In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7.

In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after six month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times human exposure at 40 mg/day based on
Similar findings have been seen with other drugs in this class.

Pregnancy
Pregnancy Category X

See CONTRAINDICATIONS

In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating

In pregnant rats given oral gavage doses of 2, 20, 50 mg/kg/day from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, systemic exposures ≥12 times human exposure at 40 mg/day based on body surface area comparisons.

In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation day 6 to lactation day 18 (weaning), exposures equivalent to human exposure at 40 mg/day based on body surface area comparisons, decreased fetal viability and maternal mortality was observed.

Nursing Mothers
It is not known whether rosuvastatin is excreted in human milk. Studies in lactating rats have demonstrated that rosuvastatin is secreted into breast milk at levels 3 times higher than that obtained in the plasma following oral gavage dosing. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rosuvastatin, a decision should be made whether to discontinue

nursing or administration of rosuvastatin taking into account the importance of the drug to the lactating woman.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Karen Davis-Bruno
6/11/03 02:49:34 PM
PHARMACOLOGIST
Labeling comments for Crestor NDA 21-366

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: March 24, 2003	**DUE DATE:** July 14, 2003	**ODS CONSULT #:** 01-0021-2

TO: David Orloff
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Valerie Jimenez
Project Manager
HFD-510

PRODUCT NAME:	**SPONSOR:**
Crestor (Rosuvastatin Calcium Tablets) 5 mg, 10 mg, 20 mg, 40 mg **NDA#:** 21-366	Astra/Zeneca/IPR Pharmaceuticals

SAFETY EVALUATOR: Nora Roselle, PharmD

SUMMARY: In response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a re-review of the proposed proprietary name "Crestor" to determine the potential for confusion with approved proprietary and established names as well as pending names since the final review dated February 2. Additionally, DMETS re-evaluated previous names, Carnitor, Trelstar, and Restoril, because the strengths of Crestor have been revised from the time of our initial review.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name "Crestor". DMETS considers this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name and its labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

2. DMETS recommends implementation of the label and labeling recommendations outlined in section III of this review.

3. DDMAC finds the name, Crestor, acceptable from a promotional perspective.

/S/

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 27, 2003

NDA#: 21-366

NAME OF DRUG: **Crestor**
(Rosuvastatin Calcium Tablets) 5 mg, 10 mg, 20 mg, 40 mg

NDA HOLDER: AstraZeneca/IPR Pharmaceuticals

I. INTRODUCTION:

This consult is written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for re-review of the proposed proprietary name Crestor. The proposed proprietary name, Crestor, was found acceptable by DMETS in the initial name review on September 10, 2001 (ODS Consult 01-0021) and also a final review dated February 27, 2002. In addition, DMETS has reviewed the proposed container labels and insert labeling for Crestor and has provided recommendations to help minimize confusion.

PRODUCT INFORMATION

Crestor is indicated for the treatment of hypercholesterolemia. The product will be available as an oral tablet dosage form with the following strengths: 5 mg, 10 mg, 20 mg, and 40 mg. The recommended starting dose is 10 mg once daily with a maximum daily dose of 80 mg. Crestor is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases. Crestor is also contraindicated during pregnancy and in nursing mothers. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with the use of rosuvastatin. Serious drug reactions have been identified between Crestor, warfarin and gemfibrozil.

II. RISK ASSESSMENT:

In the Division of Medication Errors and Technical Support's (DMETS) original reviews, we evaluated Crestor with the impression that it would be available in 10 mg, 20 mg, 40 mg, and 80 mg tablets. According to the package insert provided by the division dated February 2003, Crestor will instead be available as 5 mg, 10 mg, 20 mg, and 40 mg tablets. Consequently, we have re-evaluated previous names of concern based on this information. The names include Carnitor, Trelstar, and Restoril. DMETS believes that the potential for confusion between Crestor, Carnitor, Trelstar, and Restoril is minimal based on a lack of convincing look- and sound-alike characteristics, as well as a lack of overlapping product similarities.

The Division of Medication Errors and Technical Support (DMETS) has also identified three additional proprietary names that have the potential for confusion with Crestor since our last review of the name in February 2002. The names identified include Vascor, Arestin, and Proscar.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other
Crestor	Rosuvastatin calcium Tablet: 5 mg, 10 mg, 20 mg, 40 mg	One tablet daily	
Vascor	Bepridil Hydrochloride Tablet: 200 mg, 300 mg	Initial: 200 mg once daily Maintenance: 300 mg once daily	Sound-alike
Arestin	Minocycline Microspheres, 1 mg	Insert unit-dose cartridge into base of periodontal pouch and press handle to expel powder	Look-alike
Proscar	Finasteride Tablet: 5 mg	5 mg once daily	Sound-alike
*Frequently used, not all-inclusive.			

Vascor has sound-alike similarities to Crestor. Vascor (Bepridil Hydrochloride) is indicated for the treatment of chronic stable angina. Vascor is available in 200 mg and 300 mg oral tablets. The usual starting dose of Vascor is 200 mg once daily with a maintenance dose of 300 mg once daily. The maximum recommended dose is 400 mg once daily. These products share the same dosing frequency (once daily), route of administration (oral), and dosage form (tablet). Both medications could be written by similar prescriber populations and given to similar patient populations. While the two drugs do not share overlapping strengths, they do share numerically similar strengths. Vascor is available in 200 mg tablets while Crestor will be available in 20 mg tablets. In addition, the two drugs share numerically similar maximum daily doses. The maximum dose of Vascor is 400 mg once daily and the maximum dose of Crestor is 40 mg once daily. Vascor and Crestor have sound-alike suffixes ("scor" vs. "stor") and two syllables when spoken. However, when spoken, the prefixes "Vas" and "Cres" sound much different from one another. Although there are many similarities between the two drugs, DMETS believes the lack of convincing sound-alike similarity differentiates one name from the other and minimizes the risk for confusion.

Arestin was identified to have look-alike potential with Crestor. Arestin (Minocycline Microspheres) is used in the treatment of adult periodontitis. Arestin is available as a 1 mg dry powder packaged in a unit-dose cartridge. Arestin is given by subgingival administration into the periodontal pockets of gums by dental health care providers. Arestin and Crestor have look-alike similarities in that the prefix "Arest-" can look like "Crest-" because "Cr" is similar to the a capital letter "A" when written in cursive. (see below)

Arestin and Crestor share a similar numerical strength. Arestin is available in a 1 mg strength and Crestor is available in a 10 mg strength. A 1 mg dose can be communicated as 1.0 mg, which can be confused for 10 mg if the decimal is undetected by the practitioner interpreting the order (and vice versa). If a prescription is written as Arestin 1.0 mg, use as directed, with a trailing zero, there is potential for confusion with Crestor 10 mg, use as directed since both names look similar when scripted. However, there are differences between the two products. The two drugs do not share an overlapping indication for use (periodontitis vs. hyperlipidemia), route of administration (subgingival vs. oral), dosage form (dry powder in a cartridge vs. tablet), dosing schedule (every 3 months vs. once daily), and will not be stored in close proximity to one another on the pharmacy shelf whether arranged by brand or generic name. A dentist or other dental health care provider administers Arestin in a dental office, and the product is distributed directly to the physicians rather than to pharmacies. DMETS believes even though the two drugs share look-alike similarities, the differences between the products as well as the direct distribution of Arestin to physician's offices rather than pharmacies, will help minimize the potential for confusion and error between Arestin and Crestor.

Proscar was identified by DMETS to have sound-alike similarity with Crestor. Proscar (Finasteride) is indicated for the treatment of benign prostatic hyperplasia (BPH) in men with an enlarged prostate. Proscar is supplied as 5 mg oral tablets and the usual daily dose is 5 mg once daily. Proscar and Crestor both have two syllables. Each name contains a consonant letter "s" sound in the middle of the name and ends with the letter "r". However, when spoken, there are characteristics that help differentiate one name from the other. For example, the prefixes of each name ("Prŏs-" or "Prŏs-" vs. "Crēs-" or "Crĕs-") sound different from one other. Moreover, the suffix of each name ("-căr" vs. "-tŏr") sound much different from one another and help differentiate between the two names. The two drugs share an overlapping dosage form (tablet), route of administration (oral), strength (5 mg), and dosing regimen (once daily). Differentiating characteristics between the two drugs include different indications for use (BPH vs. hyperlipidemia) and the likelihood that the two will not be stored in close proximity to one another on the pharmacy shelf. Due to the lack of convincing sound-alike similarity, DMETS believes there is decreased risk for confusion between Proscar and Crestor.

III. LABELING, PACKAGING, AND OTHER SAFETY RELATED ISSUES:

DMETS has reviewed the container labels and insert labeling for Crestor and has identified some areas of possible improvement in the interest of minimizing errors.

A. CONTAINER LABEL

1. We were not able to compare the 5 mg and 40 mg strength color labels with the black and white copies of the 10 mg and 20 mg labels provided by the Division. Please ensure the labels and labeling are clearly differentiated from one another using contrasting colors, boxing, or some other means.

2. We recommend decreasing the font size of the net quantity to be equivalent in size to the word "tablets" in the upper right hand corner of the label in order to minimize the risk of the number of tablets being misinterpreted as the strength or vice versa.

3. We are unable to identify from the submitted materials, if the product is packaged with a Child Resistant Closure (CRC). Since the bottles will be available in a unit-of-use container please ensure a CRC cap is present.

B. INSERT LABELING

No comments at this time.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proposed proprietary name, Crestor. DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

B. In addition, DMETS recommends the labeling revisions in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the name, Crestor, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

/S/

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: /S/

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Nora L. Roselle
7/14/03 08:33:44 AM
CSO

Alina Mahmud
7/14/03 08:36:20 AM
PHARMACIST

Carol Holquist
7/14/03 08:37:56 AM
PHARMACIST

Jerry Phillips
7/14/03 11:15:35 AM
DIRECTOR

DEPARTMENT OF HEALTH AND HUMAN SERVICE

Public Health Service
Food and Drug Administration

Memorandum

Date: February 27, 2002

To: David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)

From: David Diwa, Pharm.D.
Safety Evaluator, Office of Drug Safety
HFD-400

Through: Carol Holquist, R.Ph.
Deputy Director, Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS) HFD-400

CC: William C. Koch, R.Ph.
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

Subject: ODS Consult 01-0021-1, Crestor (Rosuvastatin Tablets) NDA 21-366

This memorandum is in response to a January 23, 2002, request from your Division for a re-review of the proprietary name, Crestor. The goal date for this application is April 26, 2002.

DMETS has not identified additional proprietary or established names that have the potential for confusion with Crestor since we conducted our initial review on September 10, 2001 (ODS Consult 01-0021) that would render this proprietary name objectionable. Therefore, we have no objection to the use of this proprietary name.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3242.

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

/s/

David Diwa
3/1/02 11:57:32 AM
PHARMACIST

Carol Holquist
3/1/02 01:42:14 PM
PHARMACIST

9/17/01

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 07/02/01	DUE DATE: 09/14/01	OPDRA CONSULT #: 01-0021

TO:
David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:
William Koch, R.Ph
Project Manager
HFD-510

PRODUCT NAME: Crestor (rosuvastatin calcium) 10 mg, 20 mg, 40 mg and 80 mg Tablets NDA: 21-366	MANUFACTURER BY: AstraZeneca SPONSOR: AstraZeneca Pharmaceuticals LP

SAFETY EVALUATOR: David Diwa Pharm.D.

SUMMARY: In response to a consult from the Division of Metabolic & Endocrine Drug Products (HFD-510), OPDRA has performed a review of the proposed proprietary name Crestor to determine the potential for confusion with marketed drug products and pending drug names.

OPDRA RECOMMENDATION: OPDRA has no objection to use of the proprietary name, Crestor.

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document.

/S/

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B032
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 09/10/01

NDA: 21-0021

NAME OF DRUG: Crestor (rosuvastatin calcium tablets) 10 mg

NDA HOLDER: AstraZeneca Pharmaceutical LP

MANUFACTURER: AstraZeneca

I. INTRODUCTION

This consult is written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for an assessment of the proposed proprietary name, Crestor. The NDA was submitted on June 26, 2001 following an IND (52,385) application on November 29, 2000.

PRODUCT INFORMATION

Crestor (Rosuvastatin Calcium Tablets) is a synthetic inhibitor of HMGA-CoA reductase that will be used in the treatment of hyperlipidimia. The product will be available in oral tablet dosage forms of 10 mg, 20 mg, 40 mg and 80 mg. The recommended starting dose is 10 mg daily with a dosing range of 10 to 80 mg daily.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3,4] as well as several FDA databases[5] and Thomson & Thomson's SAEGIS™ database[6] for existing drug names which sound alike or look alike to Crestor to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.[7] An expert panel discussion was conducted to review all findings from the

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] Drug Information Handbook 1999-2000, Lacy CF, Armstrong LL, Goldman MP, Lance LL (eds) Lexi-Comp Inc, Hudson
[5] The Established Evaluation System [EES], the Labeling and Nomenclature [LNC] database of proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.
[6] Data provided by T&T's SAEGIS ™ online service available at www.thomson-thomson.com
[7] WWW location http://www.uspto.gov/tmdb/index.html. The US Patent & Trademark Office Trade Mark Electronic Search System (TESS)

searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies and one verbal prescription study, involving health care practitioners within the FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the proposed name Crestor.

A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

The panel identified Carnitor, Trelstar and Restoril as most problematic in terms of the potential for look-alike/sound-alike name confusion. A summary of the identified product is provided in the table below.

DDMAC has no objection to the proposed name Crestor.

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Crestor	Rosuvastatin Calcium tablets	10 to 80 mg/day	
Carnitor	Levocarnitine	1 to 3g/ day	*LA/SA
Trelstar Depot	Triptorelin Pamoate, lyophilized microgranules for injection	3.75 mg/month IM	*LA/SA
Restoril	Temazepam capsules	15 to 30 mg q HS	*LA/SA

*SA = Sound-alike *LA = Look-alike

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

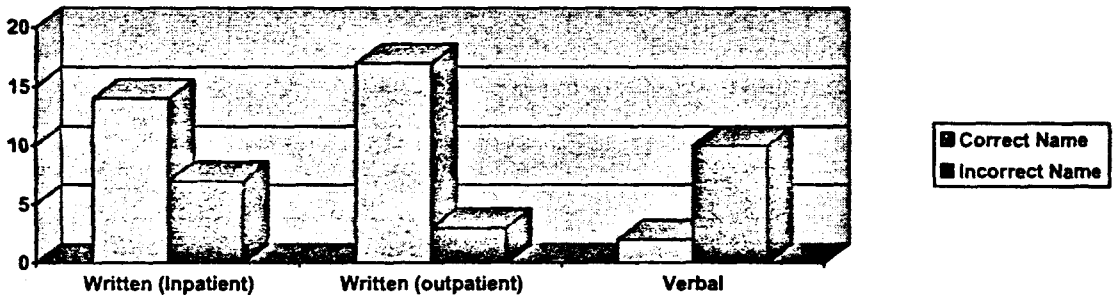
Three studies were conducted by OPDRA involving 88 health professionals comprised of pharmacists, physicians, and nurses within the FDA. The objective was to test the degree of name confusion between Crestor and other drug names due to similarity in handwriting and verbal pronunciation. Inpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Crestor (see below). These prescriptions were scanned into a computer and subsequently delivered to participating healthcare professionals via e-mail. In addition, a verbal prescription order was recorded on voice mail and sent to a sample of the participating healthcare professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient RX: Crestor 1 tab PO QD	Verbal RX: Crestor 1 tab PO QD
Outpatient RX: Crestor 1 PO QD #30 Refill(s): 0	

2. The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	28	21 (75%)	14 (67%)	7 (33%)
Written Outpatient	30	20 (67%)	17 (85%)	3 (15%)
Verbal	30	12 (40%)	2(17%)	10 (83%)
Total	88	53 (60%)	33 (62%)	20 (38%)



Thirty eight-percent (20 out of 53) of all study respondents interpreted the proposed name incorrectly. In the written studies, almost all incorrect responses were minor misspellings (one letter wrong). Incorrect responses in the verbal study were phonetic variations of the proposed name Crestor (*Cresdor, Crestar (3), Crystor, Krestar (2), Cristor (2), Crystalor*). In the written studies, 2 respondents wrote that the name reminded them of a bank, an allusion to Crestar Bank a regional subsidiary of SunTrust Financial Services. None of the inaccurate responses overlapped with an existing approved drug product. Overall, the verbal study revealed more misspellings of the proposed proprietary name. Scores of the incorrect responses are summarized in Table II below.

Table II

Incorrectly Interpreted	
Written Inpatient	Cresden
	Crestar
	Cresten
	Creston (4)
Written Outpatient	Crestar
	*(2)
Verbal	Cresdor
	Crestar (3)
	Cristor (2)
	Crystalor
	Crystor
	Krestar(2)

*Respondents associated name with a bank

C. SAFETY EVALUATOR RISK ASSESSMENT

Three drugs (Carnitor, Trelstar and Restoril) were identified as having look-alike/sound-alike qualities to the proposed name. The name Carnitor looks like Crestor. It also shares some sound-alike qualities with the name Crestor. Trelstar and Crestor share phonetic similarity. In addition, Trelstar could look-like Crestor when poorly scripted. Although *Restor*il has less sound-alike qualities with C*restor,* they share a 5-character block of letters. Thus, when poorly scripted the two could be confused.

Carnitor is a brand of levocarnitine (L-carnitine) a naturally occurring amino acid derivative used in the treatment of carnitine deficiencies. Whereas the proposed dose of Crestor ranges from 10 to 80 mg, the dose of Carnitor is 1 to 3 g/day. Moreover, Carnitor is available in 330 mg oral tablets and an oral solution of 100 mg/ml in 118 mL containers. Crestor will be available in 10, 20, 40 and 80 mg tablets. Because Crestor oral tablets will be available in multiple strengths, prescribers would have to specify the strength for appropriate dispensing. Although Carnitor and Crestor look and sound alike, the data currently available does not support the risk of significant mix-ups.

Trelstar (Triptorelin) is a synthetic agonist analog of gonadotropin-releasing hormone. It is used as palliative treatment for advanced prostate cancer. The depot formulation is available in single-dose vial containing lyophilized microgranules equivalent to 3.75 mg of triptorelin pamoate peptide base. The recommended dose is 3.75 mg of the depot formulation administered intramuscularly on a monthly schedule. The pharmacologic class, dose and method of administering Trelstar is different from Crestor. Therefore, the potential risk of sound-alike/look-alike name confusion between Trelstar and Crestor based on available data at this time appears to be minimal.

Restoril (Temazapam) is a benzodiazepine used in the treatment of anxiety, transient insomnia and adjunctively in the management of panic attacks. Restoril is available in oral capsule dosage forms in strengths of 7.5 mg, 15 mg and 30 mg. While the usual dose of Restoril is 15 to 30 mg a day, the dose of Crestor is in the range of 10 to 80 mg. Moreover, Crestor will be available in tablet strengths 10, 20, 40 and 80 mg compared to Restoril capsule strengths of 7.5, 15 and 30 mg. It is unlikely that the dose of Restoril will be mistaken for that of Crestor. In addition, Restoril is schedule IV controlled substance with different dispensing requirement from Crestor. Therefore, information available at this time does not show that Restoril poses potential risk of significant mix-ups with Crestor.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

No comments.

IV. RECOMMENDATIONS

OPDRA has no objection to use of the proprietary name, Crestor.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have any questions or need clarifications, please contact Sammie Beam at 301-827-3231.

David Diwa, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment.

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

/s/

David Diwa
9/17/01 01:11:50 PM
PHARMACIST

Jerry Phillips
9/17/01 01:19:28 PM
DIRECTOR

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-366	Efficacy Supplement Type SE-	Supplement Number N/A	
Drug: Crestor (rosuvastatin calcium) Tablets, 5 mg, 10 mg, 20mg, 40 mg		Applicant: IPR Pharmaceuticals, LLC	
RPM: Valerie Jimenez		HFD-510	Phone # (301) 827-9090
Application Type: (x) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:		
• Review priority		(x) Standard ( ) Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates	RS(6)= 08/12/03	AGD= 07/31/03
❖ Special programs (indicate all that apply)		(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track N/A ( ) Rolling Review N/A
❖ User Fee Information		
• User Fee		(x) Paid
• User Fee waiver		( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception		( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		( ) Yes (x) No
• This application is on the AIP		( ) Yes (x) No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		(x) Verified
❖ Patent		
• Information: Verify that patent information was submitted		(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii) N/A
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		( ) Verified N/A
❖ Exclusivity Summary (approvals only)		05/07/02-No Signature Page

Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 05/31/02
• Status of advertising (approvals only)	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release (x) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	07/21/03
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	02/12/03; Complete Response
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	06/11/03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	06/10/03
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	07/15/03
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	02/24/99
• Pre-NDA meeting (indicate date)	10/02/00 (2)
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other EOR, Phase 3, Filing	07/26/02, 11/01/01, 08/16/01
❖ Advisory Committee Meeting	
• Date of Meeting	07/09/03
• 48-hour alert	(Draft) July 10, 2003
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	05/31/02, 05/30/02, 05/01/02
❖ Clinical review(s) *(indicate date for each review)*	05/16/02, 05/20/02
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	MO Review-05/02/02, p. 64
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	06/01/01, 10/22/01
❖ Statistical review(s) *(indicate date for each review)*	07/21/03, 04/12/02, 04/24/02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	0/29/01, 04/15/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies- 10/11/01, 10/30/01, 03/14/02, 03/07/02, 05/20/02	
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	07/07/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	04/23/02, p. 89
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: (x) Acceptable 04/23/02 ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (x) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	06/10/03, 07/16/03
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	03/21/02
❖ CAC/ECAC report	02/06/02

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-366 /SE_____ - _____

Drug Crestor (rosuvastatin calcium) Tablets Applicant iPR Pharmaceuticals, Inc.
10 mg, 20 mg, 40 mg, 80 mg
RPM William C. Koch, R.Ph. Phone (301) 827-6412

X 505(b)(1)
☐505(b)(2) Reference listed drug _____

☐Fast Track ☐Rolling Review Review priority: X S ☐P

Pivotal IND(s) 56,385

Application classifications:
Chem Class 1
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary April 26, 2002
Secondary June 26, 2002

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: X User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☐AP X AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... _____
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... X
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☐ No
  Immediate container and carton labels X
  Nomenclature review X

- Application Integrity Policy (AIP) This application is **not** on the AIP.

  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter

- Post-marketing Commitments — N/A
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....

- Was Press Office notified of action (for approval action only)?..... ☐ Yes ☐ No
  - Copy of Press Release or Talk Paper.....

- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)]..... N/A
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... N/A

- Exclusivity Summary X

- Debarment Statement X

- Financial Disclosure — X
  - No disclosable information .....
  - Disclosable information – indicate where review is located .....SPOS.....

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings X
  - Date of EOP2 Meeting February 24, 1999
  - Date of pre NDA Meeting October 2, 2000
  - Date of pre-AP Safety Conference N/A

- Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... ~~DRAFT, not in DFS~~
- Clinical review(s) and memoranda ..... ~~DRAFT, not in DFS~~

Continued ⇨

- ◆ Safety Update review(s) ..... See above

- ◆ Pediatric Information X
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page.....
  X Pediatric Exclusivity requested? X Denied ☐ Granted ☐ Not Applicable

- ◆ Statistical review(s) and memoranda ..... 4-12-02 & 4-24-02 X

- ◆ Biopharmaceutical review(s) and memoranda..... 4-15-02 X

- ◆ Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....

- ◆ Microbiology (efficacy) review(s) and memoranda ..... N/A

- ◆ DSI Audits ..... 3-14-02 X
  X Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ CMC review(s) and memoranda ..... 4-23-02 X

- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A

- ◆ DMF review(s) ..... ~~X~~ N/A

- ◆ Environmental Assessment review/Categorical exemption ..... 4-23-02 X

- ◆ Micro (validation of sterilization) review(s) and memoranda ..... N/A

- ◆ Facilities Inspection (include EES report)
  Date completed 04-23-2002 ☒ Acceptable ☐ Not Acceptable
  ~~PN as of 04/25/02~~

- ◆ Methods Validation ..... ☐ Completed X Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ Pharm/Tox review(s) and memoranda ..... 4-12-02 X

- ◆ Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... 3-21-02 X
- CAC/ECAC report ..... 1-29-01 ..... ~~N/A~~ X

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No 0910-0297
Expiration Date 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19850-8355

2 TELEPHONE NUMBER *(Include Area Code)*
302 886 7272

3 PRODUCT NAME
CRESTOR™ (rosuvastatin calcium) Tablets

4 DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THE FORM

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____
(APPLICATION NO CONTAINING THE DATA)

5 USER FEE I D NUMBER
4153

6 LICENSE NUMBER / NDA NUMBER
N021366

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?
☐ YES ☒ NO
(See reverse if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to.

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Maurice Briggs	Regulatory Affairs Director	MAY 3 1 2001

FORM FDA 3397 (5/98)

Created by Regulatory Systems Administration Group

Paid
06/06/01
$309,647.00

USER FEE VALIDATION SHEET

NDA # 21-366 Supp. Type & # N000 UFID # 4153
(e.g., N000, SLR001, SE1001, etc.)

1. YES NO **User Fee Cover Sheet Validated?** **MIS_Elements Screen Change(s):**

2. (YES) NO **APPLICATION CONTAINS CLINICAL DATA?**
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.**

3. YES (NO) **SMALL BUSINESS EXEMPTION**

4. YES (NO) **WAIVER GRANTED**

5. YES (NO) **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).**
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO **BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required**
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. P (S) **PRIORITY or STANDARD APPLICATION?**

S 06/28/01

PM Signature / Date

CPMS Concurrence Signature / Date

2/14/00

Food and Drug Administration
Division of Metabolic and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 12, 2003

To: Mark Eliason	From: Valerie Jimenez
Company: AstraZeneca	Division of Metabolic and Endocrine Drug Products
Fax number: (302) 885-5334	Fax number: (301) 443-9282
Phone number: (302) 885-5294	Phone number: (301) 827-9090

Subject:

Total no. of pages including cover: 26

Comments:

Document to be mailed: ☐ YES ☑ NO

Regulatory Contact, Mark Eliason, received faxed AP letter & labeling on August 12, 2003 @ 4:50pm

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	1601
CONNECTION TEL	913028855334
CONNECTION ID	
ST. TIME	08/12 16:47
USAGE T	10'29
PGS. SENT	26
RESULT	OK

Food and Drug Administration
Division of Metabolic and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 12, 2003

To: Mark Eliason	From: Valerie Jimenez
Company: AstraZeneca	Division of Metabolic and Endocrine Drug Products
Fax number: (302) 885-5334	Fax number: (301) 443-9282
Phone number: (302) 885-5294	Phone number: (301) 827-9090

Subject:

Total no. of pages including cover: 26

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 21-366
Crestor (rosuvastatin calcium) Tablets,
5 mg, 10 mg, 20 mg, and 40 mg

The preceding action letter has been reviewed by the undersigned:

Name	Discipline	Signature	Action	Date
David Orloff, M.D.	Division Director			
Mary Parks, M.D.	Deputy Director		MP	7/18
William Lubas, M.D.	Medical Reviewer		AP	7/17/03
Karen Davis Bruno, Ph.D.	Supervisor, Pharmacologist		AP	7/17/03
John Gong, Ph.D.	Pharmacology Reviewer		AP	7/17/03
Stephen Moore, Ph.D.	Chemistry Team Leader		AP	7/17/03
Sharon Kelly, Ph.D.	Chemistry Reviewer		AP	7/17/03
Hae-Young Ahn, Ph.D.	Biopharmaceutrics Team Leader		AP	7/17/03
Sang Chung, Ph.D.	Biopharmaceutrics Reviewer		AP	7/17/03
Todd Sahlroot, Ph.D.	Statistics Team Leader			7/17/03
Joy Mele, M.S.	Statistics Reviewer		AP	7/17/03
Enid Galliers	Chief, Project Management Staff		—	7/17/03

* see my note

TO: CDER-APPROVALS

Date of Approval: August 12, 2003

NDA #(s)/Supplement #(s): 21-366

Name of drug: Crestor (rosuvastatin calcium) Tablets; 5, 10, 20, and 40 mg

Name of sponsor: iPR Pharmaceuticals

Indication(s) [or state what is new]:

1. To reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.
2. As an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV).

3. As an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, non-HDL-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).

Dosage form/route of administration: Tablet/Oral

Is this dosage form/route of administration NEW?: No

Rx, OTC, or Rx-to-OTC switch: Rx

Drug classification and review priority rating: 1S, Standard

TO: FDR

SUBJECT: Pick-up information for action package to be copied

Division of Metabolic and Endocrine Drug Products (HFD-510)

Project Manager Name: Valerie Jimenez **Phone: (301) 827-9090**

Location for pick-up of action package: 14B19

Number of volumes in action package: 3

Date available for pick-up (within 1 week of AP): August 19, 2003

Electronic Mail Message

Date: 6/28/01 9:30:05 AM
From: Karen Davis-Bruno (DAVISBRUNOK)
To: Jeri El Hage (ELHAGEJ)
To: John Gong (GONGJ)
Cc: William C. Koch (KOCHW)
Subject: FWD: EDR - NDA 021366 from IPR drug name CRESTOR(ROSUVASTATIN CALCIUM)10

All,

Apparently the NDA for crestor is in the EDR. I know John has reviewed the IND and therefore it's logically that he is assigned the NDA. Jeri do you still want to handle this one or should I?

Karen

Electronic Mail Message

Date: 6/28/01 8:06:19 AM
From: William C. Koch (KOCHW)
Subject: FWD: EDR - NDA 021366 from IPR drug name CRESTOR(ROSUVASTATIN CALCIUM)10

Lipid Altering Team Leaders,

I am forwarding the server location for the new Crestor NDA from AstraZeneca.

Bill

Electronic Mail Message

Date: 6/27/01 6:48:21 PM
From: Enid Galliers (GALLIERS)
Subject: FWD: EDR - NDA 021366 from IPR drug name CRESTOR(ROSUVASTATIN CALCIUM)10

Please inform team leaders and reviewers about this NDA and forward the EDr info to them.

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

ADRA Review #2 of Action Package for NDA 21-366, Crestor (rosuvastatin calcium) Tablets

Reviewer: Lee Ripper, HFD-102
Date received in HFD-102: July 18, 2003 Date of Review: July 29, 2003
Actn goal date: July 31, 2003 UF GOAL DATE: August 12, 2003

Indication: Lipid lowering

Action type: AP RPM: Valerie Jimenez/Peggy Simoneau
Drug Classification: 1S Date original NDA received: June 26, 2001
505(b)(1) application
Patent Info: Received, acceptable
EER: AC 4/23/02. No changes 7/29/03.
Clinical Inspection Summary: AC 3/13/02, 3 U.S. sites inspected
OPDRA review of tradename: AC 7/2/01, 2/27/02, 7/14/03
DDMAC review of PI: There are no reviews by DDMAC in either the action package or DFS.
Debarment statement: *AC*
EA: Categorical exclusion
Financial disclosure information/review: 7/29/03 email to PM requesting copy of forms signed by iPR per NA letter, item #12. *Rec'd 7/29, forms were in the 2/12/03 AZ.*
Safety Update: See comment #2 below.

1. The debarment statement in the package certifies AstraZeneca did not use anybody debarred and is signed by an AZ official as agent for iPR. Applicant needs to submit a new debarment certification saying "iPR hereby certifies . . ." (iPR is in Puerto Rico, so debarment statement may be signed by applicant or by agent). *New debarment statement faxed in 7/28/03.*

2. The 7/23/03 MOR doesn't list the submissions it covers and is only attached to the 2/12/03 AZ submission. There is nothing to show that the 6/10/03 SU and other clinical amendments were reviewed. *Dr. Lubas will write an addendum to his review.*

3. The Exclusivity Summary needs to be redone for the division director's signature and signed by both the division director and the RPM. The answers to some questions need to be corrected.

4. A pediatric checklist needs to be added to the package.

Leah Ripper
ADRA, ODE II

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

/s/

Leah Ripper

7/31/03 02:56:37 PM

CSO

ADRA Review #1 of Action Package for NDA 21-366, Crestor (rosuvastatin calcium) Tablets

Reviewer: Lee Ripper, HFD-102
Date received in HFD-102: May 3, 2002 Date of Review: May 7, 2002
Actn goal date: May 24, 2002 (11 mo) UF GOAL DATE: June 26, 2002 (12 mo)

Indication: Lipid lowering

Action type: AE RPM: Bill Koch/Enid Galliers7-6412
Drug Classification: 1S Date original NDA received: June 26, 2001
505(b)(1) application
Patent Info: Received, acceptable
EER: AC 4/23/02
Clinical Inspection Summary: AC 3/13/02, 3 U.S. sites inspected
OPDRA review of tradename: AC 7/2/01 and 2/27/02.
DDMAC review of PI: Not done, we are not sending labeling comments
Debarment statement: Not acceptable, see item #1 below.
EA: Categorical exclusion
Financial disclosure information/review: AC, but see comment #2 below.
Safety Update: Per MOR section 7.8, p. 64, data in SU were included in review section 7.4

1. The wording of the submitted debarment statement is inadequate (i.e., "use in connection with this application" rather than "use in any capacity") and does not include the title and company of the person signing it. A new debarment certification should be submitted. It should use the wording in the draft guidance "Submitting Debarment Certification Statements." The signer's signature block should include name, title, company.

2. The MOR addresses the single investigator reporting SPOOS, but does not address the investigators that did not report at all. Although not many (study 8-1 investigator, study 27-14 investigators, study 30-1 investigators [numbers do not include investigators listed as "Did not participate"]), the impact of these investigators on the results of the studies and what was done to mitigate that impact should also be addressed.

3. We should discuss revising the letter so that item #1 under CLINICAL, the 80-mg dose, is located in a discrete, not approvable section of the letter.

4. The P/T review says preclinical studies are adequate to support 10 mg and 20 mg/day. Our letter says that 80 mg/day is NA, but that 40 mg/day is AE. If additional nonclinical studies are needed for the 40 mg/day dose and we are going to say 40 mg is AE, the letter should specify those studies.

5. If the labels were not already sent to DMETS, they should be sent when a major amendment comes in.

C:\Data\Wpfiles\N21366AE.doc
LWR 5/7/02

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

/s/

Leah Ripper
5/7/02 04:34:01 PM
CSO

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products

MEMORANDUM

Date: February 24, 2003

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

Subject: NDA 21-366; MR dated June 7, 2002

To: CDER-DRTL-FDR

The requested meeting was GRANTED on June 14, 2002.

Refer to attached fax form.

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 12/21/01
12:00:17 PM

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

/s/

William Koch
1/2/02 09:07:16 AM

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

DATE: October 25, 2001

COMMENTS:

Attached is a Division request for information regarding NDA 21-366.

Please don't hesitate to call with any questions.

TO:

Name: Maurice Briggs, Ph.D.
Associate Director, Regulatory Affairs
Fax No. (302) 886-2822
Phone No. (610) 695-1942

Location: AstraZeneca Pharmaceuticals LP

FROM:

Name: William C. Koch, R.Ph.
Regulatory Project Manager
Fax No. (301)-443-9282
Phone No. (301)-827-6412

Pages (including this cover sheet): three (3)

MESSAGE CONFIRMATION

10/25/01 16:29
ID=DMEDP-CDER-FDA

NO.	MODE	BOX	GROUP
795	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
10/25 16:29	00'40"	8862822	003/003	OK		0000

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

DATE: October 25, 2001

COMMENTS:

Attached is a Division request for information regarding NDA 21-366.

Please don't hesitate to call with any questions.

TO:

Name: Maurice Briggs, Ph.D.
Associate Director, Regulatory Affairs

FROM:

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

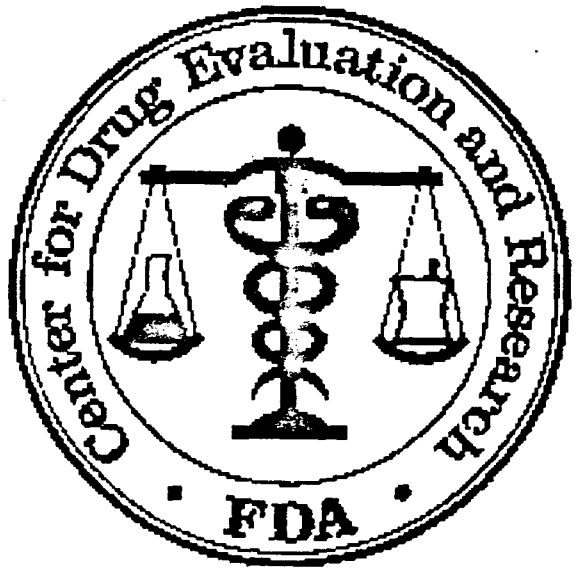
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

DATE: October 9, 2001



COMMENTS:

Attached is a Division request for information regarding NDA 21-366.

Please don't hesitate to call with any questions.

TO:

Name: Maurice Briggs, Ph.D.
Associate Director, Regulatory Affairs
Fax No. (302) 886-2822
Phone No. (610) 695-1942

Location: AstraZeneca Pharmaceuticals LP

FROM:

Name: William C. Koch, R.Ph.
Regulatory Project Manager
Fax No. (301)-443-9282
Phone No. (301)-827-6412

Pages (including this cover sheet): four (4)

MESSAGE CONFIRMATION

10/09/01 18:17
ID=DMEDP-CDER-FDA

NO.	MODE	BOX	GROUP
762	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
10/09 18:16	00'51"	8862822	004/004	OK		0000

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

DATE: October 9, 2001

COMMENTS:

Attached is a Division request for information regarding NDA 21-366.

Please don't hesitate to call with any questions.

TO:

Name: Maurice Briggs, Ph.D.
Associate Director, Regulatory Affairs

FROM:

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

DMEDP, HFD-510

Industry Meeting Tracking System Data Entry Documentation (IMTS)

Project Manager: Koch

Meeting Request Receipt Date: 10/29/01

Requester: Industry/CDER (circle one)

Notification Date: 10/30/01 (date industry was notified)

Meeting Status: (circle one)

Cancel- Late Package
Cancel- Other (give reason): _____
Granted
Denied
Withdrawn

Formal Meeting Date: 11/01/01 (actual meeting date)

Application Type: NDA/IND (circle one) **Application No:** 2-136-6

Sponsor's Name: (Fill in if there is no application type)

_____

Meeting Types: (circle one)

90 DAY	90 DAY
ADPRO	ADVERTISING/PROMOTION
BIOEQ	BIOPHARM/BIOEQUIVALENCE
CMC	CHEMISTRY
COMPL	COMPLIANCE
CP	CRITICAL PATH
ELECT	ELECTRONIC SUBMISSION
EOP1	END OF PHASE 1
EOP2	END OF PHASE 2/PRE-PHASE 3
EOR	END OF REVIEW
FC	FILING CONFERENCE
GUID	GUIDANCE
LABEL	LABELING
560FB	OTC MONOGRAPH FEEDBACK
OTHER	OTHER
PHTOX	PHARM/TOX
PH_4	PHASE 4
P-IND	PRE-IND
P-NDA	PRE-NDA/SUPPLEMENT
SAFTY	SAFETY ISSUES
SPC	SPECIAL PROTOCOL, CHEMISTRY
SPM	SPECIAL PROTOCOL, MEDICAL
SPX	SPECIAL PROTOCOL, PHARM/TOX

Meeting Minutes Issued Date: 01/02/02
(date mtg minutes were sent to participants)

Meeting ID _____