Item 16 DEBARMENT CERTIFICATION

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

Signed: Marvin F Blanford
Marvin F. Blanford, PharmD

Title: Vice President of Compliance

Date: 8-17-00

Telephone Number: 305-512-7007 or 800-211-2534, ext. 7007

APPEARS THIS WAY
ON ORIGINAL

VI. Review of Financial Disclosure

Financial disclosure information was reviewed for the two controlled clinical studies MA-14 and MA-06. There were no financial disclosures submitted for any of the uncontrolled studies.

A. Protocol MA-98-010406

There were 23 Principal Investigators at 23 sites nationally. All 23 Investigators (100%) submitted financial disclosure information. None of the Investigators were employees of Kos Pharmaceuticals, and no Investigator had a significant equity interest in Kos Pharmaceuticals.

[

]

Comments: Protocol MA-06 was a double-blind, placebo-controlled study. The blind was maintained throughout the study. Lipid results were also blinded to the study Investigators. The financial bias at these study centers is unlikely to have affected the results of the study.

B. Protocol MA-98-010414

There were 14 Principal Investigators and 4 Co-Investigators at 16 sites nationally. All 18 Investigators (100%) submitted financial disclosure information. None of the Investigators were employees of Kos Pharmaceuticals.

[

]

Comments: Protocol MA-14 was a double-blind, placebo-controlled study. The blind was maintained throughout the study. Lipid results were also blinded to the study Investigators. The financial bias at this study center is unlikely to have affected the results of the study.

APPEARS THIS WAY
ON ORIGINAL

Item 19 FINANCIAL INFORMATION

I. Investigators Who Had Financial Interest or Financial Arrangements

Details of disclosable financial arrangements for the following investigators are provided. A completed Form FDA 3455 for each investigator is provided on the following pages.

MA-98-010406, Evaluation of the Safety and Efficacy of Nicostatin: A Dose-Ranging Study

[redacted]

MA-98-010414, Evaluation of the Safety and Efficacy of Nicostatin: A Dose-Response Study

[redacted]

Steps taken to minimize the potential bias of study results.

In order to minimize the potential bias of clinical study results, both studies employed double-blind methods, which were maintained throughout the entire study. Active and placebo tablets matched as did number of tablets taken per dose interval. The blind was not broken before database lock for any reason including serious adverse events.

In addition to medication blinding, lipid results were also blinded to the study investigators. All lipid results following patient randomization were sent directly to the Clinical Data Management department at Kos. These results were inserted into the case report forms as they were received. No member of the Clinical Research department, including study managers, has access to these lipid results. Also data-monitoring committee or interim analyses were used which would have required unblinding of data.

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II. Investigators Who Did Not Have Financial Interest or Financial Arrangements

A completed certification (Form FDA 3454) for investigators and sub-investigators who did not have financial interest or financial arrangements is provided on the following page. A list of the investigators who did not have financial interest or financial arrangements for each covered clinical study follows the Form 3454.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

A:		
S		

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Marvin F. Blanford, Pharm.D.	Vice President of Compliance
FIRM/ORGANIZATION	
Kos Pharmaceuticals, Inc.	
SIGNATURE: Marvin F Blanford	DATE: 8-17-00

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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MEMO TO FILE:	21-Sep-2001
Medical Reviewer:	Anne Pariser, M.D.
NDA#:	21-249, N 000 B2
Submission:	17-Sep-2001, Response to Approvable Letter dated 20-Jul-2001, proposed revisions to the Package Insert (PI)
Sponsor:	Kos Pharmaceuticals, Inc.
Drug:	Advicor (niacin extended-release and lovastatin)

Introduction

Kos Pharmaceuticals submitted a response to the Approvable Letter dated July 20, 2001 for NDA 21-249. The response contained updated chemistry, manufacturing and controls (CMC) information (which is deferred to the Chemistry Reviewer), and proposed revisions to the Package Insert (PI) which will be considered below.

Review

The sponsor is proposing:

1) A description of the potency of each active ingredient as mg added after both numbers (Niaspan mg/lovastatin mg), eg., 500 mg/20 mg, 750 mg/20 mg, etc. For consistency, changes were made throughout the label.

2) A description of the color of each tablet by dosage form has been added to the How Supplied section.

3) Reference to [redacted] as the manufacturing site was replaced by the corporate address as "Miami, FL 33131"

4) A formatting change to Table 8 was made, and the words "data from" were added prior to the words "Controlled, Double-Blind Studies" in the title.

5) A typographical correction was made in the Warnings Section with the symbol > replaced by ≥ in the following sentence: "Myopathy and/or rhabdomyolysis have been reported when lovastatin is used in combination with lipid-altering doses (≥1g/day) of niacin."

6) Trademark symbols were discontinued after first use with a brand name.

7) Prothrombin time spelled fully in first use then abbreviated PT.

8) Deciliters consistently abbreviated as dL.

9) Abbreviations in text consistently shown as LDL-C, HDL-C, TC and TG.

10) Grammatical error corrections.

The above revisions (1-10) are minor and do not represent new data or findings. There is no objection to these changes.

11) Revisions to the Clinical Studies sections of the label in order to clarify the study design and dosing scheme so as to provide a clearer explanation of the study findings to the practicing physician. The revisions are as follows (addition bold and underlined): "In a multi-center, randomized, double-blind, parallel, 28-week, active-comparator study in patients with Type IIa and IIb hyperlipidemia, ADVICOR was compared to each of its components (NIASPAN and lovastatin). Using a forced dose-escalation study design, patients received each dose for at least 4 weeks. **Patients randomized to treatment with ADVICOR initially received 500mg/20mg. The dose was increased at 4-week intervals to a maximum of 1000 mg/20 mg in one-half of the patients and 2000 mg/40 mg in the other half. The NIASPAN monotherapy gourp underwent a similar titration from 500 mg to 2000 mg. The patients randomized to lovastatin monotherapy received 20 mg for 12 weeks titrated to 40 mg for up to 16 weeks.** Up to a third of the patients randomized to ADVICOR or NIASPAN discontinued prior to Week 28. In this study, ADVICOR decreased LDL-C, TG and Lp(a), and increased HDL-C in a dose-dependent fashion (Tables 2, 3, 4 and 5 below)."

The additions above (#11) provide greater clarity to the clinical study description and for the interpretation of the data in the tables that follow. There is no objection to these changes.

12) Changes in the Dosage and Administration Section, reordered (not shown) and reworded for clarification of the recommended use and administration of Advicor. The changes are as follows: "ADVICOR should be taken at bedtime, with a low fat snack, and the dose should be individualized according to patient's response. ADVICOR tablets should be taken whole and should not be broken, crushed, or chewed before swallowing. The dose **of ADVICOR should not** be increased by **more than** 500 mg daily (based on the NIASPAN component) every 4 weeks. **The lowest dose of ADVICOR is 500 mg/20 mg.** Doses of ADVICOR greater than 2000 **mg**/40 **mg** daily are not recommended. **If ADVICOR therapy is discontinued for an extended period (>7 days), reinstitution of therapy should begin – with the lowest dose of ADVICOR** ——————— '

The reordering of information (not shown) and revisions above (#12) provide greater clarity of Dosage and Administration. There is no objection to these changes.

Conclusions

The revisions to the label do not represent any new information, data, or results. The revisions were predominantly corrections or clarifications, and there is no objection to any of the proposed changes. Additional revisions to the CMC section will be deferred to the Chemistry Reviewer and will not be commented upon here by this Reviewer.

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/s/

Anne Pariser
9/27/01 08:13:50 AM
MEDICAL OFFICER

Mary Parks
9/27/01 11:44:18 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION	DATE: June 28, 2001 Time: 1520 hrs
FDA Attendees: Anne Pariser, M.D., Clinical Reviewer William C. Koch, R.Ph., Regulatory Project Manager **Objectives:** To request that the applicant submit final efficacy data from the MA-98-010407 study **Discussion:** The Division requested that the final efficacy data for this trial be submitted to the NDA. The Division requested all available data for all endpoints. The Division also requested a breakdown of the numbers of patients completing the study at particular doses. **Conclusion(s):** The applicant will submit the requested data.	**Telecon initiated by:** FDA **NDA** 21-249 **Product name:** Advicor **Firm name:** Kos Pharmceutical **Name and title of person with whom conversation was held:** Ms. Valerie Ahmuty, Manager of Regulatory Affairs **Telephone #:** (305) 512-7002
{See appended electronic signature page} William C. Koch, R.Ph. Date Regulatory Project Manager	

APPEARS THIS WAY
ON ORIGINAL

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/s/

William Koch
5/29/01 11:21:13 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION	DATE: 04/12/01 Time: 04:45 PM
FDA Attendees: Enid Galliers, Chief, Project Mgmnt staff William C. Koch, R.Ph., Project Manager **Objectives:** To discuss trade name approval process and use of the proposed trade name before the NDA's action date. The Applicant has proposed two trade names, —— and Advicor, for consideration by the Division. **Discussion:** The Applicant asked if the Agency had objection to the internal use of the trade name, Advicor, based upon OPDRA's completed consult. For example, they want to use the name in early stages of a proposed promotional campaign, and to communicate the name to the stockholders. The Division advised that no promotional use of the name could be used until an approval letter is issued, and that any use of the proposed name is at the risk of the applicant because the name is tentative until an approval letter issues. It was pointed out that OPDRA would perform another name comparison within 90-days of the action date to ensure that no drug(s) with similar sounding or looking names were approved subsequent to the original consult. **Conclusion(s):** The Division advised the Applicant of the risks of formulating a promotional campaign around the proposed trade names until the action letter issues. The Division also advised the Applicant to state their preference for the name in an amendment to the NDA.	**Telecon initiated by:** Sponsor **NDA** 21-249 **Product name:** (fixed combination niacin extended release and lovastatin tablets) **Firm name:** Kos Pharmaceuticals **Names and titles of persons with whom conversation was held:** Marvin Blanford, Pharm.D.,Vice President, Compliance David Warnock, Ph.D., Director, Regulatory Affairs **Telephone #:** (305) 512-7051
{See appended electronic signature page} William C. Koch, R.Ph. Date Regulatory Project Manager	

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/s/

William Koch
4/24/01 04:05:20 PM
CSO

Enid Galliers
4/25/01 08:21:03 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: March 5, 2001 Time: 01:00 PM Location: PKLN Room #14B-45

NDA 21-249 Nicostatin (niacin timed-release and lovastatin) Tablets

Type of Meeting: Guidance Telephone Conference

External Participant: Kos Pharmaceuticals Inc.

Meeting Chair: David G. Orloff, M.D., Division Director

External Participant Lead: Ms. Valerie Ahmuty, B.S., Manager, Regulatory Affairs

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

FDA Attendees and titles:

David G. Orloff, M.D., Division Director
Mary Parks, M.D., Acting Team Leader
Anne Pariser, M.D., Clinical Reviewer
Joy Mele, M.S., Mathematical Statistician, Biometrics 2
Indra Antonipillai, Ph.D. Pharmacology Reviewer
Sharon Kelly, Ph.D. Chemistry Reviewer
Hae-Young Ahn, Ph.D.; Biopharmaceutics Team Leader
Sang Chung, Ph.D., Biopharmaceutics Reviewer
William C. Koch, R.Ph., Regulatory Project Manager

External participant Attendees (by phone) and titles:

Daniel Bell, President and Chief Executive Officer
Mark McGovern, M.D., Vice President, Medical Affairs
Eugenio Cefali, Pharm.D., Ph.D., Vice President, Clinical Development
Marvin Blanford, Pharm.D.,Vice President, Compliance
Marijke Adams, Director of Clinical Pharmacology
Rosemary Evans, M.D. Director of Clinical Research
David Warnock, Ph.D., Director, Regulatory Affairs
Phillip Simmons, M.S., Associate Director, Biostatistics
Ms. Valerie Ahmuty, B.S., Manager, Regulatory Affairs
Kim Gilchrist, M.D., M.B.A., Executive Director, Health Outcomes Research (DuPont)

Meeting Objectives:

To obtain from the Applicant clarification of some general biopharmaceutics issues.

Discussion Points:

The Division stated that the lovastatin-alone arm of study MA-98-010414 (MA-14) did not show levels of LDL lowering as would be predicted by the literature or the drug labeling for Mevacor. The data showing superiority of Nicostatin over lovastatin alone in MA-14 is not reliable in light of the inconsistent LDL-lowering efficacy observed in the lovastatin alone arm.

The results of the lovastatin-alone arm in MA-14 are, therefore, un-interpretable without a biopharmaceutics study establishing bioequivalence between the lovastatin used in the lovastatin-alone arm of the clinical trials and the lovastatin as it is formulated in Nicostatin. This study would establish that the combination (Nicostatin) is being compared to its individual component.

The biopharmaceutics reviewers also recommend that bioequivalence be established between the lovastatin used in the clinical trial with Merck's lovastatin product.

The Division cautioned the Sponsor that even if the bioequivalence studies established bioequivalence between the lovastatin arm and comparator groups (lovastatin in Nicostatin and Merck's lovastatin), this would not necessarily guarantee an approval of this application given other inconsistencies in the application which are outlined as follows:

> The Nicostatin arms of the clinical trials, where the niacin dose was held constant and the lovastatin component was doubled, produced LDL lowering which was predicted by the literature.
>
> The Division stated that lovastatin-alone patients enrolled in the MA-14 trial at center #7 had results suggesting niacin exposure (i.e. increased HDL, decreased triglycerides, and flushing).

The Applicant stated that, based upon the literature reviewed by the Applicant, the results of trial MA-14 were "within the scope" of the results that could be expected.

The Division requested that the Applicant provide an explanation for the poor response of the lovastatin-alone arm in MA-14 compared to historical data in light of the responses seen in the nico/10, nico/20 and nico/40 groups in study MA-14.

The Applicant stated that the lovastatin formulation used in the lovastatin-alone arms was linked to the innovator product by in-vitro dissolution.

> The Division responded that in-vitro dissolution would not predict in-vivo performance unless the Sponsor has established an in-vitro/in-vivo correlation. Therefore, in-vitro dissolution data would not provide the necessary link between the Applicant's clinical dosage form and the innovator lovastatin.

Decisions (agreements) reached:

The Sponsor agreed to check the records of the three patients in study MA-14 at center #7 with the unexpectedly low responses to lovastatin alone in order to address the Division's concerns regarding the validity of the data.

Unresolved or issues requiring further discussion:

The LDL response in the lovastatin-alone arm of study MA-14.

Action Items:

The Applicant will submit any data from their re-evaluation of the records of the MA-14, center #7.

{See appended electronic signature page}

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

{See appended electronic signature page}

Concurrence: _____, Meeting Chair
David G. Orloff, M.D. date
Division Director

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/s/

William Koch
4/24/01 05:32:05 PM
CSO

David Orloff
4/25/01 03:34:58 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION	DATE: February 01, 2001 Time: 1300 hrs
FDA Attendees: Mary Parks, M.D., Acting Clinical Team Leader Anne Pariser, M.D., Clinical Reviewer William C. Koch, R.Ph., Regulatory Project Manager **Objectives:** To discuss format and data of the four month safety update submitted to the NDA submitted on January 17, 2001. **Discussion:** The Division requested details of the data to be submitted from the efficacy study MA 010409 since this study was not in the original NDA submission. The Applicant stated that this study MA 010409 was considered by them as a [redacted] study. The Applicant stated that [redacted]. Only safety data from this study would be submitted to the 8-month safety update. The Division requested that all adverse events are reported in the safety updates regardless of whether or not the event is considered to be related to the study drug. The Division further requested that the incidence of flushing be included in the adverse event tables. In table #9 concerning the adverse events reported, the number of patients initiating the study in column #1 does not equal the total number of patients from which data were collected in column #4. The applicant stated that the disparity in the numbers would be reconciled. The Division requested that all clinical labs be submitted to the NDA, including labs that were abnormal at baseline and worsened during the study. **Conclusion(s):** The Applicant agreed to comply with the Division requests and submit the information to the NDA.	**Telecon initiated by:** FDA **NDA** 21-249 **Product name:** Nicostatin **Firm name:** Kos Pharmaceuticals Inc. **Name and title of person with whom conversation was held:** Valerie Ahmuty, Manager, Regulatory Affairs **Telephone #:** (305) 512-7002
{See appended electronic signature page} William C. Koch, R.Ph. Date	

/s/

Mary Parks
4/6/01 01:23:58 PM

William Koch
4/4/01 10:00:29 AM

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: October 30, 2000 Time: 1:30 PM Location: PKLN 14B45

NDA 21-249 Nicostatin (fixed combination niacin extended-release and lovastatin tablets)

Type of Meeting: NDA Filing (45-day)

Meeting Chair: David G. Orloff, M.D., Division Director

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

FDA Attendees and titles:

HFD-510

David G. Orloff, M.D., Division Director
Mary Parks, M.D., Acting Team Leader
Anne Pariser, M.D., Medical Officer
Karen Davis-Bruno, Ph.D., Pharmacology Team Leader
Indra Antonipillai, Ph.D. Pharmacology Reviewer
Stephen Moore, Ph.D. Chemistry Team Leader
Sharon Kelly, Ph.D. Chemistry Reviewer
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
Todd Sahlroot, Ph.D., Team Leader, Biometrics 2
Joy Mele, M.S., Mathematical Statistician
William C. Koch, R.Ph., Regulatory Project Manager

HFD-46 (OMP/DSI/GCPB1):

Roy Blay, Ph.D., Senior Regulatory Review Officer

Filing Discussion:

- Clinical – Fileable, issues presented by biometrics

  Financial Disclosure – information included in original submission

  Request for pediatric waiver – granted

- Pharmacology – no information submitted
- Micro - Not Needed
- Devices - Not Applicable
- Chemistry - fileable, no issues

- Biopharmaceutics – fileable, no issues
- Biostatistics – refer to "45-Day Screening of NDa's"
- DSI – sites to be decided

REGULATORY SECTION

Priority or Standard Review schedule: Standard

Clinical Audit sites (list):

To be discussed with Medical Officer

Advisory Committee Meeting: No

Consults needed:

OPDRA – trade name review

Environmental

Review Timelines/Review Goal Date (with labeling):

Consults Due:	06.05.01
Reviews Completed:	**06.25.01**
To Division Director:	07.02.01
To Office Director	07.13.01
10 month calendar due:	07.22.01

cc: Original NDA 21-249
HFD-510: WKoch
HFD-510: reviewers & attendees
HFD-46: RBlay

Drafted by: WKoch/10.27.00
filename: C:/Windows/Desktop/NDA21249/MTGfile21249.doc

MEETING MINUTES - FILING

Meeting Date: June 21, 2000 Time: 11:00 AM Location: Third Flr Conf. Room "B"

IND —— Nicostatin (niacin extended release & lovastatin)

Type of Meeting: Pre-NDA Meeting

External Participant: Kos Pharmaceuticals, Inc.

Meeting Chair: John K. Jenkins, M.D., Acting Division Director

External Participant Lead: Marvin Blanford, Pharm.D.,Vice President, Compliance

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

FDA Attendees and titles:

John K. Jenkins, M.D., Acting Division Director
David G. Orloff, M.D., Deputy Director
Shiao-Wei Shen, M.D., Medical Officer
Stephen Moore, Ph.D. Chemistry Team Leader
Sharon Kelly, Ph.D. Chemistry Reviewer
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
Joy Mele, M.S., Mathematics Statistician
Ronald W. Steigerwalt, Ph.D.; Pharmacology Team Leader
William C. Koch, R.Ph., Regulatory Project Manager

External Participant Attendees and titles:

Kos Pharmaceuticals, Inc.

Daniel Bell, President and Chief Executive Officer
Mark McGovern , M.D., Vice President, Medical Affairs
Eugenio Cefali, Pharm.D., Ph.D., Vice President, Clinical Development
Marvin Blanford, Pharm.D.,Vice President, Compliance
James Tanguay, Ph.D., Director, Analytical Chemistry
David Warnock, Ph.D., Director, Regulatory Affairs
Phillip Simmons, M.S., Associate Director, Biostatistics
Ms. Valerie Ahmuty, B.S., Manager, Regulatory Affairs

DuPont Pharmaceuticals Company

Kim A. Gilchrist, M.D., M.B.A., Executive Director, Health Outcomes Research
Marjorie H. Christie, Ph.D., Senior Director, Regulatory Affairs

Meeting Objectives:

To discuss with Kos Pharmaceuticals the planned NDA submission for their combination of niacin extended release and lovastatin.

Discussion Points: (Questions submitted by industry)

Chemistry, Manufacturing and Controls Section

1. Is our Categorical Exclusion claim from the Environmental Assessment acceptable?

2. What are the reviewer comments on the Drug Master Files for [redacted]

3. Are the proposed Regulatory Specifications acceptable and proposed commercial stability protocol acceptable?

4. Do the stability data to be included in the original NDA and subsequent amendment remain acceptable to support a proposed expiry period of 24 months?

5. Are there any other reports required for filing in addition to those proposed in the following lists?

Clinical/Statistical Section

1. By what criteria would FDA consider combination products a first-line therapy for dyslipidemias? In addition to LDL-C, will FDA consider changes in other lipoproteins (e.g., HDL-C and triglycerides) in making this determination?

2. [redacted]

3. Does the FDA have any comments on our proposal for providing and updating human safety information?

4. In the FDA fax dated May 9, 2000, the FDA statistician asked to discuss documentation for SAS data sets:
   - PROC CONTENTS output
   - Listing of about 50 observations
   - Data Dictionary

5. Kos plans to submit CRTs as domain profiles only. Do we need to obtain a waiver from the requirement to submit patient profiles?

6. What is the status of the Kos request for a waiver from the requirement to provide pediatric data?

Decisions (Agreements) reached:

Chemistry, Manufacturing and Controls Section

1. The Division's CMC team found that an exclusion claim from environmental assessment would be acceptable, and reminded the applicant to submit the single page request for Categorical Exclusion.

2. The Division's CMC team stated that the information from the Drug Master Files for the ———— were not needed to be submitted in the NDA, and that the open file DMF's for the ———— were acceptable.

3. The Division stated that both the Regulatory Specifications and the commercial stability protocol appear to be acceptable.

4. The Division considers that the stability data submitted will support a 24 month expiration date.

5. The Division stated that the proposed reports would provide adequate information for a complete review.

Nonclinical Pharmacology and Toxicology Section

- The Pharmacology/Toxicology team leader reminded the applicant that the referenced data to support the proposed pharm/tox labeling sections must be submitted, and that a summary of the pertinent literature relating to the safety of these products be provided.

- Referenced study data in support of the safety margins for the highest proposed doses must also be submitted.

Clinical/Statistical Section

1. The Division stated that since each component of the combination addresses a different aspect of the lipoprotein profile there is no dose-sparing effect of one component on the other; the combination, therefore, should be used only in patients who are optimized on the components individually. Sufficient data has not been presented to demonstrate superiority, other than convenience, of this combination as first line therapy over the individual components optimized separately. Further discussion of this issue should be deferred to the labeling meetings.

2. The Division requested that the applicant provide data to support this claim. The Division stated that this question involves a review issue which cannot be resolved at a pre-NDA meeting.

3. The Division considers the proposed plan for providing and updating human safety information acceptable. The Division reminded the applicant to enumerate duration of exposure by dose, and to send in the second safety update eight months into the review clock.

   The Division Director added that a standard review clock was anticipated for this application.

4. The Division Biometrics reviewer requested to see representative examples of the proposed documentation.

5. The Division does not require patient profiles, and will research the requirement for a waiver for submitting them.

6. The Division will not require the submission of pediatric data because this combination is

   not indicated in pediatric heterozygous Frederickson Type II hypercholesterolemia. The Request for Pediatric Waiver is still under review.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Post-Meeting Activity:

The Division CMC team discussed the content and format for the proposed NDA with the Applicant's regulatory affairs manager, and stated that the sponsor has up to this point provided useable summaries of CMC issues.

The Division asked for a table in the beginning of the CMC section of the proposed NDA containing commercial establishment information including the CFN number of the establishment and what role the establishment has in the manufacture of the marketed product. This table will be provided to the Investigations and Pre-approval Compliance Branch to assist in their inspections.

The Division asked if the applicant will continue to do in-house testing in support of the DMF's, and applicant responded in the affirmative.

The Division asked about the percentage of overage in the Drug product added to meet specifications. The applicant responded that no overage was added to the drug product.

The Division asked if there was any re-processing of drug product that did not meet final specifications. The sponsor responded that no re-processing occurred.

The Division asked that the DMF authorization letters submitted include the establishment's CFN number, the date of the last establishment evaluation inspection, and the page number(s) in the DMF where the drug component is referenced.

OWNERS NOT RESPONDING

Regarding the organization of the CMC submission the Division requested that proposed Section II, sub-sections E.2.e through E.2.i be moved between headings "G" and "H".

F

To heading "H" the Division requested a table of Data Analysis, and a summary of statistical analysis.

The Division reminded the applicant that although there is no labeling section of the CMC section a desk copy of the draft labeling should be sent to the CMC reviewer.

Prepared by: WCK _____ 07/27/00, Meeting Recorder
William C. Koch, R.Ph. date
Regulatory Project Manager

Concurrence: _____ 7-27-00, Meeting Chair
John K. Jenkins, M.D., date
Acting Division Director

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT:

Table of Contents for CMC Section
Kos Pharmaceuticals, Inc. "Summary of Pre-NDA Meeting"

cc: HFD-510 Lipid Altering Agents (original) & background & Attachments
HFD-510/Div. Files
HFD-510/Meeting Minutes files
HFD-510/CSO
HFD-510/reviewers & attendees

Drafted by: WKoch/06.13.00
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JMele07.21.00/SShen07.21.00/Dorloff07.27.00
final: WKoch/07.27.00
filename: C:/Windows/desktop/IND ——MTGmin062100.doc

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: November 15, 2001

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

TO: NDA 21-249
Advicor (niacin extended release and lovastatin) tablets
Kos Pharmaceuticals, Inc.

SUBJECT: NDA review issues and recommended action, after review of response to AE letter dated July 20, 2001

Background
An "approvable" letter was issued to this NDA on July 20, 2001, citing deficiencies noted in a recent inspection of manufacturing facilities. The sponsor submitted a complete response to the action letter on September 12, 2001.

Labeling
The medical officer has reviewed the minor changes to the label submitted with the September 12, 2001, submission. All changes were acceptable to her and, where relevant, to the CMC reviewer.

Chemistry/ Microbiology
The establishment inspection was acceptable for the finished dose manufacturing site cited in the original withhold recommendation from Compliance. The applicant has adequately responded to the FDA Form 483 issues.

Recommendation
This application may be approved.

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/

David Orloff
11/15/01 09:38:17 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: November 15, 2001

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

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Recommendation
This application may be approved.

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

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

DATE: July 17, 2001

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

TO: NDA 21-249
Advicor (niacin extended release and lovastatin) tablets
Kos Pharmaceuticals, Inc.

SUBJECT: NDA review issues and recommended action

Background

Advicor is a combination drug product containing Niaspan (sustained-release niacin) and lovastatin developed by Kos Pharmaceuticals, Inc., the manufacturer of Niaspan. Originally conceived by the sponsor as a first-line lipid-altering drug, this issue has been a central focus of discussions between the division and Kos dating to 1998. Specifically, the Division has held that, while there may well be a rationale for combination lovastatin-niacin therapy in patients with mixed lipid abnormalities (elevated LDL-C, TG, and low HDL-C, in particular), a combination drug product would be a convenience product for patients titrated to optimum effect on each drug individually. In notes made by me after a telephone conference with the sponsor on 2-22-98, the following points were recorded that are germane to the consideration of this NDA:

1. Niacin is a unique drug in that low doses, relatively ineffective in lipid altering, must nevertheless be used temporarily in all patients for the purposes of titration only, in order to permit tolerance of higher, optimally effective, lipid altering doses.
2. In general, because of adverse events in common as well as possible drug interactions, patients destined to be treated with combination therapy consisting of a statin and a nicotinic acid product are started on one drug at a time. Analogous to the case for combination anti-hypertensive therapies, only when lipid abnormalities are unresponsive to monotherapy is the second drug added and titrated to tolerance and desired effect.
3. In contrast to the case for anti-hypertensive combination therapy, where multiple drugs, even if acting through independent mechanisms, all simply lower BP, lipid altering combination therapy is undertaken with the goal of addressing different aspects of the lipoprotein profile, which though metabolically interrelated, may indeed have independent impact on the progression of atherosclerosis and therefore on CHD risk. Thus, the combination of statins and niacin effects reductions in LDL-C (statin effect predominates), TG-rich lipoproteins and Lp(a) (niacin effect) and increases in HDL-C (niacin effect). Likewise, combination statins plus fibrates are tailored to obtain LDL-C lowering with the statin and favorable changes in TG-rich lipoproteins and HDL-C as well as lipoprotein subclass profile with the fibrate. As an aside, it should be noted that the exception in this area is the combination of low-dose

statins and resins, which share a final pathway of effect to increase LDL-R expression and clearance of LDL-C.

4. Statins and niacin both have dose-dependent side effects occurring within the therapeutic dosing range. To the extent, however, that niacin is used at the highest tolerated dose in most instances, combination therapy does not spare niacin exposure.
5. Because of the great variability in lipoprotein profiles in patients requiring combination therapy, individual components of the regimen are titrated independently to treatment targets. As stated in 3, above, statins and niacin are utilized for independent lipid altering effects, even as their combined use is rationalized based on epidemiological as well as clinical trial evidence (limited to lipid altering data).
6. The above points lead to several issues impacting on the clinical evaluation, approvability, and labeling of a statin-niacin combination product.

    a. It is difficult to consider a statin-niacin combination product as a single drug, as combination therapy does not spare dose or dose-related side effects, and indeed may increase the risk of side effects as liver and muscle toxicity.
    b. Because low-dose niacin (<1000 mg/day of either ER or IR products) is not an effective LDL-C lowering drug, its use is only for the purposes of titration. Therefore, marketing a more expensive combination product containing a low dose of nicotinic acid, for use only because niacin must be titrated to tolerance, seems inappropriate.
    c. The scope of the pre-marketing clinical exposure to a combination of this type is unlikely to permit detection of rare adverse events, such as rhabdomyolysis, even if the risk is greatly increased relative to either individual monotherapy. Therefore, the warning in labeling regarding the increased risk of rhabdomyolysis with the combination will need to remain as it is in current statin labeling.
    d. Combination niacin/statin should not be labeled as first-line therapy for dyslipidemia. Even in patients in whom the physician fully expects to use both drugs, the drugs should be titrated independently. Thereafter, the combination product may serve as a convenience. The overlapping and synergistic toxicities of these two drugs mandate that they not be initiated simultaneously. Furthermore, lipid-altering drugs are rarely, if ever, indicated emergently so there is no advantage in that regard to simultaneous initiation of therapy with statin and niacin.

Medical

Efficacy

The pivotal clinical trials for this NDA were designed to establish the superiority of Advicor over Niaspan and lovastatin for LDL-C lowering. As discussed in the reviews by Drs. Parks and Pariser and by Ms. Mele, the validity of the cross-treatment comparison in study MA-14 is called to question because of the relatively flat dose-response in the lovastatin-alone arm of that trial. As such, the data were not considered in the assessment of efficacy of Advicor.

Study MA-06 permitted comparison between the proposed-for-marketing dosage strengths of Advicor (and multiples thereof) and the corresponding doses of the individual drugs. These data form the basis for labeling.

As the table on page 4 of Dr. Parks' review makes clear, for LDL-C lowering from baseline, only the 2000/40 (Niaspan/lovastatin) dose of Advicor was associated with a statistically significantly superior LDL-C lowering compared to Lovastatin alone. As Dr. Parks points out, the highest approved dose of lovastatin, 80 mg, was not studied, and it is conceivable that this dose would have been equivalent or superior to 2000/40 of Advicor for LDL-lowering. To the extent that combined niacin and lovastatin is associated with its own risks (i.e., a reported increased risk for rhabdomyolysis) and to the extent that neither is dose-sparing or clearly toxicity-sparing of the other), there is no rationale for combining the two products as an LDL-C lowering agent.

On the other hand, there is a rationale for using the drugs in combination, on the one hand to effect TG lowering, HDL-raising, and Lp(a) lowering in patients treated with lovastatin with persistent lipid abnormalities other than elevated LDL-C. On the other hand, lovastatin can be used in patients treated with niacin to target TG, HDL, and Lp(a) abnormalities but with an inadequate LDL-C response. As such, Dr. Pariser and Ms. Mele have analyzed the HDL and TG responses of Advicor vs. the individual components and this has served as the basis for labeling and approval. These data are summarized in the table beginning on page 8 of Dr. Parks' review.

In short, as summarized by Dr. Parks, the HDL-C raising effects of Advicor were statistically superior to those of corresponding doses of either lovastatin or Niaspan at all of the doses studied. The TG-lowering effects of Advicor were statistically superior to those of corresponding doses of Niaspan at doses of 750/20 and greater and to those of corresponding doses of lovastatin at doses of 1000/20 or greater.

Thus, the study results describe the expected lipid effects of Advicor and provide rationale for combination therapy as stated in the indications, to effect greater LDL-C lowering in patients on Niaspan and to effect TG lowering and HDL-raising in patients on lovastatin.

As an aside, the guidance with regard to lipid altering treatment as put forward by NCEP are contained in the final label with a specific statement that, if after LDL-C goals have been reached (as with a statin), TG remains elevated, this becomes a secondary target of therapy (as with niacin or a fibrate). This, in effect, establishes part of the rationale for use of these products in combination.

Finally, as above, the final labeling for this product stresses that it is not for initial lipid altering therapy.

Safety

As stated in the Background section, there was never any expectation that the Advicor clinical trial experience would refute previous observations of an increased risk of myopathy and rhabdomyolysis with combination lovastatin and niacin. These are known, rare side effects of the statin class. In fact, a single case of myopathy (marked elevated CK) was observed in the clinical trials of Advicor with exposures out to 76 weeks. The warning of the risks of combined niacin and lovastatin use as expressed in the lovastatin label is contained in the final proposed Advicor label.

Also known side effects of both drugs, there was a small (1-2%) incidence of transaminase elevations to > 3 X ULN in Advicor-treated patients. There were no cases of severe liver disease, and labeling reflects the need to monitor patients in this regard and to follow up any elevations noted.

Otherwise, the adverse effects observed were attributable to Niaspan as known side effects of all niacin products, including flushing and mild increases in plasma glucose.

Labeling
Final proposed labeling as discussed above has been conveyed by the sponsor, and the Division has accepted it.

Biopharmaceutics
OCPB finds the data submitted acceptable. In effect, there are no significant pharmacokinetic interactions between lovastatin and Niaspan. There was a food effect to increase the systemic exposure to both drugs.

Pharmacology/Toxicology
There were no new preclinical data submitted to this NDA. There are no new pharm-tox issues for this combination drug of two marketed drugs.

Chemistry/ Microbiology
The ONDC reviewer deemed the CMC information adequate to assure the quality of the drug product. A categorical exclusion from the requirement for an environmental assessment was requested and granted.

Currently, the Office of Compliance has not completed the facilities inspection report. The initial report from the inspection of the finished dosage manufacturer (Kos Pharmaceuticals, Edison, NJ) contained a "withhold" recommendation. In addition, the inspection of ——— ———————————) is pending as of the date of this memorandum.

DSI/Data Integrity
DSI audited three clinical sites and found the data submitted from the investigators at those sites to be acceptable. There are therefore no issues related to data integrity raised by these inspections.

Financial disclosure
The financial disclosure information has been reviewed by Dr. Pariser and she finds no reason to question the integrity of the application on this basis.

OPDRA/nomenclature
The name Advicor is acceptable to OPDRA.

Recommendation
This application may be approved pending a satisfactory facilities inspection report from compliance. Currently, the patent protection for lovastatin (Mevacor, Merck) does not expire

until December 15, 2001, so that any approval prior to that date is tentative under 21 CFR 314.105.

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/s/

David Orloff
7/18/01 08:58:14 PM
MEDICAL OFFICER

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Welcome to the Pediatric Page Printed Page. To produce your pediatric page, simply print this page (this paragraph will not print). However, most versions of Internet Explorer will print a header on each page (i.e., the name of the web site, etc.) To eliminate these when printing the Pediatric Page, go to 'File', then 'Page Setup', and clear the 'Header' and 'Footer' Boxes. (Cut and paste to a document [or write down] the contents of these boxes first if you want to restore the headers and footers afterwards.)

PEDIATRIC PAGE

NDA Number:	021249	**Trade Name:**	ADVICOR (NIACIN ER/LOVASTATIN)
Supplement Number:	000	**Generic Name:**	NIACIN ER/LOVASTATIN
Stamp date:	9/22/00	**Action Date:**	7/20/01
Supplement Type:	N		
COMIS Indication:	ANTIDYSLIPIDEMIC AGENT		

Indication #1: Primary hypercholesterolemia and mixed dyslipidemia - Date Entered: 12/17/01

Status: A full waiver was granted for this Indication.

Reason for This Waiver: There are safety concerns

This page was printed on 12/17/01

Signature

12/17/01

Date

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ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21249/000**
Priority: **4S**
Org Code: **510**
Stamp: **22-SEP-2000** Regulatory Due: **22-JUL-2001**
Action Goal:
District Goal: **23-MAY-2001**
Applicant: **KOS PHARMS**
801 BRICKELL AVE STE 1006
MIAMI, FL 33131
Brand Name: **ADVICOR (NIACIN ER/LOVASTATIN)**
Established Name:
Generic Name: **NIACIN ER/LOVASTATIN**
Dosage Form: **EXT (EXTENDED-RELEASE TABLET)**
Strength: **500/20, 750/20, 1000/20**

FDA Contacts: **S. KELLY** **(HFD-510)** **301-827-6394 , Review Chemist**
S. MOORE **(HFD-510)** **301-827-6430 , Team Leader**

Overall Recommendation:

WITHHOLD on 19-JUL-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CFN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **16-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: [redacted]

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **1054801**
KOS PHARMACEUTICALS INC
2 OAKWOOD BLVD
HOLLYWOOD, FL 33020

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

Establishment: **2248571**
KOS PHARMACEUTICALS INC
18 MAYFIELD AVE CAMPUS 9 RARIT
EDISON, NJ 08818

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-JUL-2001**
Decision: **WITHHOLD**
Reason: **BASED ON FILE REVIEW**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

[redacted] AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-MAY-2001**
Decision: **ACCEPTABLE**
Reason:

Establishment: [redacted] DMF No:
[redacted] AADA No:

Profile: **TTR** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted] DMF No:
[redacted] AADA No:

Profile: **TTR** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted] DMF No:
[redacted] AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Exclusivity Checklist

NDA: 21-249				
Trade Name: Advicor				
Generic Name: fixed combination niacin extended release and lovastatin tablets				
Applicant Name: Kos Pharmaceuticals, Inc				
Division: HFD-510				
Project Manager: William C. Koch, R.Ph.				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	X	No	
b. Is it an effectiveness supplement?	Yes		No	X
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	X	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	X	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	THREE			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				

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ON ORIGINAL

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product. N/A	~~Yes~~		~~No~~	~~X~~
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes	X	No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes	X	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product	Niaspan			
NDA #	20-381			
Drug Product	Mevacor			
NDA #	19-643			
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	X	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	X	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes	X	No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	X
If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	X
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #:	MA-98-010406			
Investigation #2, Study #:				
Investigation #3, Study #:				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	X
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	X
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):				
Investigation #1	MA-98-010406			
Investigation #2				
Investigation #3				
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.				
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?				
Investigation #1	Yes	X	No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?				
Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

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

{See appended electronic signature page}

Signature of PM — Date:

{See appended electronic signature page}

Signature of Division or Office Director — Date:

cc:
Original NDA
HFD-510/Division File
HFD-93/Mary Ann Holovac
HFD-104/TCrescenzi

APPEARS THIS WAY
ON ORIGINAL