CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-366

Administrative Documents

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

CRESTOR® (rosuvastatin calcium) Tablets

NDA 21-366

Pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act, the information following below is made of record.

A. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

1. Trade Name:

   CRESTOR®

2. Active Ingredient(s):

   rosuvastatin calcium

3. Strength(s):

   5 mg, 10 mg, 20 mg, and 40 mg tablets

4. Dosage Form, Route of Administration:

   Tablets, Oral

5. Applicant Firm Name/Holder of New Drug Application:

   IPR Pharmaceuticals Inc.
   Carolina, Puerto Rico

   US Agent:

   AstraZeneca Pharmaceuticals LP
   1800 Concord Pike
   Wilmington, DE 19850-5437

6. Approval Date:

N/A

7. Applicable Patent(s):

(i) US Patent No. RE 37,314

(a) Expiration Date:

June 12, 2012 (subject to change if the patent term is extended pursuant to 35 USC 156)

(b) Type of Patent:

US Patent No. RE 37,314 contains drug substance claims.

(c) Name of Patent Owner(s):

Shionogi Seiyaku Kabushiki Kaisha, Japan

(d) Agent Authorized to Receive Notice:

The agent of the patent owner in the United States authorized to receive notice of patent certification under sections 505(b)(3) and (j)(2)(B) of the act and 21 CFR sections 314.52 and 314.95 is:

General Counsel
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

(e) Declaration:

The undersigned declares that US Patent No. RE 37,314 covers the formulation, composition, and/or method of use of CRESTOR® (rosuvastatin calcium) Tablets. This product is the subject of this new drug application for which approval is being sought.

(ii) US Patent No. 6,316,460

(a) Expiration Date:

August 4, 2020 (subject to change if the patent term is extended pursuant to 35 USC 156)

(b) Type of Patent:

US Patent No. 6,316,460 contains pharmaceutical composition claims.

(c) Name of Patent Owner(s):

AstraZeneca AB, Sweden

(d) Agent Authorized to Receive Notice:

The agent of the patent owner in the United States authorized to receive notice of patent certification under sections 505(b)(3) and (j)(2)(B) of the act and 21 CFR sections 314.52 and 314.95 is:

General Counsel
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

(e) Declaration:

The undersigned declares that US Patent No. 6,316,460 covers the formulation, composition, and/or method of use of CRESTOR® (rosuvastatin calcium) Tablets. This product is the subject of this new drug application for which approval is being sought.

(iii) US Patent No. 6,589,959

(a) Expiration Date:

December 23, 2019 (subject to change if the patent term is extended pursuant to 35 USC 156)

(b) Type of Patent:

US Patent No. 6,589,959 contains drug substance and pharmaceutical composition claims.

(c) Name of Patent Owner(s):

AstraZeneca AB, Sweden

(d) Agent Authorized to Receive Notice:

The agent of the patent owner in the United States authorized to receive notice of patent certification under sections 505(b)(3) and (j)(2)(B) of the act and 21 CFR sections 314.52 and 314.95 is:

General Counsel
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

(e) Declaration:

The undersigned declares that US Patent No. 6,589,959 covers the formulation, composition, and/or method of use of CRESTOR® (rosuvastatin calcium) Tablets. This product is the subject of this new drug application for which approval is being sought.

ROBERT J. ORZOLEK

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

CRESTOR™ (rosuvastatin calcium) Tablets

NDA 21-366

Pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act, the information following below is made of record.

A. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

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   rosuvastatin calcium

3. Strength(s):

   5 mg, 10 mg, 20 mg, and 40 mg tablets

4. Dosage Form, Route of Administration:

   Tablets, Oral

5. Applicant Firm Name/Holder of New Drug Application:

   IPR Pharmaceuticals Inc.
   Carolina, Puerto Rico

   US Agent:

   AstraZeneca Pharmaceuticals LP
   1800 Concord Pike
   Wilmington, DE 19850-5437

6. Approval Date:

N/A

7. Applicable Patent(s):

(i) US Patent No. RE 37,314

(a) Expiration Date:

June 12, 2012 (subject to change if the patent term is extended pursuant to 35 USC 156)

(b) Type of Patent:

US Patent No. RE 37,314 contains drug substance claims.

(c) Name of Patent Owner(s):

Shionogi Seiyaku Kabushiki Kaisha, Japan

(d) Agent Authorized to Receive Notice:

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1800 Concord Pike
Wilmington, DE 19850-5437

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(ii) US Patent No. 6,316,460

(a) Expiration Date:

August 4, 2020 (subject to change if the patent term is extended pursuant to 35 USC 156)

(b) Type of Patent:

US Patent No. 6,316,460 contains pharmaceutical composition claims.

(c) Name of Patent Owner(s):

AstraZeneca AB, Sweden

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1800 Concord Pike
Wilmington, DE 19850-5437

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George A. Gilbert

DEC 06, 2001

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

CRESTOR™ (rosuvastatin calcium) Tablets

NDA 21-366

Pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act, the information following below is made of record.

A. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

1. Trade Name:

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   rosuvastatin calcium

3. Strength(s):

   10 mg, 20 mg, 40 mg, and 80 mg tablets

4. Dosage Form, Route of Administration:

   Tablets, Oral

5. Applicant Firm Name/Holder of New Drug Application:

   IPR Pharmaceuticals Inc.
   Carolina, Puerto Rico

   US Agent:

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1800 Concord Pike
Wilmington, DE 19850-5437

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Paul Denerley

PAUL M. DENERLEY, Ph.D.

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

CRESTOR™ (rosuvastatin calcium) Tablets

NDA 21-366

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   Carolina, Puerto Rico

   US Agent:

   AstraZeneca Pharmaceuticals LP
   1800 Concord Pike
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6. Approval Date:

N/A

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(d) Agent Authorized to Receive Notice:

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1800 Concord Pike
Wilmington, DE 19850-5437

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PAUL M. DENERLEY, Ph.D.

EXCLUSIVITY SUMMARY for NDA # 21-366 SUPPL #

Trade Name Crestor Generic Name:rosuvastatin calcium

Applicant Name iPR Pharmaceuticals, LLC HFD-510
Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / X /

   If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES / X / NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Valerie Jimenez Date: August 14, 2003
Title: Regulatory Project Manager

David G. Orloff, M.D. Date: August 14, 2003
Director
Office of Drug Evaluation II

cc:
Archival NDA
HFD- /Division File
HFD-510/RPM/Valerie Jimenez
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Mary Parks
8/14/03 03:47:38 PM
for Dr. Orloff

Exclusivity Checklist

NDA: 21-366				
Trade Name: Crestor Tablets				
Generic Name: rosuvastatin calcium				
Applicant Name: iPR Pharmaceuticals Inc.				
Division: HFD-510				
Project Manager: William C. Koch, R.Ph.				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	X	No	
b. Is it an effectiveness supplement?	Yes		No	X
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	X	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	X	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	five			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes	X	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		No	X
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	X
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes		No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes		No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	
If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #:				
Investigation #2, Study #:				
Investigation #3, Study #:				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?					
Investigation #1	Yes		No		
Investigation #2	Yes		No		
Investigation #3	Yes		No		
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:					
Investigation #1 -- NDA Number					
Investigation #2 -- NDA Number					
Investigation #3 -- NDA Number					
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):					
Investigation #1					
Investigation #2					
Investigation #3					
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.					
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?					
Investigation #1	Yes		No		
IND#:					
Explain:					
Investigation #2	Yes		No		
IND#:					
Explain:					
Investigation #3	Yes		No		
IND#:					
Explain:					
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?					
Investigation #1	Yes		No		
IND#:					
Explain:					
Investigation #2	Yes		No		
IND#:					
Explain:					
Investigation #3	Yes		No		
IND#:					
Explain:					

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	
If yes, explain:				

{See appended electronic signature page}

Signature of PM

Date:

{See appended electronic signature page}

Signature of Division or Office Director

Date:

B. EXCLUSIVITY INFORMATION

Applicant claims an exclusivity period of five years from the date of approval of this New Drug Application pursuant to 21 CFR 314.108(b)(2). To the best of Applicant's knowledge or belief, a drug has not been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act which contains any active moiety in CRESTOR™ (rosuvastatin calcium) Tablets, the drug product for which Applicant is seeking approval.

Item 16 - CERTIFICATION STATEMENT

Re: CRESTOR® (rosuvastatin calcium) Tablets NDA 21-366

iPR Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Gary P. Horowitz 28 July 03

Gary P. Horowitz
Executive Director, US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
Agent for IPR Pharmaceuticals, Inc.
1800 Concord Pike, P. O. Box 8355
Wilmington, DE 19803-8355

John M. Pietri R. Ph. 24 Jul 03

John M. Pietri, R. Ph.
Quality Assurance Systems Manager
IPR Pharmaceuticals, Inc.
P. O. Box 1967
Carolina, PR 00984-1967

Item 16 – CERTIFICATION STATEMENT

Re: CRESTOR® (rosuvastatin calcium) Tablets NDA 21-366

AstraZeneca Pharmaceuticals LP hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Anthony Rogers
Vice President, US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
Agent for IPR Pharmaceuticals Inc.
1800 Concord Pike PO Box 8355
Wilmington, DE 19803-8355

Office Director's Sign-Off Memorandum

Date:	Tuesday, August 12, 2003
NDA:	21-366
Sponsor:	AstraZeneca
Proprietary Name:	Crestor (rosuvastatin calcium) tablets
Date of submission:	February 12, 2003

Introduction: This is the second cycle for this drug product, which is an HMG-CoA reductase inhibitor or 'statin.' This class of drugs reduces cholesterol synthesis in the liver and thereby lowering serum cholesterol. Though not yet proven for this drug, statins have been shown to reduce cardiovascular disease and mortality. The proposed indications for this drug closely follow those of other statins, being for the treatment of hypercholesterolemia, mixed dyslipidemia, homozygous familial hypercholesterolemia and elevated TG's, all in conjuction with lifestyle management (notably, diet).

This drug received an approvable for doses of 40 mg and below and a not approvable for doses of 80 mg in May of 2002. The reason the latter action was taken is that cases of rhabdomyolysis were seen at 80 mg dose in clinical trials, as well there being some evidence of potential renal toxicity at this highest, then proposed dose (proteinuria, +/- microscopic hematuria). There were not sufficient safety data available in the original application for 20 to 40 mg daily dose to provide the necessary assurance for the approval of these doses at that time. The resultant action letter asked for more safety data to support the use of 20 and 40 mg doses, along with establishing the relationship of safety (myotoxicity) to LDL-C lowering to provide assurance that this relationship is no worse than existing statins. The letter also asked for more safety data on renal toxicity and indicated concern over concomitant dosing of rosuvastatin with gemfibrozil and cyclosporine. (See Dr. Kweder's and Dr. Orloff's memoranda from May 2002).

In response to the action letter, the sponsor ceased development of the 80 mg dose and dropped all patients in their on-going studies down to 40 mg. The resubmission contains additional data to support approval of doses from 5 to 40 mg daily, including data on the efficacy and safety of 20 and 40 mg (including patients who for a time received 80 mg daily). The total database currently is approximately 12,500 patients. The resubmitted application was brought to the Endocrine and Metabolic Advisory Committee on July 9th, 2003 who voted unanimously (9 votes to zero) for approval of Crestor at doses of 5 to 40 mg, with the recommendation for 10 mg as the starting dose.

Dr. Orloff and Dr. Parks have written ex
cellent summary memoranda and these should be referred to for more detailed discussions.

CMC: All CMC issues have been resolved. The drug will be available in 5, 10, 20 and 40 mg tablets. Crestor has a categorical exclusion from the environmental assessment. The facility inspections was given an overall acceptable recommendation on April 23,

2003 with all pertinent testing and production facilities receiving acceptable recommendations.

Pharm/Tox: The toxicology data in the resubmission were limited to qualification studies (gene-tox) of various impurities and data related to the effects of rosuvastatin and other statins on protein handling by opossum and human kidney cells in vitro. These latter studies suggest, but by no means establish, that proteinuria occurs based on a pharmacologic effect of the statins, in that there was a dose-dependant inhibition of albumin transport by statins in these in vitro models. This inhibition was ameliorated by mevalonate, suggesting it is the direct action of the statin that leads to this protein transport perturbation. While there were also studies looking at the in vitro cholesterol-inhibiting effects of the available statins compared to rosuvastatin in human myocytes, the data in this study did not reflect what was seen clinically in terms of risk of myopathy. Rosuvastatin was a weaker inhibitor of cholesterol synthesis in myocytes than drugs such as atorvastatin by an order of magnitude, yet atorvastatin 80 mg has not had the same level of myopathy as rosuvastatin 80 mg did in clinical trials.

Biopharmaceutics: The biopharmaceutics data in this resubmission included data relating rosuvastatin exposure to various degrees of renal impairment, pharmacokinetics in children, and systemic exposure data on patients with either myopathy or renal failure. The latter data showed that the average exposure for patients with myopathy and/or renal failure at 80 mg was higher than the mean data for all patients receiving 80 mg, however, there was considerable overlap. In fact, there are some exposures in the 40 mg group that overlap those of the subjects with myopathy/renal failure. So, while there is a trend suggestive that these adverse events are related to higher exposures, exposure alone does not account for the occurrences.

One biopharm issue deserves some mention. In Japanese patients residing in Japan and in Singaporians of Chinese descent, the exposure to rosuvastatin was approximately 2 fold higher than Caucasians. This would appear to be due to enhanced absorption, since the clearance rate, if anything, was higher in these studies than otherwise. While it is not clear if this higher exposure is true of Asians in the US, this should be explored. If it holds to be true, one could argue that the appropriate dose for Asians may be half that of other populations.

Clinical / Stastical: The efficacy of rosuvastatin for lowering LDL cholesterol is not in question. It has been established in a series of trials examining a range of doses and has included comparisons to many marketed statins. In a 6-week dose-ranging study, rosuvastatin doses of 1 mg to 80 mg all lowered LDL-C significantly, ranging from a reduction from baseline of 33% for the 1 mg group to a mean decrease of 65% at 80 mg. In head-to-head trials, rosuvastatin shows roughly a two-fold higher potency on a mg-per-mg basis compared to atorvastatin on LDL-C. On HDL-C raising, rosuvastatin appears to be more potent than any other statin, with a mean increase of almost 10% in HDL–C at doses of 20 and 40 mg, compared to about 5% in atorvastatin at comparable doses, with roughly the same 5% in pravastatin and simvastatin. There was also a study showing efficacy of rosuvastatin on lowering triglycerides (TG). This study was a 6-week study in patients with type IV hyperlipidemia. Rosuvastatin lowered TG by about

20% to 40% in doses from 5 mg to 40 mg, though the dose-response was flat at 10 mg and above.

To date, there are no outcome data with Crestor, so this approval is limited to biochemical claims only. However, there are on-going outcomes trials which we have every reason to believe will show that the effect of Crestor, as seen with other statins, will translate into decreased mortality and cardiovascular events.

The main question for the resubmission was not efficacy, but rather safety, particularly the potential for rhabdomyolysis. Crestor is the first statin to be submitted to FDA since the marketing withdrawal of Baycol (cerivastatin) and the first to show evidence of rhabdomyolysis in clinical trials, albeit at the now withdrawn dose of 80 mg. The sponsor did provide additional data on the safety of the 20 and 40 mg doses. The total database presented was very large, indeed, at over 12,500 patients studied in 27 trials. The sponsor included patients in this program with a commendable lack of exclusions, which resulted in a reasonable demographic distribution (except, perhaps for Asians – see below) including patients with moderate renal impairment and elderly patients (over 915 were 75 years old or older). Approximately 3000 patients were treated with doses of 40 mg or higher, though the extent of long term data at 40 mg (i.e., 48 weeks or longer) was only 276 at 40 mg and 545 at 20 mg.

The only case of rhabdomyolysis in the entire database occurring at a dose lower than 80 mg was in an elderly patient on 10 mg who had a complicating issues (e.g., sepsis), which makes interpretation difficult. A particularly compelling part of the sponsor's response to our AE letter is a graphical representation using their own comparative study data of the relationship between %LDL-C lowering and incidence of CPK elevations of > 10 times the upper limit of normal. In this graph (see Dr. Parks' secondary memorandum for the graphic itself), the amount LDL-C lowering for rosuvastatin at doses of 5 to 80 mg is only overlapped by simvastatin 80 mg and atorvastatin 20 through 80 mg. Yet, the percent occurrence of significant CPK elevations for rosuvastatin at all doses below 80 mg is approximately the same if not lower than doses of other statins. Cerivastatin (Baycol) in particular had a much greater propensity to raise CK at its mid to highest dose than any other statin at any of their respective doses (with the exception of 80 mg of rosuvastatin), yet had the least LDL-C effects. Thus, normalized for LDL effects, doses of rosuvastatin up to and including 40 mg appear to as safe or safer than other marketed statins for muscle effects. From the CPK data with rosuvastatin, it appears that renal insufficiency, advanced age and hypothyroidism were predisposing factors to myopathy.

The primary reviewer did note some occurrence of proteinuria and microscopic hematuria in the clinical trials database. The occurrence of >= 2+ proteinuria with hematuria >= 1+ was 1.3 % with rosuvastatin 40 mg and 6.1 % with 80 mg. This compares with rates of 0 – 0.8% with other statins in AstraZeneca's comparative trials. The sponsor presented evidence that the protein appeared to be of tubular origin (i.e., it was less albumin and more low molecular weight proteins than with a glomerular proteinuria). The data for hematuria showed some dose relationship, however, it appeared not to persist in individual patients and with both the proteinuria and the hematuria, there was little evidence that these occurrences was linked to any persistent, identifiable renal disease. The preclinical studies for rosuvastatin showed nephropathic effects, but only at very high, moribund-inducing doses – except for the monkey study

where renal effects (tubular degeneration) took place at non-moribund doses. There were 11 cases of renal insufficiency/failure in the clinical trials database. Most of these were ascribable to other causes, including rhabdomyolysis. There were three cases that did not, all at 80 mg. One of these cases, a 69 year old on the study drug for 1+ years occurred in the background of prior renal disease and seemingly got better while still on drug. However, he showed increases in urinary protein on rechallenge not only by rosuvastatin but also atorvastatin. The other two occurred within weeks of starting drug and are not terribly confounded. One had a renal biopsy suggestive of ATN, perhaps a similar pathology to the animals.

Late in the review cycle, a post-market report of renal failure in an elderly woman in the UK was received. She developed renal failure while receiving the 10 mg dose of rosuvastatin for about 8 – 10 weeks prior to the diagnosis. She was on a number of concomitant meds (atenolol/chlorthalidone (beta-blocker/diuretic), flucloxacillin (started just proximate to the diagnosis), ASA 75 mg qd, and diclofenac 150 mg daily (started 3 months before diagnosis)). Her baseline Cr was 0.9 mg/dL. The patient was diagnosed 2.5 months after starting Crestor with a Cr 9.5 mg/dL, she was admitted to a hospital and all her medications were discontinued. There was no role of rhabdomyolysis in this, as her CK was only 215. She was reportedly euvolemic on admission. Her urinalysis showed blood and protein. Her Renal US was normal, but her biopsy showed degeneration of tubular epithelial cells w/ areas of regeneration, with intact glomeruli. There was also mild interstitial nephritis and infiltration of lymphocytes and eosinophils. The patient improved following inpatient treatment with a Cr of 2.1 at last report. Though by no means definitive, this case is worrisome for Crestor being a contributing cause.

While the preclinical data do not establish the proteinuria (and certainly not the hematuria) to be a class effect nor a benign, direct pharmacologic action of the drug, the clinical data do not strongly indicate a problem with renal damage with rosuvastatin, despite a very large database. While several of the Advisory Committee members recommended renal monitoring in patients on Crestor, it is hard to know what we would recommend in terms of frequency of monitoring and in terms of what one would do with the data, given the background rate of hematuria and proteinuria in the likely target population. However, since the 40 mg dose did show some hematuria occurrences along with the proteinuria, the labeling will at least suggest monitoring of urinalyses done as a part of routine health care.

Hepatic safety has always been a background issue for statins and hepatic monitoring is in all approved labels and rosuvastatin's proposed label. However, rosuvastatin showed a very low occurrence of ALT elevations in the clinical trials, with only the 80 mg dose having any occurrence that might be taken as significant (1.4% of patients exposed at 80 had elevations of at least 3 times the upper limit of normal on 2 occasions). In relating this to the other statins from their own comparative trials, the sponsor showed that the rate of persistent elevations of ALT was as low or lower for rosuvastatin compared to other statins. No hepatic failure suggestive of drug effect was seen in the trials. Therefore, the labeling of rosuvastatin for hepatic safety will be standard for this class and no additional measures are needed at this time.

Labeling and nomenclature: DMETS has no objection to the name Crestor, but had some helpful suggestions on container labeling. The labeling for the drug will largely follow that of other statins. It will recommend 5 - 10 mg as a usual starting dose, except for patients on cyclosporine (where the dose will be limited to 5 mg only) and gemfibrozil, where the top dose will be limited to 10 mg due to significant PK interactions. Patients with pre-existing renal dysfunction will start at 5 mg and have a top dose of 10 mg.

Regulatory Conclusions: There are some concerns with this drug in terms of its safety profile – specifically potential, dose-related kidney and proven dose-related muscle toxicities. On the other hand, the safety database for this drug is very large indeed and the toxicity vs. lipid lowering analyses done by the sponsor are compelling along with this database to support that Crestor is sufficiently safe for marketing.

Crestor should be approved for marketing, with a starting dose of 5 to 10 mg and a top dose of 40 mg that should be reserved only for patients failing to achieve goals at 20 mg. A post-marketing commitment to further study the PK of this drug in Asian populations is needed. We will also make note in the approval letter of the sponsor's voluntary measures to help assure that 40 mg is not over-used, given this dose's proximity to the 80 mg dose that showed serious myositis in clinical trials. We also will have an agreement from the sponsor to provide 5 mg samples, in addition to the planned 10 mg samples as soon as feasible. The idea is to limit the dosing of Crestor to the appropriate dose in all patients. Since 67% of patients with routine hypercholesterolemia can be brought to target goals with 5 mg, I believe that marketing should not overly emphasize the 10 mg dose. AstraZeneca has agreed not to sample anything other than the 10 mg (and 5 mg) dose and will not routinely stock the 40 mg dose in pharmacies, but it will rather have to be special ordered. I believe this caution about the 40 mg dose is warranted as we monitor the post-marketing experience for any safety signals of Crestor, especially rhabdomyolysis and renal dysfunction to make sure it is no worse than that of other marketed statins.

/S/

Robert J. Meyer, MD
Director,
Office of Drug Evaluation II

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/s/

Robert Meyer
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MEDICAL OFFICER

Office Director's Memorandum

DATE: May 30, 2002

SUBJECT: NDA 21-366
Crestor™ (rosuvastatin calcium)
IPR Pharmaceuticals, Inc.

I have reviewed the Action Package for NDA 21-366 for Crestor (rosuvastatin calcium) tablets. The sponsor has requested approval for doses of 10, 20, 40 and 80-mg per day for the treatment of patients with primary hypercholesterolemia and mixed dyslipidemia (Frederickson Type IIA and IIB). Summary recommendations from the medical staff for action on the NDA are as follows:

***Medical Officer**: Approval of doses of 1, 2.5, 5mg with further long-term safety data required for approval of doses of 10 and 20-mg per day.*

***Medical Team Leader**: Approvable for doses 10-40-mg, pending additional studies of safety, particularly prospective evaluations of the potential for renal toxicity.*

***Division Director**: Approvable for doses up to 40-mg, with a requirement for doses of 20 and 40-mg to be more completely assessed (particularly renal toxicity). If the sponsor wishes to market doses lower than 10-mg, full CMC for these dosage strengths is required.*

I find the sum package of this NDA of great concern. The 80-mg per day dose is not approvable. Substantial questions remain about the other doses requested by the sponsor in the NDA for the reasons listed below, but an approvable action is acceptable. While the medical officer's recommendation is not unreasonable, the sponsor does not have CMC data to support it at present.

1. Optimal dosing for rosuvastatin has not been determined.

The sponsor proposes a starting dose of 10-mg and has focused their pivotal clinical trials accordingly, with most patients ultimately receiving 80-mg per day. At these doses there is no question about the drug's efficacy, compared to placebo or any of the other marketed HMG-CoA reductase inhibitors. From the design of the studies it is apparent that a factor in the sponsor's targeting this dosage range is rosuvastatin's 2:1 mg per mg potency in comparison to atorvastatin. However, in clinical trials of rosuvastatin that did include lower doses, the greatest reductions in lipids occurred at doses of 1 to 10-mg per day. Dose increases beyond 10-mg did show additional lipid lowering, but at much lower rates. Of most concern is that the dosage increase from 40mg to 80-mg per day increased efficacy by only a few percentage points on any measure, but was associated with a much worse safety profile. As pointed out in the review by Dr. Lubas, it appears that a more rational starting dose for this drug is well below 10-mg per day.

The sponsor's dosing strategy for efficacy has led to an incomplete assessment of the safety profile of the drug. For drugs in this class, the Division has routinely required a minimum of 200 patients exposed at a given dose level for at least one year. From the Medical Officer's Review, Table 18, I have summarized the maximum continuous duration of treatment for the doses of rosuvastatin proposed for marketing. These numbers include patients from both controlled and uncontrolled trials.

Patients Exposed per Rosuvastatin Dose

Cumulative Treatment	5 mg	10-mg	20-mg	40-mg	80-mg
> 48 weeks	445	730	67	82	810
>72 weeks	145	311	11	8	446
Mean days Of treatment	240	251	92	93	338

As can be seen from these data, doses of 20 and 40-mg, those in the middle of the sponsor's proposed dose range, have very little long-term use data. If the 80-mg dose was clearly safe, then this would certainly not be an issue. However, the safety profile of the 80-mg dose is unacceptable for marketing approval. These data raise significant concerns about the other doses as well.

2. The safety database in the NDA does not allow a complete assessment of the risk to benefit profile of rosuvastatin.

Of specific concern is the occurrence of myotoxicity and renal toxicity. I agree with the Medical Officer, Team Leader and Division Director that the hepatoxicity profile of rosuvastatin appears to be consistent with that of other drugs in the class. This toxicity is well known in the clinical community and monitoring for it is standard. Rhabdomyolysis, though well described in association with this class of drug, has been very rare. For all other products in this class, rhabdomyolysis has not been apparent in premarket clinical trials in databases of similar size to rosuvastatin's. It has only been reported after products have been on the market and used in a wider range of patients than in the clinical trials. For example, cerivastatin (Baycol) was withdrawn from the market in 2001 because of a high rate of rhabdomyolysis, including patients who died as a result. There were no overt signals in that NDA database to suggest that rhabdomyolysis would occur at the incidence ultimately seen. In this NDA for rosuvastatin, the 8 cases of rhabdomyolysis occurred at a rate that leaves no question but that the drug is a potent myotoxic agent. The mean duration of rosuvastatin at the time of diagnosis was 160 days (5.3 months). The median duration was 150 days (range 20-384 days).

The rate of markedly elevated CK (>10x ULN) with associated myopathy for rosuvastatin at the 80-mg dose (1.1%) is within the range seen in clinical trials of Baycol across its dose range (0.2-2.1%). There were a few cases of myopathy with elevated CK levels at lower doses of rosuvastatin, however the duration of dosing in the lower ranges was so short that conclusions about their safety can not be made. These cases were also in patients with a history of recent vigorous exercise. Even though confounded by exercise, myopathy is concerning in the 20 and 40 mg patients, because there were no cases in patients on active control agents or placebo. Risk factors for CK elevations and for myopathy appeared to be decreased renal function, being elderly and being female.

As is pointed out in all of the other medical reviews of this NDA, the renal toxicity signal for rosuvastatin is based on urine dipstick results in the clinical trials, but is nonetheless worrisome. Manifestations include proteinuria, hematuria and in some patients elevations of serum creatinine. Signals for toxicity were evident at the 40 and 80-mg doses, but the data hint that with more careful monitoring these findings may well extend down to lower doses, at least for proteinuria and hematuria. Comparative analyses did not show a similar signal for any other statins or placebo in the controlled trials. Nephrotoxicity is well known to occur in the setting of rhabdomyolysis, and several of the patients with that condition did have renal complications. However, there were two cases of renal failure and one case of renal insufficiency in patients who did not have myopathy. This makes the possibility of primary nephrotoxicity unique to rosuvastatin and of substantial concern. In addition, the full effects of mild to moderate renal insufficiency on the pharmacokenetics of rosuvastatin have not been assessed, as is pointed out in the FDA Clinical Pharmacology and Biopharmacology review.

Analyses of cases in which nephrotoxicity occurred suggest that renal tubular and interstitial damage may be the pathophysiologic mechanism by which the toxicity develops. This is unusual for a drug that is not primarily renally excreted. It is not known whether the proteinuria and hematuria are reversible; the percentage of patients who may progress to renal failure; the relationship of treatment duration to toxicity and what the relationship of risk to benefit for this toxicity is for rosuvastatin across its full dosage range. The risk of nephrotoxicity at the 80-mg dose make it unacceptable in light of its meager added benefit. Whether the same is true for 20-mg and 40-mg can not be determined, but may well be the case.

In sum, in order to determine an acceptable therapeutic window for rosuvastatin more complete analyses of relationships among dose, duration, toxicity, efficacy and plasma levels are required.

3. Managing risks associated with rosuvastatin may not be practical.

Standards of clinical practice for management of hyperlipidemia may make managing risks associated with rosuvastatin extremely difficult. It is standard clinical practice to use both a "statin" and gemfibrozil to manage hyperlipidemia, especially in patients with elevated triglyceride levels. Experience with cerivastatin's (Baycol) increased myotoxicity compared to other statin drugs demonstrated that combination use with gemfibrozil increased the risk

for this toxicity. Public warnings, including prominent label changes and several "Dear Prescriber" letters had little effect on curtailing the combined use of the drugs. This experience suggests that the role of a statin that is not able to be used with gemfibrozil (unless the statin obviates the need for the combination) is limited. Some would suggest that there is no role for such an agent. In this NDA database only one study addressed combination use, and it was a pharmacokinetics study of a single 80 mg dose of rosuvastatin.

The clinical pharmacology data and analyses of toxicity versus plasma levels of rosuvastatin are very concerning. Dr. Lubas' medical review of steady state plasma levels of rosuvastatin at 20-mg, 40-mg and 80-mg compared to levels from 9 patients with muscle and renal toxicity shows overlap between these individuals' levels and those of patients at 40-mg and 80-mg overall. Most of the 9 patients' levels fell in the upper range of steady state plasma levels associated with the 80-mg dose. Figure 7 in his review also suggests that there are patients, generally, who are outliers, in that their steady plasma levels greatly exceed the mean. Most of the 9 patients with severe toxicity were among them. Unfortunately, other than in very general terms (older women, mild renal insufficiency) identifying such patients prospectively is not possible.

Putting this limited analysis of elevated plasma levels in patients with toxicity together with the clinical pharmacology study of gemfibrozil and rosuvastatin suggests that these two drugs should not be used in combination. Healthy subjects receiving 600 mg twice daily of gemfibrozil who were given a single dose of 80-mg rosuvastatin had Cmax and AUC levels of the latter that were twofold that of rosuvastatin alone. No multiple dose studies or studies at other doses or mechanistic work to understand this interaction were performed. It is true that other HMG CoA reductase inhibitors on the market also have elevated plasma levels when used in combination with gemfibrozil. However, the apparent myotoxic potency of rosuvastatin suggests that clinically behave more like Baycol than not. Further study , using clinical endpoints as well as pharmacokinetics across a range of ceruvastatin doses with gemfibrozil are essential. Such studies will ultimately determine whether marketing of the drug is advisable at all, given the multiple alternatives already available.

4. The racial and ethnic diversity of patient populations studied in the NDA is wholly inadequate.

There is no regulation or guidance that requires racial and ethnically diverse populations to be included in the clinical trials database for a new drug. Even without a guidance from FDA, the public's expectation is that drugs will be tested in populations who will likely take them once marketed. In the U.S., cholesterol lowering drugs are used to treat a broad spectrum of patients, yet the clinical trials database in this NDA consisted mostly of Caucasians (n=2,390). I acknowledge the difficulties that exist in the clinical trials community of enrolling a diverse population. Nonetheless, given the widespread nature of hypercholesterolemia, it is striking that there were only 86 patients who were Blacks, 48 who were Hispanic and 31 who were Asian. Adding to the concern about this lack of population representativeness is the suggestion that CK elevations were more frequent in these subgroups (Blacks 7.0%, Hispanic 4.2%, and Asian 6.5% vs Caucasian 1.8%). Any

future trials of rosuvastatin should address representativeness in a more meaningful way than the current database does.

Summary

I have substantial concerns about the role of rosuvastatin as an added member of HMG-COA reductive inhibitors on the market. The sponsor's critical way forward to obtain market approval must rely on their demonstration that the risk of rhabdomyolysis, normalized to LDL-lowering efficacy, is not in excess of other drugs in the class. Use of patients already in clinical trials who were previously taking 80-mg per day and have had their dose lowered to 40-mg should not be part of the data set on 40-mg. In addition, the sponsor must provide more complete information and a similar risk to benefit analysis of nephrotoxicity, and provide a more comprehensive assessment of the potential role and risks of the combined use of rosuvastatin and gemfibrozil. Finally, the sponsor should be advised to seriously reconsider their proposed dosing regimen to begin at a dose well below 10-mg.

Sandra L. Kweder, M.D.
Acting Director
Office of Drug Evaluation II

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/s/

Sandra L. Kweder
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MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: May 2, 2002

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-366
Crestor (rosuvastatin calcium) tablets
Astra Zeneca Pharmaceuticals
Treatment of dyslipidemia

SUBJECT: NDA review issues and recommended action

Background

Rosuvastatin is a synthetic HMG-CoA reductase inhibitor that shares structural similarities to the other members of the statin class. On a per mg basis, it is more potent than any currently marketed statin, and, excluding cerivastatin (Baycol) which was withdrawn from the worldwide market in August 2001, it is the most potent statin ever proposed for marketing in the US. In addition, it has been proposed for marketing at doses (high dose 80 mg) that effect greater LDL-C lowering than any labeled dose of any of the 5 currently marketed members of this class. In short, with this NDA, the sponsor has "pushed the envelope" farther than any of its predecessors.

Statins act by inhibition of cellular cholesterol biosynthesis, presumed depletion of intracellular pools of cholesterol, and resultant derepression of expression of the gene for the LDL-receptor. The increased number of functional LDL-receptors on the surfaces of cells, most importantly of hepatocytes (the liver being the primary site of clearance of plasma LDL), results in enhanced clearance of LDL from the circulation and reduced steady-state levels of LDL-C. In addition, statins may act directly to reduce hepatic synthesis and secretion of VLDL particles, the TG-rich precursors of LDL, IDL, and atherogenic remnant particles, thereby contributing to the reduction in total apo B-containing lipoproteins and effecting modest reductions in plasma TG levels.

The effectiveness of statins to reduce levels of atherogenic lipoproteins (mainly LDL-C) is well established, and rosuvastatin shares this efficacy. In addition, in many clinical trials, various statins have been shown to impact favorably the course of atherosclerotic disease, either by altering progression of anatomically defined vascular lesions and/or by reducing cardiovascular events, including MI, stroke, and need for CABG or PTCA, relative to placebo.

Statins as a class are not without side effects. All statins have been associated with dose-dependent hepatic effects, seen as increases in the incidence of transaminase elevations considered "clinically significant." Based on the extensive clinical trial experience with these agents, it would appear that the transient, mild transaminase elevations are not, however, markers

of risk for serious hepatic disease. Indeed, there is no evidence that these drugs have a specific tendency to cause significant hepatitis, cholestasis, nor frank hepatic failure.

The most serious adverse effect of the statin class is myopathy, which can present along a spectrum from mild muscle aches without CK elevations, to muscle weakness and pain with moderate (e.g., up to 5 or 10 X ULN) CK elevations, to frank rhabdomyolysis with marked CK elevations, myoglobinuria, and acute renal failure. As for any form of rhabdomyolysis, this is an extremely serious adverse effect and in some cases has resulted in death. While the incidence of mild myopathy is relatively common, the incidence of rhabdomyolysis is extremely low, with estimates in the literature of 1 in 10,000 or more. Predisposing factors (based on case reports) for serious myopathy and rhabdomyolysis include drug-drug, drug-food interactions that result in increased plasma levels of active drug, old age, renal failure, and multiple medical problems. The mechanism of myotoxicity of statins is not known.

Cerivastatin (Baycol) was withdrawn from the worldwide market based on a marked increase in the reporting rate (cases per prescriptions) for rhabdomyolysis (including fatal cases) with high-dose monotherapy as well as in combination with gemfibrozil. Several facts about Baycol are notable and bear on the risk-benefit assessment of rosuvastatin. First, Baycol was extremely potent on a per mg basis, approximately 100X as potent as lovastatin. Indeed, the highest approved dose of Baycol was only 0.8 mg (it was colloquially referred to as the "microstatin"). Second, though very potent per mg, at the highest approved dose, which was associated with a substantial risk of rhabdomyolysis as monotherapy, LDL-C was lowered only about 40% (mean). As such, per LDL-lowering effect, the drug conferred a disproportionate risk of muscle injury. Though the lower doses of cerivastatin were apparently less prone to induce muscle injury, by definition, they possessed a risk-benefit profile that was unfavorable relative to the rest of the class.

In light of our experience with cerivastatin, it is clear that not all statins possess identical risk-benefit profiles. More precisely, the risk per LDL-lowering potency may not be identical for each compound. As above, cerivastatin differed from the other statins in its propensity to cause muscle injury per LDL-lowering potency. In light of this finding, and in light of the concerns raised in the review of rosuvastatin safety experience, while the drug is obviously effective, further information must be brought to bear on the question of the relationship between LDL-lowering efficacy and risk of adverse effects. Notable in the clinical experience thus far with rosuvastatin are 6 cases of serious myopathy/rhabdomyolysis at the 80 mg dose and renal findings (proteinuria, hematuria, and creatinine elevations), also seen at the higher doses. In light of the availability of other members of the class, 3 of which (lovastatin, pravastatin, simvastatin) have been studied in large "clinical endpoint" trials, there is no place in the armamentarium for a new member of the class of inferior safety.

Clinical

Dr. Parks', Dr. Lubas', and Ms. Mele's reviews detail the clinical efficacy and safety findings.

Briefly, with regard to efficacy, analyses of dose-response data from parallel-group dose-ranging studies as well as forced-titration dose-ranging studies (including the studies in a small number of patients with homozygous FH, who show modest mean responses without an evident dose-

response) support a conclusion of a plateau of efficacy at the highest doses. Specifically, while incremental LDL-lowering efficacy proceeds as expected for a statin through the 40 mg dose (approximately 5-6% incremental lowering relative to baseline with progressive doublings), the additional LDL lowering with 80 mg falls short of this increment. Inasmuch, therefore, that it confers little in the way of additional benefit, and in light of the safety concerns (myotoxicity) with the 80 mg dose, this dose is not currently approvable, even for patients with severe hypercholesterolemia (i.e., homozygous FH). In the future, if susceptibility to myopathy with this statin or with the class generally can be prospectively identified, safe use of this dose may be possible.

With regard to safety, the drug has been studied at doses of 10, 20, 40, and 80 mg daily with exposures beyond 1 year. Of note, and summarized in table 11 of Dr. Parks' review, the long-term exposures were skewed toward the high and low doses, with relatively few patients exposed beyond 12 weeks at the 20 and 40 mg doses. Indeed, fewer than 100 patients received these doses for 1 year. In light of the finding of rhabdomyolysis (80 mg group) and potential renal toxicity based on urine dipstick findings of increased protein and heme relative to baseline (40 and 80 mg groups), we have concluded that these exposures are inadequate to exclude similar toxicity of these intermediate doses. It is important to point out that although there were large numbers of "starts" at 20 and 40 mg, such that the cited incidence rates for categorical CK elevations are no different than for the 5 and 10 mg groups, duration of exposure may well be important in the development of myopathy as well as renal toxicity, thus the requirement for additional long-term clinical experience.

Finally, it must be emphasized that the renal findings with rosuvastatin have not previously been noted in studies of HMG-CoA inhibitors. Indeed, in the current development program, there were significant exposures to atorvastatin in comparator arms of the randomized trials. As pointed out in the reviews of Drs. Parks and Lubas, there was no dose-related elevation in the incidence of dipstick-assessed increases in urinary protein or heme from baseline to end of treatment in the atorvastatin-treated patients.

In sum, significant myotoxicity was found at the 80 mg dose, with cases of severe myopathy/rhabdomyolysis occurring in the carefully controlled setting of a clinical trial. Save perhaps for the trial experience with cerivastatin 0.8 mg, in which a number of patients developed marked (> 10 X ULN) CK elevations requiring discontinuation, there have been no cases of severe myopathy/rhabdomyolysis reported in the NDA databases for the statins. Indeed, in all the 5-year statin "megatrials" there has only been one case of rhabdomyolysis reported, in a patient who discontinued drug in order to undergo major surgery and developed rhabdomyolysis post-operatively. In that same trial, two placebo patients developed rhabdomyolysis. Though based on inadequate ascertainment methods, the finding of potential renal toxicity at the 40 and 80 mg doses of rosuvastatin bears further prospective investigation. Finally, though the safety of the 10 mg dose (the lowest proposed for marketing) appears acceptable, the lack of adequate safety exposures at doses between 10 and 80 mg does not permit conclusions as to the toxic-therapeutic ratio at this dose, or, indeed for the chemical entity itself.

Labeling

No labeling has been negotiated at this time. Should the drug be approved, labeling will be finalized at that time.

Biopharmaceutics
The absolute bioavailability of rosuvastatin was 20% in Caucasian normal volunteers and 29% in Japanese volunteers. The major route of elimination is in the feces, with the majority excreted as parent drug. The drug is neither an inhibitor nor an inducer of CYP oxidases, and there was a significant PK interaction noted with cyclosporine and with gemfibrozil. There was a tendency toward drug accumulation with multiple dosing at the 80 mg dose but not at lower doses. Exposures were increased in severe renal impairment. The biopharm reviewer concluded that the drug was approximately four times as potent as atorvastatin (the statistical reviewer concluded that rosuvastatin was at least twice as potent as atorvastatin). The biopharm reviewer was not satisfied that the pharmacokinetic data presented supported the sponsor's conclusion of no safety concerns in patients with mild or moderate renal insufficiency and the action letter will therefore ask for additional clinical data to bolster this conclusion. Finally, because of the finding of drug accumulation at the high dose, OCPB recommends a starting dose of 10 mg or lower.

Pharmacology/Toxicology
Pharmacology/toxicology concludes that the preclinical data support the safety of 10 and 20 mg with no further studies required. The target organs for toxicity of rosuvastatin include liver in rats, mice, and dogs, at exposures equivalent to 1-7 times the human exposures at 80 mg. The carcinogenicity assessment of the drug in rats and mice showed induction of hepatic carcinomas in mice, consistent with the class, and uterine polyps and a single sarcoma in the rats.

In dogs, the drug induced corneal opacities, also consistent with the class. Testicular toxicity was found, a class effect.

Renal toxicity, including tubular degeneration and necrosis was seen in multiple species, with the pregnant rabbit (low multiples) and monkeys (human equivalent exposures) most susceptible.

Chemistry/ Microbiology
The recommendation from ONDC is approvable, pending satisfactory response to certain minor deficiencies identified and described in the action letter. The establishment inspections were acceptable overall.
A categorical exclusion from the environmental assessment was claimed by the sponsor and granted by the Agency.

DSI/Data Integrity
A Form 483 was issued to one of the clinical investigators citing temperature out of range in the drug storage facility, though the magnitude was small (———) and the excursions did not occur on consecutive days. The VAI letter is still under review by OCC and DSI has promised to report and further input from counsel. None is anticipated given the minor nature of the cited deficiencies in procedure.

Financial disclosure

The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

OPDRA/nomenclature
DMETS has no objection to the name Crestor. The name will have to be re-reviewed as any approval will clearly be beyond 90 days from the last review.

Recommendation
Approvable. Clinical safety of intermediate doses (20, 40 mg) must be more completely assessed. Potential renal toxicity must be investigated using accurate assessment techniques. CMC deficiencies must be addressed. If the sponsor wishes to market doses lower than 10 mg (doses of 1, 2.5, and 5.0 mg have been studied), full CMC for these dosage strengths is required.

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/s/

David Orloff
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MEDICAL OFFICER

MEDICAL TEAM LEADER'S MEMO ON NEW DRUG APPLICATION

NDA #: 21-366
Drug Sponsor: AstraZeneca Pharmaceuticals
Drug Product: Crestor® (rosuvastatin)
Drug Class: HMG-CoA reductase inhibitor
Indication: Treatment of dyslipidemia
Date of Submission: June 26, 2001

Primary Medical Reviewer: William Lubas, MD, PhD
Statistical Reviewers: Joy Mele, MS and Cynthia Liu, MA

EXECUTIVE SUMMARY

Crestor (rosuvastatin sodium) is a new HMG-CoA reductase inhibitor developed for the treatment of Fredrickson Types IIa, IIb, and IV dyslipidemia and treatment of homozygous familial hypercholesterolemia. The medical and statistical reviews of this NDA reveal several features regarding rosuvastatin which distinguishes this drug from the currently marketed statins: lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin.

The first feature is that of efficacy - the LDL-lowering effect of rosuvastatin across the dosage range studied (1.0, 2.5, 5.0, 10, 20, 40, and 80 mg) is more potent than any currently marketed statin. The sponsor has proposed to market 10, 20, 40 and 80 mg doses for treatment of Fredrickson Types IIa, IIb, and IV dyslipidemia and homozygous FH patients. Compared to atorvastatin across the entire dosage range of both drugs in the Types IIa and IIb population, rosuvastatin achieves similar or slightly better LDL-lowering as twice the dose of atorvastatin. Significant reductions are seen within 1 week of therapy and most of the effects is achieved by 2 weeks. The LDL-lowering efficacy is dose-related; however, across several studies, there is a consistent finding that titration from 40 to 80 mg does not provide any significant additional benefit. Although the 80 mg dose provides a mean –2 to –4% further reduction in LDL-C, the range of responses is quite similar to that of 40 mg. This lack of clinically significant benefit is counterbalanced by the greater risk for myopathy and rhabdomyolysis observed at the 80 mg dose. The effect of rosuvastatin on TG-lowering and HDL-raising is not dose-related and appears to reach maximal response at the 10 mg dose in the IIb/IV populations studied.

The second feature for this product is its safety. Rosuvastatin at its highest proposed dose has been associated with 6 cases of rhabdomyolysis – a finding that was absent in the premarketing application of all currently approved statins. At the next lower doses of 20 and 40 mg, inadequate long-term safety exposures preclude any conclusions that these doses are without similar muscle toxicity. In addition, a novel and concerning safety signal for renal toxicity was associated with the 40 and 80 mg doses. Patients at these two doses had a higher incidence of proteinuria, proteinuria with hematuria, and associated increases in serum creatinine levels. The clinical studies in this NDA were not designed to determine whether these changes will progress to more severe renal deterioration, are reversible, or if adequate monitoring could select out patients who should not be treated or have treatment interrupted.

Overall, the safety findings for rosuvastatin either outweigh any benefits (at the 80 mg dose) or require further evaluation prior to approval. The 80 mg dose should not be approved for marketing since there is no additional efficacy over the 40 mg dose but