

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-740/S008/S013**

**CORRESPONDENCE**

**FAX COVER SHEET**

<b>TO:</b> Ms. Margaret Simoneau	<b>FROM:</b> W.E. Maguire
<b>COMPANY:</b> FDA	<b>DATE:</b> September 22, 1999
<b>FAX NUMBER:</b> (301) 443-9282	<b>SENDER'S FAX NUMBER:</b> (203) 812-5029
<b>PHONE NUMBER:</b>	<b>SENDER'S PHONE NUMBER:</b> (203) 812-2435
<b>RE:</b> NDA 20-740; Efficacy Suppl.	<b>TOTAL NO. OF PAGES INCLUDING COVER:</b> 4

URGENT  FOR REVIEW  PLEASE REPLY  AS REQUESTED  CONFIDENTIAL

**NOTES/COMMENTS:**

Dear Margaret,

Today, Bayer submitted an efficacy supplement for Baycol NDA #20-740 as an electronic submission. In accordance with the information in the guidance for these submissions and your telephone call, we are sending the CD with a copy of the cover letter and 356H form to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 12229 Wilkins Avenue, Rockville, MD 20852.

In addition, we are sending to the Division, care of the Document Control Room, 14b-04 a binder with the original cover letter, 356H and other signed documents as called for in the guidance.

**NOTICE**

The information contained in and transmitted with this facsimile may be confidential, subject to the attorney-client privilege, attorney work product, and/or exempt from disclosure under applicable law and is intended only for the individual or entity named above. If you are not the intended recipient, you are hereby notified that inadvertent disclosure of this information to you does not constitute a waiver of confidentiality or privilege and that any review, disclosure, copying, or use of the contents of this facsimile by you is prohibited. If you have received this facsimile in error, please immediately call the sender collect at the above phone number.

Finally, attached to this facsimile is a copy of the cover letter for you.

Please note on page two of the cover letter that from conversations we had with Dr. Orloff and with other reviewers, that we will be submitting under separate cover a review copy for the clinical, human pharmacology and chemistry reviewers. The copies for the human pharmacology and chemistry reviewers have been formatted in accordance with their specific requests. While Dr. Orloff did not specifically request a reviewer aid, we are providing a CD in MS Word format (all documents included on the archive CD are in PDF or SAS Transport file format) containing the pivotal clinical study report text portions, key summaries and the proposed package insert. We anticipate that we will be sending these to you for distribution tomorrow or Friday, September 24, 1999.

If you have any questions, please give me a call at (203) 812-2435.

  
Bill Maguire

Attachment

APPEARS THIS WAY  
ON ORIGINAL

## Meeting Minutes

Division of Metabolic and Endocrine Drug Products  
NDA 20-740/S-008

Date: Friday, November 12, 1999

Location: Parklawn 1456

Time: 9:00-9:45 AM

### FDA Attendees:

Dr. Orloff

H.Y. Ahn

R. Steigerwalt

Jim Wei

M. Simoneau

This was a **Filing meeting** for an efficacy supplement, (SE2), received September 22, 1999 to add a new, higher strength tablet, 0.8 mg dose to the subject NDA.

### Discussion:

- Clinical- Dr. Shen is the Medical Reviewer for this supplement. Dr. Orloff said there were no filing issues.
- Pharmacology- Ron Steigerwalt said that there were no filing issues.
- Chemistry- Xavier Ysem is the Chemistry Reviewer for this supplement. After the meeting, the Project Manager was told there were no filing issues.
- Biopharm-filable according to Jim Wei (see enclosure for additional comments).
- Biostatistics-Todd Sahlroot is the Statistician reviewing this supplement. He was on leave status and will be consulted on his return.
- DSI- Required. Project Manager will sent an e-mail to Roy Blay to request this.
- Submission will be a standard review.
- Clinical audits- Roy Blay will contact the Medical Officer to discuss the audits required.
- Advisory Committee- not needed.
- Review Goal Date with labeling-  
UFGD for 10 months is July 23, 2000. Final reviews are due by June 23, 2000.

File date for this supplement is November 22, 1999.

Minutes preparer: M. Simoneau           /S/          12-7-99          

Concurrence Chairman: Dr. Orloff           /S/          12-7-99          

cc:Original NDA 20-740/S-008  
DivFile

**NO ADVISORY  
COMMITTEE MEETING**

NDA 20-740/S-008 & S-013

Bayer Corporation  
Attention: William E. Maguire  
Director, Regulatory Affairs  
400 Morgan Lane  
West Haven, CT 06516

Dear Mr. Maguire:

We acknowledge receipt of your supplemental applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Baycol (cerivastatin) Tablets

NDA Number: 20-740

Supplement Numbers: S-008 and S-013

Date of Supplements: September 22, 1999

Date of Receipt: September 23, 1999

Our review of the changes proposed in your submission indicates that they must be administratively unbundled into two supplements

These supplements propose the following changes:

**Supplement-008** adds a new, higher dosage strength tablet, 0.8 mg, and extends the dosage range to 0.8 mg daily.

**Supplement-013** adds the new indication of increasing HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb) and will include summary data for these changes in the CLINICAL PHARMACOLOGY section of the labeling.

Clinical data are required to support S-008 and S-013. A user fee is assessed for each supplement that requires the review of clinical data. The appropriate user fee was paid for Supplement-008, but no fee was paid for Supplement-013. Thus, payment of a user fee for Supplement-013 is now due. Please obtain a new user fee identification number for Supplement-013 and submit a User Fee Cover Sheet for that supplement.

Payment should be submitted to the following address:

Food and Drug Administration  
P.O. Box 360909  
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Mellon Bank  
Three Mellon Bank Center  
27<sup>th</sup> Floor (FDA 360909)  
Pittsburgh, PA 15259-0001

**NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number is on the enclosed check.**

These applications were filed under section 505(b) of the Act on November 22, 1999, in accordance with 21 CFR 314.101(a). The primary user fee goal date will be July 23, 2000, and the secondary user fee goal date will be September 23, 2000.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). We note that you have received a Written Request to study the use of Baycol in children with heterozygous familial hypercholesterolemia.

APPEARS THIS WAY  
ON ORIGINAL

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Attention: Division Document Room 14B-19  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, contact William Koch, R.Ph., Regulatory Management Officer, at (301) 827-6412.

Sincerely yours,



Enid Galliers  
Chief, Project Management Staff  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

cc:

Archival NDA 20-740/S-008, S-013  
HFD-510/Div. Files  
HFD-510/WKoch  
HFD-510/Reviewers and Team Leaders  
HFD-5/User Fee staff  
DISTRICT OFFICE

Drafted by: emg/July 20, 2000  
final: emg/7.20.00  
filename: \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

ACKNOWLEDGMENT (AC)

SEP 28 1999

NDA 20-740/S-008

Bayer Corporation Pharmaceutical Division  
Attention: William E. Maguire  
Director, Clinical Quality Compliance  
400 Morgan Lane  
West Haven, CT 06516-4175

Dear Mr. Maguire:

We acknowledge receipt of your efficacy supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Baycol® (cerivastatin sodium) Tablets
NDA Number:	20-740
Supplement Number:	S-008
Therapeutic Classification:	Standard (S)
Date of Supplement:	September 22, 1999
Date of Receipt:	September 23, 1999

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 22, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 23, 2000, and the secondary user fee goal date will be September 23, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in

accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Attention: Division Document Room, 14B-19  
5600 Fishers Lane  
Rockville, Maryland 20857

APPEARS THIS WAY  
ON ORIGINAL

NDA 20-740/S-008

Page 3

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Management Officer,  
at (301) 827-6418.

Sincerely,

/S/

9.27.99

Enid Galliers

Chief, Project Management Staff

Division of Metabolic and Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

**Pharmaceutical  
Division**

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone 203 812-2000

July 20, 2000

John Jenkins, MD  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD-510  
ATTENTION: DIVISION DOCUMENT ROOM 14B-19  
5600 Fishers Lane  
Rockville, Maryland 20857

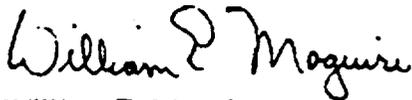
RE: NDA 20-740, Supplement's 008 and 013  
Baycol (cerivastatin sodium)

Dear Dr. Jenkins:

As a result of telephone discussions held with Dr. David Orloff on July 19, 2000, Bayer is hereby submitting a revised final Package Insert for Baycol (cerivastatin sodium).

If you have any questions, please do not hesitate to contact me at (203) 812-2435.

Sincerely yours,



William E. Maguire  
Director, Clinical Quality Compliance,  
Regulatory Affairs

WEM/cac  
attachments

cc: William Koch (via FAX)

**APPEARS THIS WAY  
ON ORIGINAL**

DUPLICATE

Bayer 

NEW COPY  
SNC

Pharmaceutical  
Division

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone 203 812-2000

July 19, 2000



John Jenkins, MD  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II HFD-510  
ATTENTION: DIVISION DOCUMENT ROOM 14B-19  
5600 Fishers Lane  
Rockville, Maryland 20857

RE: NDA 20-740  
Baycol (cerivastatin sodium)  
Financial Disclosure

Dear Dr. Jenkins:

I certify that all clinical investigators participating in and contributing data to the pivotal efficacy study, D97-008, were requested and did provide to Bayer the requisite financial disclosure information.

Sincerely yours,

  
William E. Maguire  
Director, Clinical Quality Compliance,  
Regulatory Affairs

WEM/cac

APPEARS THIS WAY  
ON ORIGINAL

Pharmaceutical  
Division

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone 203 812-2000

July 13, 2000

John Jenkins, MD  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II HFD-510  
ATTENTION: DIVISION DOCUMENT ROOM 14B-19  
5600 Fishers Lane  
Rockville, Maryland 20857

RE: NDA 20-740  
Baycol (cerivastatin sodium)

Dear Dr. Jenkins:

As a result of discussions held with the Division during a teleconference on July 12, 2000, Bayer is hereby submitting a revised Package Insert for Baycol (cerivastatin sodium). We are providing this insert in both paper as well as on a diskette in MS Word format.

In addition, during the same teleconference the division requested that we provide citations/documentation for two statements contained in the proposed insert. Attachment 1 provides the citation reference for the  $C_{max}$  of 0.8-mg cerivastatin at steady state. Attachment 2 describes the metabolism information. This document had been sent to Dr. Steigerwalt as a facsimile on May 22, 2000, but was not officially submitted to NDA 20-740.

Finally, we have decided to place the statement concerning myopathy in elderly females in the Warnings and Geriatrics sections instead of the Precautions and Geriatrics sections.

APPEARS THIS WAY  
ON ORIGINAL

July 13, 2000  
John Jenkins, MD  
Page Two

If you have any questions, please do not hesitate to contact me at (203) 812-2435.

Sincerely yours,

  
William E. Maguire  
Director, Clinical Quality Compliance,  
Regulatory Affairs

WEM/cac  
Attachments

cc: William Koch (cover letter via FAX)

APPEARS THIS WAY  
ON ORIGINAL

SE2-008 152



Pharmaceutical  
Division

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone: 203-812-2000

July 7, 2000

John Jenkins, M.D., Acting Director  
Division of Metabolism and Endocrine Drug Products  
Office of Drug Evaluation II HFD-510  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTN: Document Control Room 14B-04  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 20-740; S-008  
BAYCOL® (cerivastatin sodium tablets)  
Draft Labeling

Dear Dr. Jenkins,

In response to a request from Mr. William Koch, CSO, Bayer is providing an electronic version of the draft labeling for this sNDA. The labeling is being provided on a diskette in Microsoft® WORD 97 and is highlighted to indicate changes from the current approved labeling.

Included in this labeling are changes in the "Contraindications", "Warnings", and "Concomitant Therapy" sections which were incorporated in Bayer's "Changes Being Effected" supplement to this NDA, — submitted to FDA on December 3, 1999.

Please note that the changes in the "Pharmacokinetics", "CNS and other toxicities", and "Carcinogenesis, Mutagenesis, Impairment of Fertility" sections were discussed with Dr. R. Steigerwalt and accepted in his FAX to Bayer on June 21, 2000.

If there are any questions regarding this submission please contact me at (203) 812-2435.

Sincerely,

William E. Maguire  
Director, Regulatory Affairs

/fks

attachment

cc: W. Koch (FDA)

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> FINAL <input type="checkbox"/> MEMO
<i>ISI</i> <i>07/10</i>
CSO INITIALS DATE

June 27, 2000

**Pharmaceutical  
Division**

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone: 203 812-2000

John Jenkins, MD  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD-510  
ATTENTION: DIVISION DOCUMENT ROOM 14B-19  
5600 Fishers Lane  
Rockville, Maryland 20857

RE: Baycol (cerivastatin sodium)  
NDA 20-740, S008  
Safety Update - 0.8-mg Efficacy Supplement

Dear Dr. Jenkins:

Pursuant to 21 CFR 314.50(d)(5)(vi)(b) Bayer Corporation Pharmaceutical Division submits the attached Safety Update to the subject NDA.

For reporting purposes we have established March 31, 2000 as the cut-off date for data to be included in this submission. Since the data cut-off date for the 4-Month Safety Update to the Efficacy Supplement (September 30, 1999), submitted to FDA on January 20, 2000, four studies with Baycol 0.8-mg have completed.

Final reports for these four studies will be submitted to IND — in the next Information Amendment. These studies are:

Study 588001, "A Multinational, Multi-Centre, Randomised, Double-Blind, Parallel Group Comparative Study of Cerivastatin [0.2 mg, 0.4 mg, and 0.8 mg Once Daily] versus Pravastatin [10 mg, 20 mg and 40 mg Once Daily] in Patients with Primary Hypercholesterolemia"

Study 71, "Multinational, Multi-centre, Randomised, Double-Blind, Parallel Group Study Comparing Cerivastatin Sodium [0.4 mg and 0.8 mg once daily] Against Atorvastatin [10 mg and 20 mg once daily] in Patients with Primary Hypercholesterolemia"

**APPEARS THIS WAY  
ON ORIGINAL**

Study 100166, "Randomized, Double-Blind, Parallel Group, Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of \_\_\_\_\_ Cerivastatin \_\_\_\_\_ vs Placebo in Patients with Hypercholesterolemia"

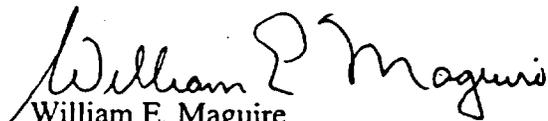
Study 10048, "A Single-Center, Randomized, Non-Blind, Controlled Three-Way Crossover Interaction Study to Investigate the Mutual Influence of Concomitantly Administered Single Oral Doses of 200 mg Fenofibrate [Micronized, Lipidil®] and 0.8 mg BAY w 6228 cerivastatin sodium, Lipobay®] on the Pharmacokinetics, Safety and Tolerability of Each Drug in Healthy Male Volunteers"

As the 0.8-mg Efficacy Supplement to NDA 20-740, (S008) and the 4-Month Safety Update were submitted as electronic submissions following the guidelines provided in the Guidance for Industry: Providing Regulatory Submissions in Electronic Format-NDAs dated January 1999 we are also providing this Safety Update electronically. All documents are provided in PDF format with a paper copy of those documents requiring a signature also being included.

We certify that we have taken precautions to ensure that the data files are free of computer viruses and authorize FDA to use anti-virus software as appropriate. Anti-virus software used at Bayer is \_\_\_\_\_, version: \_\_\_\_\_ and \_\_\_\_\_ for Windows \_\_\_\_\_ version \_\_\_\_\_

If you have any questions, please do not hesitate to contact me at (203) 812-2435.

Sincerely yours,



William E. Maguire

Director, Clinical Quality Compliance, Regulatory Affairs

Enclosure

Copy: Mr. William Koch (cover letter)

APPEARS THIS WAY  
ON ORIGINAL

DUPLICATE

Bayer 

**NDA SUPP AMEND**

*S-008 AS*

Pharmaceutical  
Division

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone: 203 812-2000

June 27, 2000

John Jenkins, M.D., Acting Director  
Division of Metabolism and Endocrine Drug Products  
Office of Drug Evaluation II HFD-510  
Center for Drug Evaluation and Research  
Food and Drug Administration  
**ATTN: Document Control Room 14B-04**  
5600 Fishers Lane  
Rockville, MD 20857



Re: **NDA 20-740; S-008**  
**BAYCOL® (cerivastatin sodium tablets)**  
**Response to FDA Questions**

Dear Dr. Jenkins,

On June 23, 2000 T. Sahlroot telephoned Bayer with questions concerning the submission noted above. In response to his questions, Bayer is providing the following information.

A listing of upper limit of normal (ULN) values used by Bayer for AST, ALT, and CK.

CK                   ULN = 120 mu/ml  
SGOT (AST)   ULN = 22 mu/ml  
SGPT (ALT)   ULN = 25 mu/ml

A listing of patients in study D97-008 who completed weeks 2, 4, 6, 8, 24, and 52. (attached)

If there are any questions regarding this submission please contact me at (203) 812-2435.

Sincerely,

  
William E. Maguire  
Director, Regulatory Affairs

/fks

attachment

cc: T. Sahlroot (FDA - Desk Copy)

**APPEARS THIS WAY  
ON ORIGINAL**

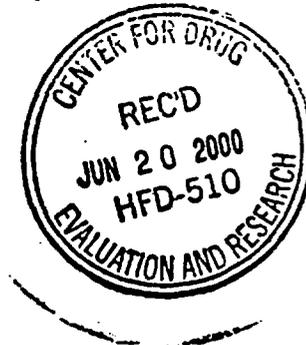
Pharmaceutical  
Division

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone: 203 812-2000

**ORIGINAL**

June 19, 2000

John Jenkins, M.D., Acting Director  
Division of Metabolism and Endocrine Drug Products  
Office of Drug Evaluation II HFD-510  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTN: Document Control Room 14B-04  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 20-740; S-008  
BAYCOL® (cerivastatin sodium tablets)  
Response to FDA Questions

Dear Dr. Jenkins,

In response to a request from Dr. Shen on June 16, the following information is being provided.

Tables listing the actual lab values for study D97-008 for:

Alkaline Phosphatase  
LDH

If there are any questions regarding this submission please contact me at (203) 812-2435.

Sincerely,



William E. Maguire  
Director, Regulatory Affairs

/fks

attachment

cc: Dr. Shiao Wee Shen (FDA - Desk Copy)

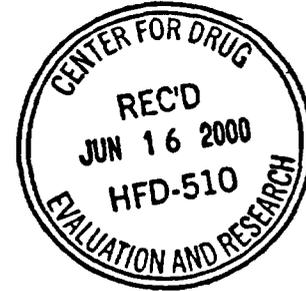
REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

5E2-008156

Pharmaceutical  
DivisionBayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone: 203 812-2000

June 15, 2000

John Jenkins, M.D., Acting Director  
Division of Metabolism and Endocrine Drug Products  
Office of Drug Evaluation II HFD-510  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTN: Document Control Room 14B-04  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 20-740; S-008  
BAYCOL® (cerivastatin sodium tablets)  
Response to FDA Questions

Dear Dr. Jenkins,

In response to questions raised by Dr. Shen on June 9 and June 14, the following information is being provided.

- 1) Table – Patients with CK elevations greater than 5 times the upper limit of normal (ULN) by gender and weight.
- 2) Tables listing the actual lab values for study 17
  - a) High Chemistry
  - b) High Hematology
  - c) Low Chemistry
  - d) Low Hematology

The n's (185 for CER and 184 for SIMVA) in Tables 2-10 to 2-13 in the 4-month safety update are for all patients valid for safety. However, the actual number of patients at risk for a treatment-emergent abnormality varies with each lab parameter. A treatment emergent high abnormality pertains to a high lab value in a patient with a normal or low value at baseline. Conversely, a treatment emergent low abnormality pertains to a low lab value in a patient with a normal or high value at baseline. The % calculations in each table are based on this and thus each parameter may have a different denominator other than the n at the top of each table.

- 3) A listing of patient weights for attachment B - "Table 12-22 - Patients with CK Elevations > 10 \* ULN" which was submitted June 12.

4) A listing of treatment emergent total bilirubin values for the patients listed in the sNDA integrated safety summary, Table 8.7-23 - Study D97-008 "Treatment-Emergent High Serum electrolytes/Chemistries.

If there are any questions regarding this submission please contact me at (203) 812-2435.

Sincerely,



William E. Maguire  
Director, Regulatory Affairs

/fks

attachment

cc: Dr. Shiao Wee Shen (FDA - Desk Copy)

REVIEWS COMPLETED	
REG ACTION: -	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CS/INITIALS	DATE

APPEARS THIS WAY  
ON ORIGINAL

ORIGINAL

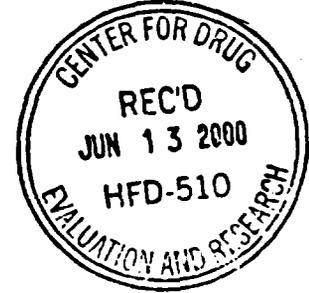
NDA SUPP AMEND  
SE2-008 BM

Pharmaceutical  
Division

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone 203 812-2000

June 12, 2000

John Jenkins, M.D., Acting Director  
Division of Metabolism and Endocrine Drug Products  
Office of Drug Evaluation II HFD-510  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTN: Document Control Room 14B-04  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 20-740; S-008  
BAYCOL® (cerivastatin sodium tablets)  
Response to FDA Questions

Dear Dr. Jenkins,

The attached information is being submitted in response to questions raised by Dr. Shen during a teleconference held on June 7, 2000 to discuss the submission noted above.

If there are any questions regarding this submission please contact me at (203) 812-2435.

Sincerely,

William E. Maguire  
Director, Regulatory Affairs

/fks

attachment

cc: Dr. Shiao Wee Shen (FDA - Desk Copy)

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

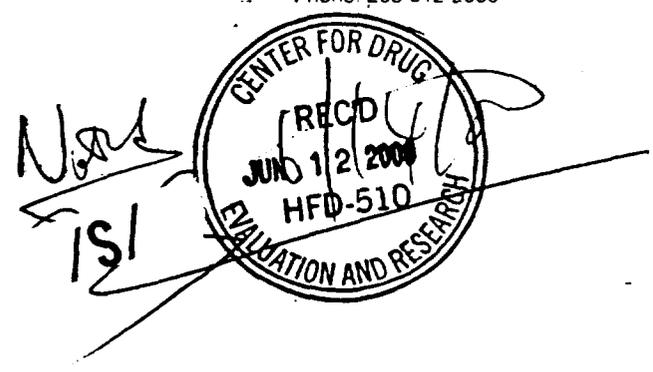
SNC

Pharmaceutical  
Division

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone: 203 812-2000

June 9, 2000

John Jenkins, M.D., Acting Director  
Division of Metabolism and Endocrine Drug Products  
Office of Drug Evaluation II HFD-510  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTN: Document Control Room 14B-04  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 20-740  
BAYCOL® (cerivastatin sodium tablets)  
Response to FDA Questions

Dear Dr. Jenkins,

On June 1, 2000 representatives of Bayer Corporation held a teleconference with Dr. R. Steigerwalt regarding the calculation of the toxicity safety margins in the labeling for BAYCOL®. The attached information is in response to questions raised by Dr. Steigerwalt during that teleconference.

If there are any questions regarding this submission please contact me at (203) 812-2435.

Sincerely,

*William E. Maguire for*

William E. Maguire  
Director, Regulatory Affairs

/fks

attachment

cc: R. Steigerwalt - FDA

REVIEWS COMPLETED	
<input type="checkbox"/> MAIL	<input type="checkbox"/> MEMO
	DATE

January 20, 2000

Pharmaceutical  
Division

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone: 203 812-2000

John Jenkins, MD  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD-510  
ATTENTION: DIVISION DOCUMENT ROOM 14B-19  
5600 Fishers Lane  
Rockville, Maryland 20857

RE: Baycol (cerivastatin sodium)  
NDA 20-740, S008  
4-Month Safety Update - 0.8-mg Efficacy Supplement

Dear Dr. Jenkins:

Pursuant to 21 CFR 314.50(d)(5)(vi)(b) Bayer Corporation Pharmaceutical Division submits the attached Safety Update to the subject NDA.

For reporting purposes we have established September 30, 1999 as the cut-off date for data to be included in this submission. Since the data cut-off date for the 0.8-mg Efficacy Supplement, submitted to FDA on September 22, 1999, three studies with Baycol 0.8-mg have completed. For one of these studies, Study 100192, "A Randomized, Three-way Crossover Study of the Pharmacokinetic Interaction Between Itraconazole and 0.8 mg Cerivastatin and 20 mg Atorvastatin and 40 mg Pravastatin" an interim report summary was included in the Efficacy Supplement. For this reason we are including the final report for this study in this Safety Update. Of the other two studies, the final report for Study 10014, "Influence of a seven-day pre- and co-treatment of orlistat (Xenical) 120-mg t.i.d. on the pharmacokinetics, safety and tolerability of a single dose of 0.8-mg BAY w 6228 using a randomized, non-blind, controlled two-way crossover study in young healthy male subjects" was submitted to IND \_\_\_\_\_ on October 7, 1999 in an Information Amendment; the final report for Study 17, "A multinational, multi-center, randomised, double-blind parallel group study comparing cerivastatin sodium (0.2 mg, 0.4 mg and 0.8 mg once daily) against simvastatin (10 mg, 20 mg and 40 mg once daily) in patients with hypercholesterolemia" will be submitted to IND \_\_\_\_\_ in the next Information Amendment.

As the 0.8-mg Efficacy Supplement to NDA 20-740, (S008) was submitted as an electronic submission following the guidelines provided in the Guidance for Industry: Providing Regulatory Submissions in Electronic Format-NDAs dated January 1999 we are also providing

this Safety Update electronically. All documents are provided in PDF format with a paper copy of those documents requiring a signature also being included.

We certify that we have taken precautions to ensure that the data files are free of computer viruses and authorize FDA to use anti-virus software as appropriate. Anti-virus software used at Bayer is \_\_\_\_\_, version \_\_\_\_\_ and \_\_\_\_\_ for Windows \_\_\_\_\_ version \_\_\_\_\_

If you have any questions, please do not hesitate to contact me at (203) 812-2435.

Sincerely yours,

  
William E. Maguire  
Director, Clinical Quality Compliance

Enclosure

Copy: Ms. Margaret Simoneau (cover letter)

APPEARS THIS WAY  
ON ORIGINAL

**FOOD AND DRUG ADMINISTRATION**  
**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN**  
**ANTIBIOTIC DRUG FOR HUMAN USE**  
*(Title 21, Code of Federal Regulations, 314 & 601)*

Expiration Date: April 30, 2000  
See OMB Statement on page 2.

**FOR FDA USE ONLY**

APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT Bayer Corporation Pharmaceutical Division		DATE OF SUBMISSION 1/20/00
TELEPHONE NO. (Include Area Code) 203-812-2435		FACSIMILE (FAX) Number (Include Area Code) 203-812-5029
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 400 Morgan Lane West Haven, CT 06510-4175	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE	

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		NDA 20-740
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Cerivastatin	PROPRIETARY NAME (trade name) IF ANY Baycol	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)		CODE NAME (if any)
DOSAGE FORM: Tablets	STRENGTHS: 0.8-mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:  
Hypercholesterolemia

**APPLICATION INFORMATION**

APPLICATION TYPE (check one)

NEW DRUG APPLICATION (21 CFR 314.50)    
 ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)  
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE    
 505 (b) (1)    
 505 (b) (2)    
 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application
--------------	--------------------------------

**TYPE OF SUBMISSION**

(check one)

ORIGINAL APPLICATION    
 AMENDMENT TO A PENDING APPLICATION    
 RESUBMISSION  
 PRESUBMISSION    
 ANNUAL REPORT    
 ESTABLISHMENT DESCRIPTION SUPPLEMENT    
 SUPAC SUPPLEMENT  
 EFFICACY SUPPLEMENT    
 LABELING SUPPLEMENT    
 CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT    
 OTHER

**REASON FOR SUBMISSION**

4-Month Safety Update

PROPOSED MARKETING STATUS (check one)    
 PRESCRIPTION PRODUCT (Rx)    
 OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: <u>1</u>	THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC
---------------------------------------	---

**ESTABLISHMENT INFORMATION**

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFR), DMP number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 810(k)s, IDEs, BMFs, and DMFs referenced in the current application)

X	1. INDEX
	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (e)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
X	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (v) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 308 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3367)
	19. OTHER (Specify)

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 620.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 800.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE William E. Maguire Director, Clinical Quality Compliance	DATE 1/20/00
ADDRESS (Street, City, State, and ZIP Code) 400 Morgan Lane West Haven, CT. 06516		Telephone Number (203) 812-2435

Public reporting burden for this collection of information is estimated to average 40 hours 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 (0910-0335)  
Hubert H. Humphrey Building, Rcom 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.

September 23, 1999

Pharmaceutical  
Division

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone 203 812-2000

Ms Margaret Simoneau  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Office of Drug Evaluation II (HFD-510)  
CDER, Bldg. PKLN  
ATTENTION: DOCUMENT CONTROL ROOM 14B-04  
5600 Fishers Lane  
Rockville, Maryland 20857

RE: Baycol (cerivastatin sodium tablets)  
NDA 20-740  
Efficacy Supplement: 0.8 mg Dose

Dear Ms Simoneau,

As noted in the cover letter to our NDA 20-740 Efficacy Supplement which was sent to the agency on September 22, 1999, Bayer would be providing certain reviewer aids under separate cover. Attached for distribution are these reviewer aids for the Clinical, Human Pharmacology, and Chemistry reviewers.

For the various reviewers the following is included:

Clinical

One CD containing MS Word versions of the text portions \_\_\_\_\_ of the pivotal study report (100183), the integrated summary of efficacy, integrated summary of safety (in two files, the ISS and ISS Appendix), the risk/benefit summary, the overall summary, and the proposed package insert.

Human Pharmacology

One CD containing MS Word versions of the text portions \_\_\_\_\_ of the five clinical pharmacology study reports and the overall summary, and, — oinders containing the complete Human Pharmacology Section and the Overall Summary.

Chemistry

Eight binders containing the Chemistry Section without the Methods Validation Section (as requested by the reviewer).

Please inform the reviewers receiving the CDs that Bayer also has included on each a folder called *Fonts* that contain several fonts that will be needed to properly view some of the material provided. The fonts included are MS Line Draw, Lotus Line Draw and SAS monospace fonts. These should be copied to the windows\fonts directory.

Also, as noted in the cover letter, once the sNDA has been loaded onto the FDA's network and read only access has been granted to the reviewers, Bayer is prepared to meet with the reviewers to walk them through the submission and answer any questions that may arise.

If you have any questions regarding this material, please give me a call at (203) 812-2435.

  
William E. Maguire  
Director, Clinical Quality Compliance

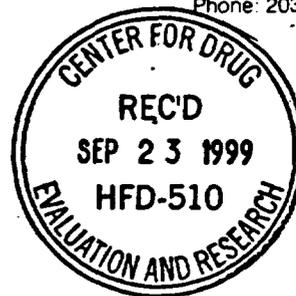
APPEARS THIS WAY  
ON ORIGINAL

September 22, 1999

NDA NO. 20-740 REF NO. PD 8  
Pharmaceutical  
NDA SUPPL FOR SE 2 Division

Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Office of Drug Evaluation II (HFD-510)  
CDER, Bldg. PKLN  
ATTENTION: DOCUMENT CONTROL ROOM 14B-04  
5600 Fishers Lane  
Rockville, Maryland 20857

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
Phone: 203 812-2000



RE: Baycol (cerivastatin sodium tablets)  
NDA 20-740  
Efficacy Supplement: 0.8 mg Dose

Dear Dr. Sobel:

Bayer Corporation, Pharmaceutical Division, files this Supplement in accordance with 21 CFR 314.71, to add a 0.8 mg dose to the subject NDA. The dosage form is a distinct 0.8 mg tablet. The product is currently marketed as 0.2 mg, 0.3 mg and 0.4 mg tablets

On October 23, 1998 Bayer submitted to IND — its plan for the clinical section of this NDA Supplement. In that submission it was noted that the clinical section would consist of efficacy data from pivotal trial D97-008 on all patients (up to 24 weeks) with safety data for the first 200 patients at 52 weeks; the remaining safety data would be submitted in the 4-Month Safety Update. On December 18, 1998, we were notified that the proposal was acceptable with the understanding that terminology be clarified in that efficacy data would be provided on all patients through 24 weeks and safety data for the first 200 patients through 52 weeks. Since that time, Bayer has decided to submit efficacy and safety data on all patients treated through 52 weeks in a single report, and to forego the proposed submission described above. This decision was based upon feedback from the review of the 0.4 mg sNDA where it was noted that the multiple medical reports, necessitated by the 52-week subset plan, had increased the complexity of the medical review. Subsequently Bayer believes that the inclusion of 52-week data on all patients in a single report in this NDA Supplement should facilitate the medical review of the submission.

On March 12, 1999, in a telephone conversation with the division, Bayer indicated that we would be submitting this efficacy supplement as an electronic submission following the guidelines provided in the Guidance for Industry: Providing Regulatory Submissions in Electronic Format-NDAs dated January 1999. While it was generally agreed that an electronic submission as provided for in the guidance was acceptable, Bayer was informed that, in addition to the electronic versions, the CMC reviewer would like the Drug Product Section,

Batch Records and Overall Summary in paper and the human pharmacology reviewer would like the entire Human Pharmacology Section, except for raw data, and the Overall Summary in paper. No other reviewer aids would be required. On April 9, 1999 Bayer provided the division with a copy of the proposed Table of Contents, as it would appear in the electronic submission and a description of the intended contents of the submission.

This supplemental NDA is being provided to the division in two sections, the Archival Copy and, in accordance with the above, a review copy. Included with this letter is the Archival Copy on 1 CD formatted in accordance with the guidance. All documents are provided in PDF format with a paper copy of those documents requiring a signature also being included. Data listings for all six clinical studies are provided as SAS Transport Files.

Under separate cover we are providing a review copy for the Human Pharmacology, Clinical, and Chemistry reviewers as noted below:

1. Human Pharmacology: On 1 CD are MS Word versions of the five human pharmacology reports (text portions only) and the paper copies as requested.
2. Clinical: On 1 CD are MS Word versions of the one clinical study report (text portions only), the integrated summaries of efficacy, safety and risk/benefit and the proposed package insert.
3. Chemistry: paper copies as requested.

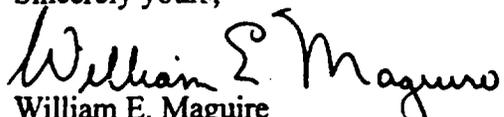
We certify that we have taken precautions to ensure that the data files are free of computer viruses and authorize FDA to use anti-virus software as appropriate. Anti-virus software used at Bayer is \_\_\_\_\_, version \_\_\_\_\_ and \_\_\_\_\_ for Windows  
\_\_\_\_\_ version \_\_\_\_\_

Finally, once the supplemental NDA has been loaded onto the CDER network and the read-only copy created, appropriate Bayer staff is prepared to meet with the reviewers to walk them through the submission.

The User Fee for this original NDA supplement (User Fee ID Number: 3719) was submitted on September 3, 1999.

If any additional questions arise with regard to the information provided, please do not hesitate to contact me at (203) 812-2435.

Sincerely yours,

  
William E. Maguire  
Director, Clinical Quality Compliance

Enclosure  
Copy: Ms. Margaret Simoneau (cover letter)

APPEARS THIS WAY  
ON ORIGINAL