopathy and their combined use with statins have been shown to result in an increased risk of myopathy and rhabdomyolysis, special dosing recommendations in labeling is warranted for the combined use of rosuvastatin with these two drugs.

Other drug interactions of interest include increases in INR levels when rosuvastatin is administered with warfarin. Co-administration with antacids decreases rosuvastatin drug levels by 54%. These interactions are also discussed in labeling.

Special Populations

Pharmacokinetic studies were also conducted in special patient populations. Patients with severe renal impairment (CrCl < 30 ml/min/1.73m²) had a 3-fold increase in rosuvastatin plasma concentrations compared to healthy subjects. The proposed maximum dose of rosuvastatin in patients with severe renal impairment is 10 mg daily.

Rosuvastatin C_{max} and AUC were increased 60% and 5%, respectively in patients with Child-Pugh A liver disease. In patients with Child-Pugh B liver disease, C_{max} and AUC were increased 100% and 21%, respectively. Rosuvastatin is contraindicated in active liver disease and in patients with unexplained, persistent transaminase elevations.

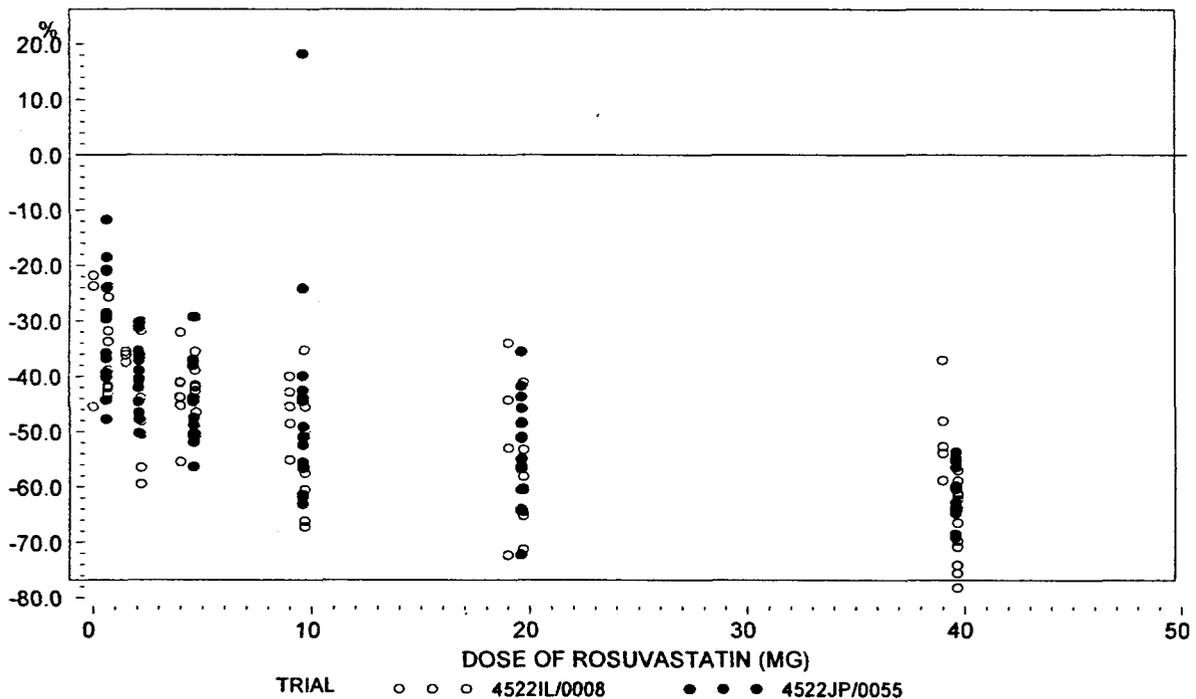
Pharmacokinetics in Japanese (residing in Japan) and Chinese (residing in Singapore) Patients

A pharmacokinetic study conducted in Japanese subjects residing in Japan demonstrated a 2-fold increase in rosuvastatin drug levels compared to Caucasians. Absolute bioavailability is also higher in Japanese patients (29%) compared to 20% in Caucasians. According to Dr. Sang Chung (FDA clinical pharmacology reviewer), the difference in pharmacokinetics is not due to differences in body weight. In an ongoing pK study in Singapore, a subset of 19 patients of Chinese descent demonstrated a similar 2-fold increase in rosuvastatin drug levels.

There are no pK studies evaluating Asians residing in the United States to evaluate if the differences observed in the above-mentioned studies are due to genetic or environmental factors. The sponsor has 5 ongoing studies in Asians residing in Singapore (described above), Japan, Korea, Thailand, and Taiwan, and a study of Asian Indians residing in the US. Except for the study in Singapore, these studies are all multi-dose studies evaluating the pharmacodynamics of rosuvastatin. Two clinical efficacy studies are planned in Asian subjects living in India and China. In response to the Division's proposal to include specific dosing recommendations for patients of Asian ethnicity, the sponsor has submitted additional data from several of these ongoing studies (document received July 18, 2003). This submission provides only a summary of the interim analyses; no datasets are submitted for review by the statistical team. The sponsor argues that in several studies, the lipid-lowering effect of rosuvastatin in certain Asian subgroups is comparable to that observed in Caucasian patients.

The following graph (provided by sponsor) summarizes the range of LDL-C changes from baseline by dose and two different studies. Study 008 (primarily Caucasians) was previously submitted to the original NDA and Study 055 (Japanese residing in Japan) is currently ongoing. The two trials had similar study designs.

Figure 5. Wk 6 % Change in LDL at Rosuvastatin 1, 2.5, 5, 10, 20, and 40 daily doses in Japanese (055) and Caucasian (008) Studies



This analysis shows comparable LDL-lowering within dose groups between the Japanese subjects (Study 055) and Caucasian subjects (Study 008).

A study (Study 62) of heterozygous familial hypercholesterolemic Japanese patients is currently evaluating the efficacy and safety of rosuvastatin for 52 weeks. This trial involves patients with markedly elevated baseline LDL-C levels (mean baseline LDL-C was 304 mg/dL; eligibility criterion for fasting LDL-C \geq 220 mg/dL). This patient population reflects the small percentage of patients who require aggressive lipid-lowering therapy.

After a 4-wk dietary lead-in period, 37 patients were treated with rosuvastatin 10 mg. After 6 weeks, patients were titrated to 20 mg followed by titration to 40 mg after another 6 weeks. Patients remained on rosuvastatin 40 mg daily for 40 weeks. The mean LDL-lowering response during the dose-titration period is summarized in the following table:

Table 11. % LDL Change in Japanese Patients with HeFH

Study design	10 mg daily		20 mg daily		40 mg daily	
	← O to Wk 6 →		← Wk 6 to Wk 12 →		← Wk 12 to Wk 52 →	
Week	2	6	12	18	18 LOCF	
n	36	36	36	34	37	
Mean % chg	-38.5	-49.2	-53.9	-56.7	-56.7	
SD	10.8	10.0	10.1	10.3	9.9	

After Week 18, all patients remained on rosuvastatin 40 mg daily. The mean LDL change during 8 visits in this fixed-dose period ranged from -55.3% to 58.9%. The LOCF analysis at Wk 52 demonstrated a mean change in LDL from baseline of -58%. Since this trial involved a force-titration design, a comparison of LDL-lowering response cannot be made between the 20 and 40 mg dose.

These data support the effectiveness of rosuvastatin in different Asian subgroups; however, the trials are of too short duration and are of inadequate exposure to address safety. The recommendation for special dosing in Asians based on the pK studies in Japanese and Chinese patients are intended to address potential dose-related safety concerns. In particular, patients treated with the 40 mg dose may be exposed to drug levels expected for the 80 mg dose.

While it is possible that some patients treated with 40 mg might experience drug levels within the range for 80 mg, one cannot conclude that this exposure will absolutely result in an adverse event. The majority of patients exposed to 80 mg in this clinical development did not develop myopathy or rhabdomyolysis, hence additional factors most likely contribute to the statin-induced muscle toxicity. Nonetheless, an increased risk of myopathy will be present in these individuals regardless of the presence or absence of other factors. Use of rosuvastatin 40 mg in any patient population exposed to higher drug levels (e.g., renal insufficiency or perhaps patients of Japanese or Chinese ancestry) should be reserved only for situations in which the risk of CHD outweighs the risk of dose-related toxicity.

The 40 mg dose is not recommended as a start dose in any patient population. The label will emphasize that this dose is indicated only for those patients who have failed to achieve their LDL-C goals at the 20 mg dose with a reference to the WARNINGS,

myopathy/rhabdomyolysis section. In this WARNINGS section, prescribers will also be referred to the CLINICAL PHARMACOLOGY and PRECAUTIONS sections which discuss the PK study findings in resident Japanese patients and Chinese patients living in Singapore.

The sponsor has stated that their marketing strategy will not encourage the use of the 40 mg dose. In their July 18, 2003 submission the sponsor confirmed that the 40 mg dose will not be available as professional samples and that the 40 mg tablet bottles will not be available directly to retail pharmacies. Retail pharmacies must go through a wholesaler to obtain this dose. A combination of labeling and limited marketing of the 40 mg dose to the general population may be a sufficient risk management tool at present until further studies are conducted (see Phase 4 Studies section).

PHASE 4 COMMITMENT

On July 21, 2003 the Division requested that the sponsor conduct a PK study of Asians residing in the United States to explore the PK differences observed in Japanese residing in Japan and Chinese residing in Singapore. The sponsor has responded (July 22, 2003) with a commitment to conduct this study and submit the final report to the Agency within 26 months of the NDA approval date.

LABELING

The sponsor's proposed labeling has undergone significant changes with the input from different FDA review disciplines during several labeling negotiations. This memo will only highlight the pertinent aspects of the label, and this reviewer refers the reader to the action letter which will contain a version of the final approved label.

Rosuvastatin will be indicated for the following:

1. as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb);
2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
3. to reduce LDL-C and total-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

The safety findings pertaining to muscle toxicity are summarized under the WARNINGS; Myopathy/Rhabdomyolysis section. Special populations requiring different dosing instructions are cross referenced to the CLINICAL PHARMACOLOGY and DOSAGE ADMINISTRATIONS sections.

The renal laboratory abnormalities are described under the Laboratory Tests subsection of PRECAUTIONS and Laboratory Abnormalities subsection of ADVERSE REACTIONS. Under PRECAUTIONS, drug dose reduction is recommended for patients with persistent, unexplained renal laboratory abnormalities.

The DOSING and ADMINISTRATION section discusses rosuvastatin 5 and 10 mg doses as optional start doses in the general population. The 20 mg dose is the recommended start dose for patients with marked hypercholesterolemia or HoFH. The 40 mg dose is reserved only for those individuals not achieving LDL goals at the 20 mg

dose and is cross-referenced to the WARNINGS; myopathy section to alert the prescriber of risks associated with using the highest dose of rosuvastatin.

Special dosing recommendations are made for patients taking cyclosporine (rosuvastatin 5 mg daily only) and gemfibrozil (rosuvastatin 10 mg maximum daily dose). Patients with renal insufficiency should not receive rosuvastatin doses higher than 10 mg daily.

No specific language for dosing was recommended for patients of Asian ethnicity as this category includes a broad group of different nationalities to which the two non-US pK studies in Japanese and Chinese cannot be reasonably extrapolated. However, the persistent concern that these two studies might represent a large number of Asian Americans who have a 2-fold higher exposure to rosuvastatin drug levels compared to Caucasians requires special attention under the CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS section of the label. These sections of the label may change upon review of the Phase 4 pK study.

CONCLUSIONS

The sponsor has adequately addressed the clinical deficiencies outlined in the May 31, 2002 AE letter. Specifically, they have exposed a significantly greater number of patients at the 20 and 40 mg doses and for a longer duration of treatment to allow the conclusion that the risk of myopathy at the 40 mg and lower doses did not exceed currently marketed statins.

While findings of proteinuria with and without microscopic hematuria are still evident at the 40 mg dose, the absence of inadequate control data and the presence of co-morbid medical conditions complicate the interpretation of these findings in both the sponsor's and Dr. Lubas' analyses. Despite this, it is noteworthy that no patients treated with rosuvastatin 40 mg (1,875 pt-yrs of exposure) or lower developed clinical renal deterioration that could be attributed to drug treatment. The data from current large, controlled, ongoing studies at the 40 mg dose may further alter the current label.

While some of these safety issues remain unanswered, it is evident that the 40 mg dose is effective and will allow those patients with exceedingly elevated LDL-C levels and at high risk for a CVD event to significantly lower their cholesterol levels without resorting to combination lipid-altering therapies. The sponsor asserts that the number of patients requiring the 40 mg dose makes up a minority of patients with lipid abnormalities. A commitment on restricted marketing of the 40 mg dose by the sponsor and precautionary labeling should ensure that only those patients who require aggressive lipid-lowering will be treated at this dose.

In conclusion, NDA 21-366 should be approved for the marketing of rosuvastatin 5, 10, 20, and 40 mg.

ADDENDUM: Please see addendum to Medical Team Leader Memo submitted to DFS for NDA 21-366 on 8-12-03. This addendum discusses a post-marketing spontaneous AER from the United Kingdom received by the FDA on 7-31-03 and summarizes the changes to the Dosage and Administration section of the Crestor® label.

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/s/

Mary Parks

8/12/03 01:37:30 PM

MEDICAL OFFICER

Please see addendum to Medical Team Leader's Memo

Robert Meyer

8/12/03 02:40:10 PM

MEDICAL OFFICER

Signed for Dr. Orloff

ADDENDUM TO MEDICAL TEAM LEADER MEMO

NDA# 21-366
Drug: Crestor® (rosuvastatin)
Sponsor: Astra-Zeneca
Date of Submission: February 12, 2003
Date of Review: August 12, 2003
Reviewing Medical Officer: Mary H. Parks, MD
Deputy Director
Medical Team Leader
Division of Metabolic and Endocrine Drug Products
(HFD-510)

Spontaneous Post-Marketing Adverse Event Report

Astra-Zeneca reported to the Agency by telephone on 7-31-2003 and by facsimile on 8-01-03 a spontaneous post-marketing adverse event in the United Kingdom. This case involved an 82 year-old woman who was initiated on rosuvastatin 10 mg once daily on 5-6-03 for hypercholesterolemia (LDL-C ~ 171 mg/dL). The patient had a history of hypertension. Concomitant medications included atenolol/chlorthalidone, aspirin 75 mg once daily, and diclofenac 50 mg three times daily. The patient's baseline serum creatinine was 0.9 mg/dL (75 mmol/L). On 7-17-03 her physician prescribed flucloxacillin 500 mg four times daily for an infected sebaceous cyst and rash. The patient returned on 7-22-03 with complaints of "feeling worse". An acute wheezy bronchitis and psoriatic rash were reported. Cephalexin 500 mg three times daily was prescribed for the bronchitis and Betnovate cream was prescribed for the rash. Additional blood work performed on 7-22-03 revealed an elevated serum creatinine of 9.0 mg/dL (798 mmol/L); alkaline phosphatase and ALT levels were also increased to 263 U/L and 63 U/L, respectively. The patient was hospitalized on 7-23-03 with a peak serum creatinine of 10 mg/dL (833 mmol/L). Although her blood pressure was recorded as 190/89 and the report stated that the patient was euvolemic, treatment with intravenous fluids was initiated and subsequent serum creatinine measures declined to the 2.3 mg/dL. Serum creatine kinase level was 215 U/L; there was no evidence of rhabdomyolysis. A renal ultrasound was normal. Renal biopsy was performed on 7-25-03 and initial light microscopy showed degeneration of tubular epithelial cells with areas of regeneration. Glomeruli were intact. There was evidence of mild interstitial nephritis and infiltration with lymphocytes and eosinophils. This was reported as background changes secondary to vascular disease. Immunofluorescent and other stainings of the biopsy sample are pending.

The lowest dose of rosuvastatin marketed in the United Kingdom is 10 mg.

Discussion

While it cannot be concluded from this case that rosuvastatin therapy was the causative agent for acute renal failure, this case highlights the following question posed by the Agency to the Endocrinologic and Metabolic Drugs Advisory Committee on dosing recommendations at the July 9, 2003 Advisory Committee for Crestor®.

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?

This question was raised because the sponsor had proposed to label the 10 mg dose as the recommended start dose for the general population while reserving the 20 mg dose for individuals requiring aggressive LDL reductions (e.g., patients with baseline LDL-C > 190 mg/dL). The 5 mg dose was available for only patients treated with cyclosporine as pharmacokinetic studies demonstrated a 7-fold increase in rosuvastatin drug levels when co-administered with cyclosporine.

As summarized in this Medical Team Leader's memo, the 5 mg dose is an effective dose, achieving a mean LDL-C reduction (45%) that exceeds the average lowering observed with the lowest start doses and some intermediate start doses of other marketed statins. This dose was also shown in a clinical trial to achieve NCEP LDL-C goals in 67% of patients with Fredrickson Types IIa/IIb. Consequently, FDA reviewers have concluded that since the 5 mg dose will be marketed in the United States, this dose should also be recommended as an optional start dose based on an individual's CHD risks, baseline LDL-C levels, and target LDL-C.

This recommendation also takes into consideration concerns regarding dose-related toxicities. The sponsor has argued that their clinical development program revealed similar safety profiles for the 5 and 10 mg doses. For the entire cohort evaluated, this is the case. However, subgroups with increased risks for drug-related toxicities and myopathy comprised a small percentage of patients studied in this drug application. Specifically, patients with severe renal impairment comprised 0.3% of the cohort; Asians comprised 1.9% of the cohort, and patients 75 years and older comprised 7.3% of the cohort. These patients, along with hypothyroid patients, have been identified by the sponsor as subgroups that may be predisposed to myopathy with statin therapy. In these patients, the recommended start dose of rosuvastatin should be 5 mg once daily with dose-adjustments made based on patient response and tolerability.

The DOSAGE AND ADMINISTRATION section of the Crestor® label has been revised to include the 5 mg dose as an optional start dose for patients who require less aggressive LDL-C reductions and in patient with predisposing factors for myopathy. Patients with severe renal insufficiency should be started at the 5 mg dose and daily dose should not exceed 10 mg.

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/s/

Mary Parks
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MEDICAL OFFICER

Robert Meyer
8/12/03 02:43:29 PM
MEDICAL OFFICER
Signed for Dr. Orloff

MEMO TO DIVISION FILES

NDA# 21-366 N000 Resubmission Amendment-Addendum to Medical Officer's Review

Sponsor: IPR Pharmaceuticals Inc.

Drug Name: Crestor™

Category: lipid-lowering agents

1) Items reviewed as part of sponsor's resubmission

2/12/2003 Clinstat resubmission -ISS, financial disclosure information

5/14/2003, 6/16/2003

Foreign Spontaneous Reports and Number of Foreign Prescriptions Dispensed

5/16/2003, 5/20/2003 and 6/10/2003A

Safety SAS datasets AL_LBUR, AM_LBUR and AV_LBUR

6/10/2003 ConMed, AE, Labs DDEMOG, Urine SAS datasets, 4 month SUR

6/11/2003A Draft of Opossum Kidney Cell studies

6/12/2003 FDA advisory briefing packet

6/19/2003 Electronic narratives of cases of CK elevations and Myopathy, or ALT and bilirubin elevations requested by medical reviewer

2) The 4 month Safety Update and the 4 month Safety SAS datasets, submitted 6/10/2003, were reviewed along with the original safety data, submitted 2/12/2003, in the medical officer's safety review.

William Lubas MD-PhD

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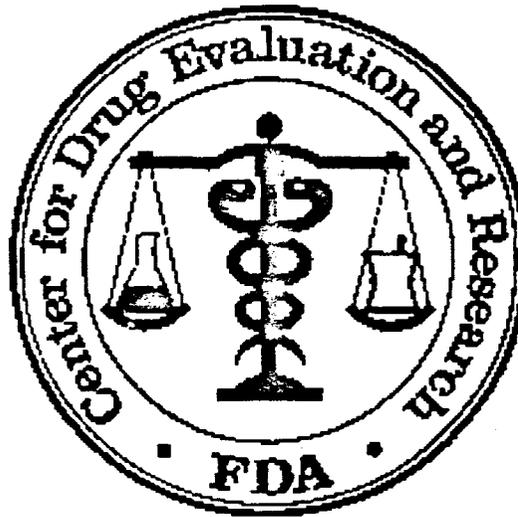
/s/

William Lubas
7/28/03 03:46:11 PM
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Mary Parks
7/29/03 12:52:44 PM
MEDICAL OFFICER

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: JUNE 14, 2002



Comments:

The Informal Meeting with the Division regarding NDA 21-366 has been scheduled for the following:

Date: July 26, 2002

Time: 01:00 PM

Place: PKLN 3rd Flr Conference Center

FDACDER Participants:

David G. Orloff, M.D., Director
Mary H. Parks, M.D., Deputy Director
William Lubas, M.D., Ph.D., Clinical Reviewer
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
Sang M. Chung, Ph.D., Biopharmaceutics Reviewer
Stephen Moore, Ph.D., Chemistry I Team Leader
Sharon L. Kelly, Ph.D., Chemistry Reviewer
Todd Sahlroot, Ph.D., Team Leader, Biometrics 2
Joy Mele, M.S., Mathematical Statistician
Enid Galliers, Chief, Project Management Staff
William C. Koch, R.Ph., Regulatory Project Manager

Don't hesitate to call with any questions!

TO:

Name: Mark S. Eliason, M.Sc.
U.S. Regulatory Affairs Project Director

Fax No.: (610) 578-8851

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Location: AstraZeneca Pharmaceuticals LP

Pages (including this cover sheet): One (1)

FROM:

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William Koch
2/24/03 05:47:41 PM
CSO

Meeting Date: July 26, 2002 Time: 01:00 PM

Location: PKLN 3rd Flr Room "L"

NDA 21-366

Crestor (rosuvastatin calcium) Tablets

Type of Meeting:

Face-to-Face Guidance End of Review Conference

External Participant:

iPR Pharmaceuticals, Inc.

Meeting Chair:

David G. Orloff, M.D., Director

External Participant Lead:

Dr. Howard Hutchinson, Executive Medical Director,
USDD

Meeting Recorder:

William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

David G. Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products (DMEDP),
ODE II

Mary H. Parks, M.D., Deputy Director, DMEDP,

William Lubas, M.D., Ph.D., Clinical Reviewer, DMEDP

Hae-Young Ahn, Ph.D., Team Leader, Division of Pharmaceutical
Evaluation II, OCPB @ DMEDP

Sang M. Chung, Ph.D., Biopharmaceutics Reviewer, Division of Pharmaceutical
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Todd Sahlroot, Ph.D., Team Leader, Division of Biometrics 2, OB @ DMEDP

Joy Mele, M.S., Mathematical Statistician, Division of Biometrics 2, OB @ DMEDP

Enid Galliers, Chief, Project Management Staff, DMEDP

William C. Koch, R.Ph., Regulatory Project Manager, DMEDP

External participant Attendees (by phone) and titles:

**APPEARS THIS WAY
ON ORIGINAL**

Dr. Howard Hutchinson	Executive Medical Director, USDD
Dr. Jim Blasetto	Senior Medical Director, USDD
Dr. Mike Cressman	Medical Director, USDD
Dr. John Pears	Medical Director, Global Clinical Development
Dr. Dennis Schneck	Senior Medical Director, Experimental Medicine
Dr. Bruce Birmingham	Assistant Director, Experimental Medicine
Dr. Richard Caplan	Director, Biostatistics
Ms. Susan Harris	Statistical Scientist, Biostatistics
Dr. Steven Miller	Executive Director, USRA
Mr. Mark Eliason	Regulatory Affairs Director, USRA
Dr. Maurice Briggs	Associate Director, USRA
Ms. Colette Clarke	Regulatory Affairs Director, Global R&D
Dr. Brian Bryzinski	Senior Medical Director, Global Clinical Development
Ms. Adele Gulfo	Therapeutic Area Leader

Meeting Objectives:

To discuss what further steps need to be taken by the applicant before this application can be approved.

Discussion Points and Questions Submitted by Industry:

1. As presented in Section 1, does the Division agree that the data for rosuvastatin, and the other presented statins, demonstrate that when it occurs an important signal of skeletal muscle toxicity is evident within 6 to 12 weeks of exposure?

The Division does not find that 6 to 12 weeks of exposure is adequate to identify important signals of skeletal muscle toxicity. The Division found that none of the 6 original cases of rhabdomyolysis had a CK elevation > 10xULN in the first 12 weeks on rosuvastatin and only 1 out of 6 patients had CK>10XULN (and rhabdomyolysis) within 12 weeks (84 days) of onset of treatment with the 80mg dose.

The applicant asked what additional exposure could be needed if a safety signal is seen in 24 weeks.

The Division cannot answer in the absence of data on the basis of which to make a judgment of concern or non-concern regarding muscle safety.

The Division asked the applicant to include AST elevations in the integrated summary of safety (ISS).

The applicant stated that AST elevations will be included.

2. As presented in Section 1.1, does the Division agree that the proposed overall exposures for 20 and 40 mg/d doses for a NDA resubmission are appropriate to evaluate the potential of myotoxicity?

The Division would want to see exposures (at the highest to be approved dose) similar to that with 80mg in the original NDA. Assuming a rate of 0.3%, the probability of observing one case of myotoxicity with 900 patients is greater than 90% and with 600 patients, the probability is 84%. The Division would be willing to accept 600 patients at >24 weeks for each dose with the understanding that additional patient exposure will be included in the applicant's real-time "snap-shot" clinical data.

The Division was concerned that an adequate number of patients with diabetes, CHD, advanced age and diminished renal function be included in these 600 patients.

The applicant stated that the patient population profiles would be similar to those in the original NDA, and no attempt would be made to select out a healthier, lower risk population.

3. As presented in Section 1.2, does the Division find acceptable the methodology for the normalization of myotoxic risk to the benefit of LDL-C reduction? What would the Division expect to be an acceptable limit for this measurement?

The Division stated that the high end of the spectrum for the currently approved statins would be an acceptable limit. The incidence of myopathy for the approved statins per percent reduction in LDL-cholesterol is < 0.3 and the incidence of myopathy per drug dose is < 0.006. The methodology proposed by the sponsor for defining benefit/risk is considered to be exploratory by the Division and does not constitute a definitive measure.

4. As presented in Section 1.3, does the Division agree that the additional non-Caucasian subject data presented in the proposal are sufficient to support approval? Further, does the Division agree that the Sponsor's clinical trial program initiated since the NDA submission are in-line with its expectations for the study of rosuvastatin in non-Caucasian populations?

The Division agrees with the proposal.

The Division asked what active controls will be used in the trial.

The applicant stated that atorvastatin would be used as an active control.

5. As presented in Section 2, does the Division agree that the Sponsors proposal for the acquisition of additional renal information from studies is appropriate to examine and understand the nature, frequency and magnitude of renal effects and to identify if any renal effects are reversible, chronic or progressive?

The Division agrees with the proposal.

The applicant added that Trial 34 has included more urinalysis, creatinine levels and quantitative data on urine proteins, which will give the data for determination if the proteinuria is transient, reversible and persistent and will determine the long-term effects.

6. As presented in Section 3, does the Division agree that the systemic exposure data for the combined use of rosuvastatin and gemfibrozil are valid and that these data are consistent with that observed for other statins? Is it further agreed that additional studies on this combination are not warranted? Does the Division agree that the available exposure data allows for appropriate dosing instructions in the label?

The Division agreed that additional studies with the combination of rosuvastatin and gemfibrozil are not warranted at this time.

The Division stated that the proposed dosage range must provide adequate safety margins for combination drug therapy wherein a pharmacokinetic interaction with rosuvastatin has been demonstrated. The labeling for rosuvastatin should specify the maximum dose used in these situations.

7. As presented in Section 4, does the Division agree that the extensive data already available on both the 5mg/d and 10mg/d doses indicate no overall difference in safety profile between the two dose regimes? If not, can the Division advise the sponsor on what additional information it seeks from a resubmission on this matter?

The Division stated that because of the way the studies were performed there were inadequate renal and urinalysis data on the 5- and 10-mg doses in the high-risk populations. However, this would only be an issue if the higher doses of 20 and 40 mg could not be approved, or if the applicant considered marketing the lower dose before doing trials with more patients on 20 and 40mg.

There is no chemistry information in the current submission for the 5-mg dose.

The applicant stated that they have a large body of data supporting a 10-mg start dose.

The Division agrees, however, we encourage a 5-mg formulation for special populations and for patients who do not require large LDL-C reductions.

The applicant stated that a 5-mg formulation will be submitted.

8. As presented in Section 4, does the Division agree that the data available on both the 5 mg/d and 10 mg/d doses in elderly subjects (>65 years) are sufficient to support the safe use of 10 mg/d as the start dose in this sub-population?

The Division agrees that the available safety data would support a start dose of 10 mg per day in the geriatric sub-population.

9. As presented in Section 5, does the Division agree that the extensive safety data presented in subjects with mild and moderate renal impairment support the conclusion that no particular safety concerns are associated with this sub-population?

The Division stated that there are still concerns that the results in patients with mild to moderate renal impairment are not conclusive.

The applicant stated that their database shows no correlation between steady-state plasma concentration and creatinine clearance when measured at 9 hours post-dose.

The Division agreed with these findings but noted that this does not rule out a correlation with AUC and creatinine clearance.

The Division suggested submitting trough concentrations to predict the clearance of rosuvastatin on a subset of patients.

The applicant stated that it is difficult to get trough levels because of the night dosing. The applicant plans to have sparse sampling to characterize the relationship between rosuvastatin AUC and CL_{cr} in an ongoing clinical trial.

The Division agrees with the proposal.

10. As presented in Sections 1, 2 and 6, does the Division agree that clinical laboratory data (CK, urine analysis, serum creatinine), along with serious adverse event reports, are the important features in assessing the potential skeletal muscle and renal issues?

The Division agrees with the applicant's proposal.

11. As presented in Sections 2 and 6, does the Division agree that an increase from baseline in serum creatinine of 30% is an appropriate alert level in identifying clinically meaningful renal toxicity?

The Division agreed to the 30% increase from baseline as a reasonable alert level for identifying clinically meaningful renal toxicity.

12. As presented in Sections 1, 2 and 6, in regards to the updated exposures to be presented in the NDA resubmission, does the Division agree with the Sponsor's position that real-time clinical laboratory data (snapshot data), along with serious adverse event reporting are acceptable for the final assessment of the overall safety profile of rosuvastatin?

The Division agrees with the applicant's proposal, but also requested that AST levels and any laboratory data resulting from hospitalizations be included in the amendment data.

13. As presented in Section 6, does the Division agree that a discussion of common Adverse Events need not be presented in the proposed updated ISS unless a significant change has occurred since the previous submission?

The Division agrees with the proposal.

Regulatory Issue:

The Division stated that the applicant's response to these issues would have a 6-month regulatory clock for review. A 4-month safety update will also be required.

Unresolved or Issues Requiring Further Discussion:

- None

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/s/

David Orloff :
8/22/02 05:34:46 PM

Meeting Date: November 1, 2001 Time: 02:00PM Location: PKLN Room #13B-45

NDA 21-366 Crestor (rosuvastatin calcium) Tablets

Type of Meeting: Phase 3 guidance

External Participant: AstraZeneca, LP

Meeting Chair: Mary Parks, M.D., Deputy Director

External Participant Lead: Mark Eliason, US Regulatory Affairs Product Director

Meeting Recorder: William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

Mary Parks, M.D., Deputy Director
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
Sang M. Chung, Ph.D., Biopharmaceutics Reviewer
William Lubas, M.D., Ph.D., Clinical Reviewer
William C. Koch, R.Ph., Regulatory Project Manager

External participant Attendees (by phone) and titles:

Dennis Schneck, M.D., Ph.D., Senior Medical Director, Experimental Medicines
Howard Hutchinson, M.D., U.S. Executive Medical director
James Blasetto, M.D., Global Team Physician
Bruce Birmingham, Ph.D.
Maurice Briggs, Ph.D., U.S. Senior Regulatory Project Manager
Mark Eliason, US Regulatory Affairs Product Director

Meeting Objectives:

To discuss the drug-drug interaction study with gemfibrozil requested by the Division on October 25, 2001

Discussion Points: (Questions submitted by industry)

1. Is there any additional background information regarding the basis for the request of October 25, 2001, that the Division can provide to AstraZeneca to produce a protocol for the requested trial that will meet both the Agency's and the sponsor's objectives?

The Division stated that not all of the recently acquired information is disclosable, but new safety data resulting from the recent withdrawal of cerivastatin from the market prompted the drug-drug interaction study request.

2. Is the Division considering class language regarding the combination use of gemfibrozil and statins?

The Division stated that class labeling is one of the options in response to the citizens petition submitted August 20, 2001, and received by the Center August 24, 2001. The Division will probably be requesting labeling changes for the already marketed products in the statin class dependent upon the metabolic pathway of the individual drug and upon the clinical relevance of concomitant administration of gemfibrozil to each individual drug.

The effect of concomitant administration of gemfibrozil with rosuvastatin on the resulting rosuvastatin label will depend upon the data from this requested study.

3. Does the Division agree with the dose choice for rosuvastatin for the requested study?

The Division would prefer that the applicant use a 40 mg dose for this study, because of the lack of a safety margin for the 80 mg dose. The Division has no concerns with the 80 mg dose for this single-dose study, but the Division would have concerns for future longer studies if this requested study were to show a 40 to 50% increase in the rosuvastatin concentration with gemfibrozil.

The applicant stated that other drug-drug interaction studies were completed using an 80 mg dose and they would prefer to keep the 80 mg dose for consistency.

- 4a. Does the Division agree to the design proposal described?

The Division considers the study design acceptable.

- 4b. Does the Division accept the use of an unmatched lactose placebo in this trial?

The Division considers the use of an unmatched placebo to be acceptable for this study.

5. Does the Division agree that the selection of a 30% difference between treatment groups in the primary endpoints is appropriate?

The Division stated that according to the Guidance for Industry *In Vivo Drug Metabolism/Drug Interaction Studies – Study Design, Data Analysis, and Recommendations for Dosing and Labeling*, 80% to 125% of a 90% confidence interval is a standard method for the sponsor to claim no drug-drug interaction.

The applicant stated that they would not seek drug interaction labeling claims from this study.

The Division will accept, however, up to a 30% difference as no clinically significant drug interaction. Data submitted from this study could be included in the label as descriptive information.

6. Does the Division agree with the proposed timelines?

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/s/

Mary Parks
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Meeting Date: August 16, 2001 Time: 02:00 PM Location: PKLN Room #14B-45

NDA 21-366

Crestor (rosuvastatin calcium) Tablets

Applicant:

AstraZeneca Pharmaceuticals LP

Type of Meeting:

NDA Filing (45-day)

Meeting Chair:

Mary Parks, M.D., Clinical Team Leader

Meeting Recorder:

William C. Koch, R.Ph., Regulatory Project
Manager

FDA Attendees and titles:

Karen Davis-Bruno, Ph.D., Supervisory Pharmacologist
John Gong, Ph.D., Pharmacology Reviewer
John K. Jenkins, M.D., Office Director (ODEII)
Mary Parks, M.D., Clinical Team Leader
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
Sang M. Chung, Ph.D., Biopharmaceutics Reviewer
Stephen Moore, Ph.D., Chemistry Team Leader
William Lubas, M.D., Ph.D., Clinical Reviewer
Todd Sahlroot, Ph.D., Team Leader, Biometrics 2
Joy Mele, M.S., Mathematical Statistician
Cynthia Liu, M.S., Mathematical Statistician
Enid Galliers, Chief, Project Management Staff
William C. Koch, R.Ph., Regulatory Project Manager

PROJECT MANAGER REVIEW

Application Submitted: June 26, 2001

Application Received: June 26, 2001

Filing Date: August 25, 2001 (notification by August 24, 2001)

New Indication(s) requested: Fredrickson Type IIa, IIb and IV.

1. Filing Discussion:

Clinical - fileable

Clinical reviewer provided information on applicant's reporting of the occurrence of myositis and rhabdomyolysis.

Financial Disclosure - provided

- Pharmacology/Toxicology - fileable
 - Micro Not Needed
 - Devices Not Applicable
 - Chemistry - fileable
1. The chemistry team leader pointed out structural similarities between the rosuvastatin calcium and cerivastatin sodium molecules.
 2. This observation may be significant since cerivastatin was recently withdrawn from the market because of the incidence of rhabdomyolysis associated with cerivastatin use (refer to Post-Meeting Activity).

Establishment Evaluation Requests (EER) – Valid for 2 years, route request to HFD-324.

Environmental Assessment (EA/FONSI) –

Categorical Exclusion – requested by applicant

- Biopharmaceutics - fileable
- Biostatistics - fileable

reviewer will request addition paper review copies of specific sections.

- DSI

specific sites for inspection will be discussed with Dr. Blay as soon as possible.

REGULATORY SECTION

1. Priority or Standard Review schedule: Standard
2. Clinical Audit sites (list): Will be provided by Clinical Reviewer
3. Advisory Committee Meeting: To be determined

4. Review Timelines/Review Goal Date (with labeling):

Consults Due:	N/A
Reviews Completed:	03/15/02
To Division Director:	03/26/02
To Office Director:	04/05/02

5. Action Items:

Because of the large amount of information required to be reviewed in this application, the team requested that the project manager schedule monthly status meetings beginning the last week of November 2001.

6. Post-Meeting Activity

Following the meeting, the chemistry team leader informed the meeting participants that the rosuvastatin structure most closely resembled cerivastatin of all the approved and investigational (under review) substances in the statin class.

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/s/

William Koch
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Meeting Date: October 2, 2000 Time: 10:00AM Location: PKLN 3rd flr "chesapeake"
IND 56,385 (rosuvastatin calcium, ZD-4522)
Type of Meeting: Pre-NDA
External Participant: AstraZeneca Pharmaceuticals
Meeting Chair: David G. Orloff, M.D., Director
External Participant Lead: Mr. Mark Eliason, US Regulatory Affairs Product Director
Meeting Recorder: William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

John K. Jenkins, M.D., Office Director (ODEII)
David G. Orloff, M.D., Director
Mary Parks, M.D., Medical Officer
Karen Davis-Bruno, Ph.D.; Pharmacology Team Leader
John Gong, Ph.D.; Pharmacology Reviewer
Todd Sahlroot, Ph.D., Team Leader, Biometrics 2
Joy Mele, M.S., Mathematical Statistician
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
Xiaoxiong Wei, M.D., Ph.D. Biopharmaceutics Reviewer
Sang M. Chung, Ph.D., Biopharmaceutics Reviewer
George Liao, Regulatory Health Information Specialist
William C. Koch, R.Ph., Regulatory Project Manager

External Participants and titles:

Dr. Dennis Schneck, Senior Medical Director, Experimental Medicines
Dr. Robert Timko, Manager, US Technical Regulatory Affairs
Dr. John Shatwell, Pharmaceutical Project Manager
Dr. David Stong, Director, Preclinical Sciences
Dr. Robert C. Scott, Global Product Team Toxicologist
Dr. Richard Caplan, Global Team Statistician
Dr. Rohini Chitra, U.S. Senior Statistical Scientist
Dr. Steven Miller, Executive Director, U.S. Regulatory Affairs
Dr. Howard Hutchinson, U.S. Executive Medical director
Dr. John Pears, Global Product Team Physician
Dr. James Blasetto, Global Team Physician
Dr. Michael Warwick, Global Kinetics Project Manager
Dr. Lisa Martin, Manager, Pharmaceutical Sciences
Dr. Andrew Jones, Senior Team Manager

Dr. Richard Olbrich, Manager, Regulatory Affairs
Ms. Lo Ann McCardell, U.S. Regulatory Operations Manager
Ms. Colette Clarke, Global Regulatory Affairs Director
Dr. Maurice Briggs, U.S. Senior Regulatory Project Manager
Mr. Mark Eliason, US Regulatory Affairs Product Director
Ms. Jacqueline Little, US Regulatory Project Manager

Meeting Objectives:

To advise the applicant on this proposed new NDA's development plan, and to answer the applicant's questions regarding the submission.

Discussion Points: (Questions submitted by industry)

- Non-Clinical Pharmacology and Toxicology

3.2.1 Does the FDA request any additional information regarding the status of the toxicokinetic portions of the early Japanese GLP studies, aside from completed reports, as part of the original NDA submission.

No

3.2.2 Does the FDA agree with the sponsor's proposal for submission of only the English translated GLP reports to the rosuvastatin calcium NDA?

Yes

3.2.3 Does the FDA agree with the sponsor's approach to the presentation of the information from non-clinical pharmacology reports?

Yes.

- Human Pharmacokinetics and Bioavailability

3.3.1 Does the FDA agree to the statistical methodology used to form the conclusions of the trial on food effect? (The 0005 study data were summarized by the sponsor).

As follow-up to the February 1999 End-of-Phase 2 meeting, does the FDA agree with the sponsor's interpretation of the food effect trial data?

Deferred. This is a review issue (as opposed to a developmental issue), therefore the Division cannot advise the sponsor until the all of the data has been reviewed.

The Division recommended that the food-effect study not be repeated until all data is reviewed.

The Division stated that no labeling recommendations could be made until the review process is completed.

3.3.2 Does the FDA consider the format for the Item 6 Summary an acceptable approach for the presentation of the Human Pharmacokinetics and Bioavailability information?

Yes. The Division requested the inclusion of a two page final synopsis of the submitted data for each study.

- Clinical

3.4.1 Would the FDA please comment on our view (regarding a priority review)?

Based on the criteria used to determine whether an application should receive priority review status it is unlikely that rosuvastatin will receive a 'P' review. Although it appears from preliminary study results that this drug product is a more effective LDL-lowering agent compared to atorvastatin and that more patients will achieve NCEP goals at the 80 mg dose than atorvastatin 80 mg-dosed patients, these endpoints are still surrogate markers of clinical benefit. The more meaningful endpoint of benefit is reductions in CV mortality and morbidity for which several marketed statins have already been able to establish in both the primary and secondary prevention populations. It is unlikely that AstraZeneca will be able to produce these results with their product to receive priority review.

3.4.2 Does the FDA agree that the plans for assessment of the rosuvastatin initiating dose and maximum dose for marketing is appropriate?

The team stated that the starting dose must demonstrate a minimum 15% LDL-C reduction from baseline compared to placebo with an adequate safety margin. Historically, the Division has required a minimum exposure of 200 patients for 1 year with exposure skewed to the higher doses to demonstrate safety. This is a deviation from the ICH guidelines for chronically administered drugs for the treatment of non-life threatening illnesses which requires a minimum of 100 patients exposed for 1 year.

3.4.3 Does the Division agree that the number of patients exposed to rosuvastatin, and the timing of its presentation in the NDA, are sufficient for the assessment of the rosuvastatin NDA?

The sponsor should submit 12-month safety exposure data up to the 80 mg dose at the time of initial NDA submission. The initial NDA submission should have available all data necessary for the determination of safe and effective use of this product at all doses. The safety update should provide any additional safety information acquired during open-labeled extension trials but the Agency should not have to rely on these data in order to establish safety at the higher doses of the dosage range.

The sponsor requested that the Division schedule a telephone conference after the submission of updated safety exposure data.

3.4.4 Does the FDA agree with this approach (presented paragraph 3.4.4 of the pre-meeting package) to presenting inflammatory marker information?

The clinical benefits of lowering inflammatory markers in patients with CAD has not been independently established. Furthermore, the direct effects of a lipid-altering drug on these markers has not been demonstrated. Given these issues, changes in CRP, IL-6, and other inflammatory markers are not appropriate in drug labeling.

3.4.5 Does the FDA find this approach (presented in paragraph 3.4.5 of the pre-meeting package) to handling the safety information from ongoing studies during the NDA review acceptable?

The Division requests open-label case reports in addition to those from the blinded studies. The Division requests narrative summaries for CRFs involving liver and muscle related events as well as for withdrawals and deaths.

3.4.6 Does the FDA agree that the trial design (Trial 4522IL0054) and the information to be made available in the original rosuvastatin NDA would be sufficient for the indication in homozygous familial hypercholesterolemia?

Yes. Provided that there is a minimum treatment duration of 6 weeks at 80 mg and that the LDL-C endpoint be obtained pre-apheresis.

3.4.7 [

3.4.8 Does the FDA find these proposals (in Appendices D and E of the pre-meeting package) for presentation of the content for the ISS and ISE to be acceptable?

Yes. The format is acceptable.

3.4.9 Does the FDA find the proposals for the production and presentation of the 4-month safety update to be acceptable in principle?

Yes. Emphasize again that the 1 year safety exposure data for 80 mg needs to be available at the time of initial NDA submission. The Division stated that data related to muscle and liver function will be monitored closely.

The Division requested that a preliminary dataset should be submitted to the biometrics team. This dataset could be reviewed and discussed in a Telephone conference if necessary.

3.5.1 Does the FDA have any comments on the format presentation of the draft package insert at this time?

Overall format is acceptable. Further consideration is required for the presentation of results from comparative trials to atorvastatin calcium. The Division stated that all comparative data may not be approved for the labeling.

3.5.2 Does the FDA agree on these proposals (presented in paragraph 3.5.2 of the pre-meeting package) for the reporting of adverse events in the final package insert for rosuvastatin calcium tablets

Yes. After the review the Division will discuss the cut-off point for reporting Adverse Event data during labeling negotiations.

3.5.3 Does the FDA agree in principle (that the NDA submission supports the labeling in the INDICATIONS AND USAGE section as presented in paragraph 3.5.3 of the pre-meeting package) ?

This is a review issue which will be addressed when all data is reviewed, but the Division stated that the label will be similar to other previously approved statins depending on what inclusions the data supports.

- Chemistry, Manufacturing, and Controls

Does the FDA agree with the selection of [

]

Does the FDA accept the proposals on dissolution testing of the bioequivalence study materials.

The Division's biopharmaceutics team reserved comment on this proposal until the Office of Clinical Pharmacokinetics and Biopharmaceutics can review and comment on the proposal. The office levels comments will be conveyed through a telephone conference.

- Electronic Submission

3.6.1 Does the Division find this approach (as stated in paragraph 3.6.1 of the pre-meeting package) to presenting the submission in electronic format acceptable?

1. The Division requests hypertext links between the table of contents and the document text.

2. The Division agreed with the font size presented. Font sizes no smaller than Times New Roman #10 are acceptable.

3. The Office's information specialist will be available to assist with the electronic submission.

3.6.2 Do the NDA reviewers agree to the sponsor's proposal for their particular NDA review copy?

Does the FDA require, as a review tool, any of the NDA text data/information in an Electronic text format, other than a word version of the annotated package insert.

Paper submissions may not be needed in all sections. The Division will clarify its requirements for paper copies after the NDA is submitted and the review process is started.

3.6.3 Will this presentation of the rosuvastatin NDA submission in electronic format be acceptable to the Division?

Does the Division request a separate approach to the NDA review copy paper Index?

The team considers the index to be acceptable except that the Financial Disclosure Section was not found.

Further information and clarification can be discussed during the review process.

3.6.4 Does the FDA find the sponsor's approach to the data warehouses acceptable?

The SAS datasets need to be discussed further.

3.6.5 Would the FDA comment on its expectations for datasets to accompany the higher level summaries in the rosuvastatin calcium tablet NDA?

The team requests more ISS data and an explanation of the term "higher level Summaries."

Meeting Date: October 2, 2000 Time: 11:30AM Location: PKLN 3rd flr "Chesapeake"
IND 56,385 (rosuvastatin calcium, ZD-4522)
Type of Meeting: Pre-NDA - CMC
External Participant: AstraZeneca Pharmaceuticals
Meeting Chair: Stephen Moore, Ph.D. Chemistry Team Leader
External Participant Lead: Mark Eliason, M.Sc., US Regulatory Affairs Product Director
Meeting Recorder: William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

Stephen Moore, Ph.D. Chemistry Team Leader
Sharon Kelly, Ph.D. Chemistry Reviewer
William C. Koch, R.Ph., Regulatory Project Manager

External Participants and titles:

Robert Timko, Ph.D., Manager, US Technical Regulatory Affairs
John Shatwell, Global Pharmaceutical Project Manager
Lisa Martin, Ph.D., Manager, Pharmaceutical Sciences
Andrew Jones, Ph.D., Senior Team Manager
Richard Olbrich, Ph.D., Global Technical Regulatory Affairs
Mark Eliason, M.Sc., US Regulatory Affairs Product Director
Jacqueline Little, M.Sc., US Regulatory Project Manager

Meeting Objectives:

To advise the applicant on this proposed new NDA's Chemistry, Manufacturing and Controls development plan, and to answer the applicant's CMC questions regarding the submission.

Discussion Points: (Questions submitted by industry)

1. Does the FDA agree that is acceptable to propose as a starting material for the bulk drug synthesis?

Yes, if the Sponsor demonstrates acceptable specifications for _____, which includes a validated impurity profile. In addition, the Sponsor should track the impurities greater than 0.1%, the _____ % w/w maximum) and the _____ % w/w maximum), in the synthesis of the Drug Substance. What is the rationale for setting these limits in the Specifications, since the batch impurity profiles for _____ material indicate that limits less than 0.1% are repeatedly achieved?

The Sponsor should provide proof of the chemical structure in the submission.

The Sponsor states that currently two external sources, _____ are used and one or more additional suppliers will be selected in the future. The Sponsor should demonstrate suitable identity tests, including an impurity test. If no impurity is greater than 0.1%, the _____ is considered equivalent from all sources. If the _____ is synthesized using different routes, the Sponsor should state the differences and track usage.

- The sponsor stated that more production data is available now (than at the time of submission of the pre-meeting package).

The Division advised the sponsor to submit as much data as possible before sending in the NDA.

2. Does the FDA agree that no site specific stability data is needed from the Carolina, PR Manufacturing Facility to support the _____ production scale manufacture, as the current stability protocol agreed with the FDA fulfills the ICH Stability Guidelines for submission?

Yes, but the Sponsor should provide a Certificate of Analysis for the Drug Product which is manufactured at the Carolina site, at the time of the original NDA submission. The Sponsor should indicate on the Certificate of Analysis which production scale was used (_____ production scale).

The Agency understands that the stability data is generated from _____ scale batches manufactured at the _____ site. The Sponsor should provide data which demonstrates that the _____ site and the Carolina site use equipment of the same design and principles for the _____ manufacturing scale.

Does the FDA agree that it is acceptable to provide the (at least) _____ tablets three months real time and accelerated stability data at each of the 'to be marketed' tablet strengths in each of the packs at the time of submission?

Yes. The Agency understands that the stability data is generated from batches manufactured at the _____ site.

Does the FDA agree that no site specific stability data from the Carolina Manufacturing Facility to support the _____ production scale will be required at time of submission, recognizing that AstraZeneca commits to placing the first 3 commercial batches at this _____ manufacturing scale on long term stability to an agreed ICH protocol?

Yes. The Sponsor should provide data which demonstrates that the _____ and the Carolina site use equipment of the same design and principles for the _____ manufacturing scale.

- The sponsor stated that the differences between the process used at the Carolina plant and the Puerto Rico plant are minimal.

The Division requested a minimum of three months data from the Carolina Plant.

- The sponsor will provide three months data on the first lot number of each strength and batch analysis data for the _____ batch manufactured at the Carolina Plant.

The Division accepts this proposal.

3. Additional site of Drug Product Manufacture- _____ facility in Puerto Rico. Manufacture will be at the _____ scale and will use the same process and the same type of equipment to that used in the Carolina facility. In order to support this additional site of manufacture, AstraZeneca proposes to provide, 3 months prior to the PDUFA date, (during the review period) Certificates of Analysis for the first three validation batches of each 'to be marketed' strength manufactured at _____ together with certification that the validation was carried out successfully. AstraZeneca also commits to placing these batches on commercial stability to an agreed ICH protocol.

Does the FDA agree that this proposal is acceptable?

Yes. The Sponsor should provide data which demonstrates that the _____ site and the Carolina site use equipment of the same design and principles for the _____ manufacturing scale.

Additional Questions from CMC pre-NDA Briefing Document submitted August 1, 2000 (serial #139):

4. AstraZeneca intends to submit an electronic version of the NDA, and will supply paper copies on request. AstraZeneca will supply the stability data in the form of an EXCEL-compatible file on request.

Does the Agency agree that this proposal is acceptable?

Yes.

The Division asked for a table summarizing the DMF information and asked that it be placed in the NDA's CMC introduction. The Division also asked for information regarding where the item is referenced in the DMF. In a separate table the Division requested a listing of all manufacturing sites and their corresponding CFN number.

Questions from Section 6:

6.2 Geometry of the 'to be marketed' Blister Packs

Does the FDA agree that this is an acceptable approach to demonstrating packaging equivalence?

Yes, provided the packaging DMF is adequate.

6.3 Materials of the 'to be marketed' Hospital Unit Dose (HUD) Blister Packs

Does the FDA agree that this is an acceptable approach to demonstrating packaging equivalence?

Yes, provided the packaging DMF is adequate. Since different packaging materials are used, at least 3 months real time and 3 months accelerated stability data should be provided.

- The sponsor stated that further information would be provided in an update to explain the Blister Packs packaging equivalence.

6.4 Bottles

AstraZeneca is evaluating the following option for the 80 mg 90 tablet count pack:- 190 ml bottle with — and the — closure as used in the — stability study.

Does the FDA agree that this data from the — stability study will be sufficient to support the introduction of this pack for the 80 mg tablet?

Yes. Three months real time data should be provided.

The stability protocol for the bulk tablet container will be discussed with the Agency. Information is supplied in the CMC pre-NDA briefing document, APPENDIX E.

Chemistry Comments regarding the NDA submission:

Please clarify the differences between the following formulations: TABLETS, ENCAPSULATED TABLETS, "TO-BE-MARKETED"

- More formulation data will be submitted to the IND (IND 56,385).

Process controls for the starting materials and intermediates need to be specified for the synthesis of the Drug Substance, particularly since the yields of the intermediates are currently given as — %.

- The sponsor stated that, the represented range of — % for the yields is to

They agree that the wide range gives the impression that — but this is not the case. They will report the yields obtained for batches produced later in the manufacturing cycle.

The sponsor states that drug substance specifications will be evaluated after the manufacture and stability data were available from the Phase III program. The specification for the impurity profile has changed since the original submission due to the development of — method. Are there any additional anticipated changes in the specifications?

- The sponsor responded that specifications will be provided in a CMC amendment submitted to the IND which is currently in preparation.

Stability indicating — are listed in Table 2 of the CMC pre-NDA briefing document, but where is Table 2?

- The sponsor responded that there was a typographical error in the submission. Table #4 was erroneously referred to as Table #2.

Unresolved or issues requiring further discussion:

- None

Action Items:

- RPM to forward second Biopharm question to Dr. Ahn.

Post-meeting Notes:

From the Chemistry, Manufacturing and Controls questions submitted by the sponsor on August 1, 2000, the sponsor would like the Biopharmaceutics team to consider the following:

Does the FDA agree that in-vitro dissolution as the means of demonstrating bioequivalence of the — scale to the — scale is acceptable?

Prepared by: _____, Meeting Recorder
William C. Koch, R.Ph. date
Regulatory Project Manager

Concurrence: _____, Meeting Chair
Stephen Moore, Ph.D. date
Chemistry Team Leader

cc:

HFD-510 Lipid Altering Agents (original) & background & Attachments
HFD-510/Meeting Minutes files
HFD-510/CSO
HFD-510/reviewers & attendees

Drafted by: WKoch/10.02.00

Initialed by: SKelly10.26.00

final: WKoch/10.26.00

filename: C:/Windows/desktop/IND56385/MTGcmcPNDA1002000.doc

MEETING MINUTES

56,385

Meeting Minutes

Division of Metabolic and Endocrine Drug Products
IND 56,385 Zeneca ZD4522

Date: Wednesday, February 24, 1999
Location: Parklawn, Conference Room "A"
Time: 9:30-11:00AM

FDA and Zeneca Pharmaceuticals Attendees:
See enclosure 1 (9 members from FDA and 11 members from Zeneca)

1. Meeting Objective

This was an End of Phase II meeting requested by the sponsor to present the clinical data for ZD4522 and to discuss the proposed Phase III clinical program to include the safety and efficacy of ZD4522 in the treatment of hypercholesterolemia and mixed dyslipidemias (enclosure 2). A separate meeting has been scheduled for April 29, 1999 for the Chemistry, Manufacturing and Control issues.

2. Discussion Points and Decisions

- Enclosure 3 is a the background package submitted January 28, 1999 with the issues and questions for discussion on page 4. An addendum to the background package was submitted on February 4, 1999 (enclosure 4).

Although FDA minutes are the official documentation of the meeting, we acknowledge receipt of your meeting minutes submitted February 4, 1999 (enclosure 5). These minutes have been reviewed by FDA attendees with agreement and the following notations:

- According to the Clinical Pharmacology and Biopharmaceutics Division, to include "with or without food" in Dosage and Administration, a study is required to show an effect on pharmacodynamics.
- The Division strongly doubts that any study could be done which can assure little to no risk of rhabdomyolysis in combination use of statins and fibrates.
- Any clinical efficacy claims based on lipid lowering will have disclaimer that clinical outcome data are not yet available with this drug.

- Regarding demographic subgroups, the Division agrees to Zeneca's approach to analyze across studies. The studies need to demonstrate a consistent result across different subgroups.

Minutes preparer: M. Simoneau

MS

3/22/99

Concurrence Chairman: Dr. Orloff

MS

4/1/99

cc: Original IND 56,385

DivFile

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commercial

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06/11/03

MEMO

To: NDA 21-366 SN000 2/12/03

From: Karen Davis-Bruno; Ph.D.; Supervisory Pharmacologist HFD-510

Re: Pharmacology/Toxicology labeling comments for supplement #SN000

Date: 6/11/03

CNS and other Toxicities

CNS vascular lesions, characterized by perivascular hemorrhages edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at day 24 at 90 mg/kg/day by oral gavage at systemic exposures 100 times the human exposure at 40 mg/day based on AUC comparisons. Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage at systemic exposures 20 times the human exposure at 40 mg/day based on AUC comparisons. Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day at systemic exposures 60 times the human exposure at 40 mg/day based on AUC comparisons. **T**

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in rats at 2, 20, 60, 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposures 20 times human exposure at 40 mg/day based on AUC. **—** Increased incidence of polyps was not seen at lower doses.

In a 107-week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay or the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus assay.