Kos Pharmaceuticals, Inc.

Research Office:
14875 Northwest 77th Avenue
Suite 100
Miami Lakes, Florida 33014
Tel (305) 512-7000
Fax (305) 512-0337

Corporate Office:
1001 Brickell Bay Drive
25th Floor
Miami, Florida 33131
Tel (305) 577-3464
Fax (305) 577-4596

February 14, 2001

David Orloff, MD
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Nicostatin™ NDA 21-249
Submission of Updated Stability Data as Previously Agreed

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Nicostatin™, an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin.

As previously agreed with FDA, Kos Pharmaceuticals is submitting updated stability data for lots manufactured at our — proposed commercial manufacturing sites. Data are provided for tablets manufactured at the ———— sites for up to 12 months and 18 months of stability monitoring, respectively. Data are for three lots of each strength of the proposed commercial tablet strengths (mg niacin/mg lovastatin: 500/20, 750/20, and 1000/20), manufactured at each proposed ——— manufacturing site. All lots were full-scale and packaged in the proposed commercial packaging configurations ———— that will be used commercially.

A CD containing the electronic document (Word file) is provided as a reviewer aid in the archival copy (blue jacket). Paper copies of the cover letter, 356h form, and stability report are provided in the Chemistry, Manufacturing and Controls copy (red jacket) as well as the archival copy. Kos certifies that a true (paper) copy of the cover letter, 356h form, and stability report have been sent to the FDA district office overseeing the Kos Edison, NJ manufacturing site (burgundy folder).

If there are any questions regarding this submission or if additional information is required, please contact me at 305-512-7051. Thank you.

Sincerely,

David H. Warnock

David H. Warnock, PhD
Director, Regulatory Affairs

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February 14, 2001

Regina Brown, Pre-Approval Program Manager
Food and Drug Administration
North Brunswick Resident Post
120 North Center Drive
North Brunswick, NJ 08902

COPY

RE: True Copy of CMC Amendment to NDA 21-249 (Stability Report)
Nicostatin™ (niacin extended-release and lovastatin tablets)

Please find enclosed the district (field) true copy of an amendment to the Chemistry, Manufacturing and Controls (CMC) section of Kos Pharmaceuticals, Inc.'s Nicostatin™, NDA 21-249. Nicostatin is a fixed-combination product containing extended-release niacin and immediate-release lovastatin for use in patients with dyslipidemia. The North Brunswick FDA office has oversight of Kos' manufacturing site located at 18 Mayfield Avenue, Edison, NJ. The Edison facility is the primary proposed commercial manufacturing site for Nicostatin. The amendment provided is the updated stability data for the proposed primary ——————— manufacturing sites.

Nicostatin is the proprietary working name of the product that is used throughout this submission. Another name will be used for commercialization of the product. The proposed commercial tradename and an alternative name were submitted to FDA on December 05, 2000. These tradenames are currently under review by FDA; therefore, the working tradename will continue to be used until a determination is made.

The CMC section of NDA 21-249 is a paper document assisted by MS Word documents; the other parts of the NDA are electronic. This true field copy is paper only and consists of the cover letter, 356h form, the stability report, and the certification required to be provided in the FDA field copy.

Please direct any written communications regarding this NDA to me at the Miami Lakes address given above. Should you have any questions during the review of this submission, please contact me by telephone at 305-512-7051. CMC questions may also be directed to Valerie Ahmuty, Manager of Regulatory Affairs, at 305-512-7002. For inspection purposes, the contact person at Kos' Edison facility is Barbara Falco, Director of Quality Assurance. Ms. Falco can be reached at 732-225-2930. Thank you.

Sincerely,

David H. Warnock

David H. Warnock, PhD
Director of Regulatory Affairs

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ORIGINAL

January 31, 2001

David Orloff, MD
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP

Re: Nicostatin™ NDA 21-249
Submission of Additional Case Report Forms

Dear Dr. Orloff:

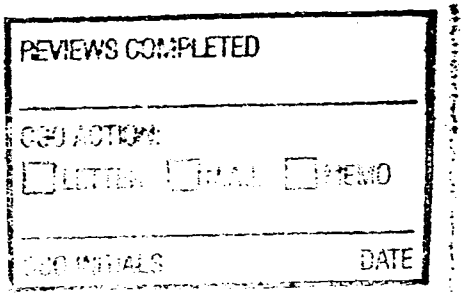
Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Nicostatin™, an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin.

On January 26, 2001, Mr. William Koch, FDA Project Manager, called to request a copy of the Case Report Forms (CRFs) for patients in the lovastatin arm of Study MA-98-010414. The study was a controlled, double-blind study comparing the dose response of the combination product to the same dose for each of the single active agents. The CRFs are provided electronically on the enclosed CD. A table of contents listing the electronic document name of each CFR is provided both electronically and on paper. The CD is provided in the archival copy (blue jacket). Paper copies of the cover letter, 356h form, and table of contents are provided in the clinical copy (manila jacket) and Project Manager's desk copy (black jacket).

If there are any questions regarding this submission or if additional information is required, please contact me at 305-512-7051. Thank you.

Sincerely,

David H. Warnock, PhD
Director, Regulatory Affairs



Dated 15 Feb 2001

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ORIGINAL

NEW CORRESP

CENTER FOR DRUG
RECD
JAN 24 2001
HFD-510
EVALUATION AND RESEARCH

January 23, 2001

Ms. Sammie Beam
Senior Project Manager
Room 15B08
Office of Post Marketing Drug Risk Assessment, HFD 400
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Nicostatin™ NDA 21-249
Proposed New Tradename; ———

Dear Ms. Beam:

Please refer to NDA 21-249 and the submission dated December 05, 2001 regarding a proposed new tradename for Nicostatin™. Please also refer to the telephone conversation between you and me on January 19, 2001 during which you requested a copy of the ——— survey to support the proposed tradename. In accordance with your request, enclosed is a copy of the ——— report.

If there are any questions regarding this submission, please contact me at 305-512-7051.

Sincerely,

David H. Warnock, PhD
Director, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

cc: Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Kos Pharmaceuticals, Inc.
Research Office:
14875 Northwest 77th Avenue
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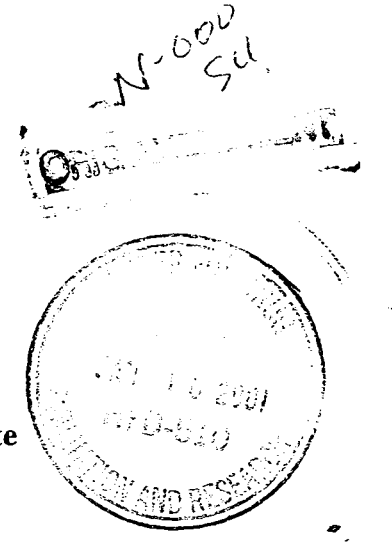
Original

January 17, 2001

David Orloff, MD
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Re: Nicostatin™ NDA 21-249
Submission of 4-Month Safety Update

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Nicostatin™, an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin. In our original application, we indicated our intent to replace the working tradename "Nicostatin" with a different tradename for commercial use. The proposed tradename was submitted to your office on December 05, 2001. However, until the proposed tradename is accepted, correspondence will continue to use the working tradename Nicostatin.

Please find enclosed the required 4-month safety update to NDA 21-249. This safety update is an electronic submission. In addition to the electronic copy, two paper review copies of the safety update report text are provided (manila folder for the clinical reviewer and a black folder desk copy for the Regulatory Project Manager). Case report forms and case report tabulations are provided only in electronic files. The guidance for electronic NDAs has been followed as much as possible. A revised index for the NDA that is hypertext linked to all sections of the original NDA as well as the 4-month safety update is also provided. This should allow an overwrite of the original NDA index (ndatoc.pdf) in your system.

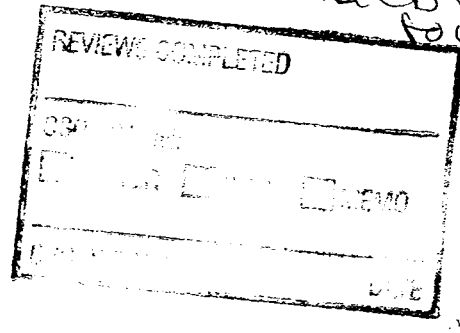
If there are any questions regarding this submission or if additional information is required, please contact me at 305-512-7051. Thank you.

151
31-Jan 2001
Send CD to EDR
to update file

Sincerely,

David H Warnock

David H. Warnock, PhD
Director, Regulatory Affairs



Kos Pharmaceuticals, Inc.
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December 05, 2000

ORIGINAL

David Orloff, MD
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Nicostatin™ NDA 21-249
Submission of Proposed New Tradename; ———

NEW CORRESP

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Nicostatin™, an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin. In our original application, we indicated our intent to replace the working tradename "Nicostatin" with a different tradename for commercial use.

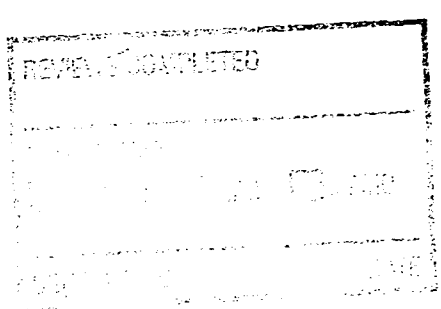
Kos has selected ——— as the preferred tradename for our combination niacin and lovastatin product. In the event that FDA finds " ——— " objectionable in some regard, Kos proposes "Advicor™" as the alternative tradename. Kos engaged the services of ———— ——., an independent agency, in the selection process to establish the acceptability of the proposed tradename(s). We believe that FDA will find our new tradename acceptable, and look forward to your review and concurrence.

If there are any questions regarding this submission or if additional information is required, please contact me at 305-512-7051. Thank you.

Sincerely,

David H. Warnock

David H. Warnock, PhD
Director, Regulatory Affairs



Kos Pharmaceuticals, Inc.
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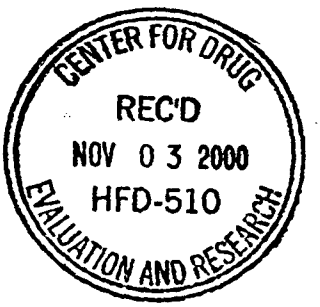
ORIGINAL

November 02, 2000

David Orloff, MD
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: Correspondence to Nicostatin™ NDA 21-249

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Nicostatin™, an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin.

It is our understanding that the NDA has been determined fileable and is currently under active review. Roy Blay, PhD, of the Division of Scientific Investigations, requested the attached information on November 01, 2000, to use in the selection of clinical sites from our pivotal studies for audit. The information was provided to Dr. Blay on November 01 by fax. Dr. Blay suggested that we send the review division a copy of the correspondence for the NDA file. There is no new information in the materials provided to Dr. Blay. Many of the pages are taken directly from the clinical reports submitted to the NDA.

If there are any questions regarding this submission or if additional information is required, please contact either Valerie Ahmuty, Manager of Regulatory Affairs, or myself at 305-512-7000. Thank you.

Sincerely,

David H Warnock

David H. Warnock, PhD
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

KOS Pharmaceuticals, Inc.
Laboratory:
Two Oakwood Boulevard
Suite 140
Hollywood, Florida 33020
Phone (954) 920-7200
Fax (954) 920-7272

Corporate Office:
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Miami, Florida 33131
Phone (305) 577-3464
Fax (305) 577-4596

ORIGINAL

October 09, 2000

P10

David Orloff, MD
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Request for Pediatric Waiver for Nicostatin™ NDA 21-249 under §314.55

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Nicostatin™, an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin. We have received the acknowledgement letter from FDA dated September 29, 2000. This letter noted the requirement to either submit plans for pediatric drug development or to request a waiver with supporting information and documentation in accordance with the provisions of 21 CFR §314.55 within 60 days from the date of the letter.

On March 21, 2000, we had been advised by FDA to submit a request for a Pediatric Waiver under §314.55 to our Nicostatin™ IND ——— as an amendment. The request for waiver was submitted to the IND as serial number 054, dated March 28, 2000. However, we did not make reference to this specific IND submission in the NDA cover letter or in other sections of the NDA. The waiver request is provided to NDA 21-249 with this letter. We look forward to your review and approval of our request for a Pediatric Waiver.

If there are any questions regarding this submission or if additional information is required, please contact either Valerie Ahmuty, Manager of Regulatory Affairs, or myself at 305-512-7000. Thank you.

Sincerely,

David H. Warnock, PhD
Director, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

NDA 21-249

SEP 29 2000

Kos Pharmaceuticals, Inc.
Attention: David H. Warnock, Ph.D.
Director, Regulatory Affairs
14875 NW 77th Avenue, Siute 100
Miami Lakes, FL 33014

Dear Dr. Warnock:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Nicostatin (niacin extended-release/lovastatin) Tablets, 500/20, 750/20, and 1000/20 mg
Review Priority Classification:	Standard (S)
Date of Application:	September 21, 2000
Date of Receipt:	September 22, 2000
Our Reference Number:	NDA 21-249

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 21, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 22, 2001, and the secondary user fee goal date will be September 22, 2001.

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 approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver 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 make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. 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) 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 review your pediatric drug development plan and notify you of its adequacy. 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 NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA 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, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

/S/

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

cc:
Archival NDA 21-249
HFD-510/Div. Files
HFD-510/W.Koch
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: ddk/September 27, 2000
Initialed by: Galliers 9.27.00
final: ddk/September 29, 2000
filename: 21249AC.DOC

ACKNOWLEDGEMENT (AC)

Kos Pharmaceuticals, Inc.
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Fax (305) 577-4596

September 21, 2000

Food and Drug Administration
Central Document Room Staff
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

RE: Submission of Original New Drug Application for Nicostatin™ (niacin extended-release and lovastatin tablets) for the Treatment of Dyslipidemia

Pre-assigned NDA #: 21-249

Dear Administrator:

Kos Pharmaceuticals is submitting this original 505(b)(2) New Drug Application (NDA) for Nicostatin™, a fixed-combination product containing extended-release niacin and immediate-release lovastatin, for use in patients with dyslipidemia. The NDA number 21-249 was previously assigned. Nicostatin is the proprietary working name of the product that is used throughout this submission. Another name will be selected prior to commercialization.

The archival copy of NDA 21-249 for Nicostatin is a fully electronic NDA with the exception of the Chemistry, Manufacturing, and Controls (CMC) section. The electronic archival submission was prepared by ———————————, or by Kos Pharmaceuticals under the guidance of —. The electronic files consist of Adobe Acrobat PDF files that are read with version 4.0 and higher of the Acrobat Reader, SAS data sets that are included as SAS transport files, Excel 97 files, and MS Word 97 files. The CMC section is a paper document assisted by MS Word documents.

Electronic files are provided on a total of 8 CDs. There are 3 CDs provided in the archival copy and 5 CDs with files for the technical reviewers (1 CD per discipline). Each technical review copy contains a CD with an MS Word 97 copy of the labeling, an MS Word copy of the Summary, and any other electronic Review Aids that are required or that were requested. The electronic submission is approximately 1.4 gigabytes in size. Paper copies of the non-CMC technical sections have been prepared in accordance with the FDA IT-2 and IT-3 guidances, *Providing Regulatory Submissions in Electronic Format - General Considerations, Providing Regulatory Submissions in Electronic Format - NDAs*, and the Electronic Document Room *Conformance Review Checklist for NDAs* (all January 1999). The staff of the Metabolism and Endocrine Drug Products Division was also consulted in the preparation of this NDA. Pre-agreements with the reviewing disciplines have been noted in the sections requested, including the NDA Summary, as appropriate.

The electronic submission is virus-free. The software used to ensure the electronic files are virus-free is ———— for Windows 95 by ———————————. The version

currently used is 4.53, build # 524. Updates are provided monthly. The ——— virus protection program is certified by the National Computer Security Association.

The NDA consists of 9 archival volumes in blue folders (8 paper volumes and 1 volume containing the electronic NDA). The archival copy contains all the information (electronic and paper) required for the NDA. As noted above, the archival copy of the NDA is fully electronic except for the CMC section.

The technical review sections are provided in the colored folders specified by FDA. The option has been taken to provide three copies of the Methods Validation section in the CMC technical review copy (red folders) and one copy in the archival copy (blue folders). The Biopharmaceutics reviewer has also been provided with reference copies of the Methods Validation and Stability Sections of the NDA as requested by the FDA Project Manager, Mr. William Koch (i.e., information related to dissolution). Additionally, copies of certain Niaspan study reports (NDA 20-381) have been provided as Biopharmaceutics Review Aids. All are provided in orange folders and are labeled with appropriate reference information (e.g., study number, NDA 20-381 volume number, etc).

This submission contains a certification, that concurrently with the submission of this NDA, true copies of the cover letter, Form 356h, NDA Summary and CMC sections (in burgundy folders), were sent to the local district office overseeing the Edison, NJ manufacturing facilities. The documents sent to the district office include a copy of the signed 356h form and a certification that the contents are a true copy of those provided in the NDA.

This submission also contains the certification that we, the applicant, have not and will not use in any capacity, the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)] of the Food, Drug and Cosmetic Act in connection with this NDA.

The User Fee check for the NDA was sent to Mellon Bank, Pittsburgh, PA on September 08, 2000, and receipt was confirmed as of September 11, 2000.

Please direct any written communications regarding this NDA to me at the Miami Lakes address given above. Should you have any questions during the review of this submission, please contact me by telephone at 305-512-7051. CMC questions may be directed to Valerie Ahmuty, Manager of Regulatory Affairs at 305-512-7002. Thank you.

Sincerely,

David H Warnock

David H. Warnock, PhD
Director of Regulatory Affairs

Kos Pharmaceuticals, Inc.
Research Office
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Miami Lakes, Florida 33014
Tel (305) 512-7000
Fax (305) 512-0337

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Miami, Florida 33131
Tel (305) 577 3464
Fax (305) 577 4596

March 28, 2000

John Jenkins, MD
Acting Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Nicostatin™ IND ——, Submission Serial #054

Request for Pediatric Waiver for Future Nicostatin NDA under §314.55(c)

Dear Dr. Jenkins:

Please refer to our Investigational New Drug Application (IND) Number —— for Nicostatin™ (niacin extended-release and lovastatin), an antidyslipidemic combination drug product for reducing total (TC) and low density lipoprotein serum cholesterol levels (LDL-C), reducing triglycerides (TG), and increasing high density lipoprotein cholesterol (HDL-C). The Phase 3 studies are either completed or nearing completion for this product, and we anticipate submission of the Nicostatin NDA in September 2000. NDA number 21-249 has been pre-assigned.

Mr. William Koch, Project Manager in your division, advised us by telecommunication on March 21, 2000, that a request for a Pediatric Waiver under §314.55(c) should be submitted to the IND as an amendment. This submission presents our request and justification for a Pediatric Waiver for Nicostatin.

If there are any questions regarding this submission or if additional information is required, please contact either Valerie Ahmuty, Manager of Regulatory Affairs, or myself at 305-512-7000. Thank you.

Sincerely,

David H. Warnock, PhD
Director, Regulatory Affairs

Request for Pediatric Waiver

Kos Pharmaceuticals, Inc. requests a full waiver of the requirements of paragraph (a) of § 314.55 for a pediatric-use assessment.

As directed under paragraph (c), Kos certifies that:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are highly impractical because the number of such patients is so small and geographically dispersed.

Justification

The Nicostatin product is a combination of two already marketed drug substances, niacin and lovastatin. The niacin component of Nicostatin is identical in formulation to Niaspan®, our commercially available extended-release product. In a letter dated October 28, 1999, approving NDA 20-381 Supplement S-006 (indication for Niaspan to increase HDL cholesterol), FDA waived the requirement for pediatric studies of Niaspan based on their assessment of the risks and benefits of pediatric use of this drug for the approved indications. (A copy of the letter is attached for reference.) It is our belief that the same risks and benefits of pediatric use apply to the combination product, Nicostatin.

Kos Pharmaceuticals, Inc.

14875 NW 77th Avenue, Suite 100
Miami Lakes, FL 33014
(305) 512-7000
Fax: (305) 512-0337

FAX TRANSMISSION COVER SHEET

Date: *June 28, 2000*

To: *Mr. William Koch and FDA Review Team for Nicostatin™ NDA 21-249*

Fax: *301-443-9282*

Re: *Bullet Point Summary of Pre-NDA Meeting Held on June 21, 2000*

Sender: *Valerie Ahmuty*

THIS FAX CONSISTS OF 6 PAGES, INCLUDING THIS COVER SHEET.
PLEASE CALL (305) 512-7002 IF THIS TRANSMISSION IS IMPROPERLY RECEIVED.

Dear Mr. Koch:

Enclosed please find the bullet points that summarize the general content and agreements reached during the Nicostatin™ pre-NDA meeting held June 21, 2000. The meeting was very helpful to us, and we at Kos appreciate your efforts and those of the review team on our behalf.

Please let me know as soon as possible if any point outlined in the enclosed summary requires further clarification. Thank you again for your help in this and all other matters.

Sincerely,

Valerie Ahmuty

Valerie Ahmuty
Manager, Regulatory Affairs

Summary of Pre-NDA Meeting Agreements

Type of Meeting:	Pre-NDA submission
Product:	Nicostatin™ IND —— , NDA 21-249 (pre-assigned)
Date and Time of Meeting:	Wednesday, June 21, 2000, approximately 11AM to 12:30 PM
Location:	3rd Floor Conference Room B, 5600 Fishers Lane, Rockville, MD
FDA Participants and Titles: (Alphabetical)	Hae-Young Ahn, PhD, Biopharmaceutics Team Leader John Jenkins, MD, Acting Division Director Sharon Kelly, PhD, Chemistry Reviewer William Koch, RPh, Regulatory Project Manager Joy Mele, MS, Mathematics Statistician Stephen Moore, PhD, Chemistry Team Leader David Orloff, MD, Deputy Division Director Ronald Steigerwalt, PhD, Pharmacology Team Leader Shiao-Wei Shen, MD, Medical Officer
Kos Participants and Titles: (Alphabetical)	Valerie Ahmuty, Manager of Regulatory Affairs Daniel Bell, President and CEO Marvin Blanford, PharmD, Vice President of Compliance Eugenio (Gene) Cefali, PhD, PharmD, Vice President of Clinical Development Mark McGovern, MD, Vice President of Medical Affairs Phillip Simmons, MS, Associate Director of Biostatistics James Tanguay, PhD, Director of Analytical Chemistry David Warnock, PhD, Director of Regulatory Affairs
DuPont Attendees and Titles: (Alphabetical)	Marjorie Christie, PhD, Senior Director of Regulatory Affairs Kim Gilchrist, MD, MBA, Executive Director of Health Outcomes Research

Summary of Agreements
Nicostatin Pre-NDA Meeting Held June 21, 2000

Meeting Objectives:

Kos requested a pre-NDA submission meeting as provided for in 21 CFR § 312.47. Specific objectives are listed below.

- To uncover any unresolved issues not previously addressed
- To discuss the best approach to the presentation and formatting of data in the NDA
- To assure our plans for an electronic submission will appropriately address the Division's review needs

References:
IND ——— serial # 058 dated April 06, 2000 - Request for Pre-NDA Meeting
Serial # 062 dated April 28, 2000 - Pre-NDA Meeting Agenda and List of Questions
Fax from FDA dated May 09,2000 - response to questions in April 28 submission
Fax from Kos dated May 10, 2000 - request for clarification on May 09 FDA responses
Fax from Kos dated May 10, 2000 - content and format questions for the CMC section
Fax from FDA dated May 23, 2000 - response to CMC questions in May 10 fax
Serial # 064 dated June 05, 2000 - Pre-NDA Meeting Briefing Package
Fax dated June 19, 2000 - Revised Meeting Agenda
Slide Package dated June 21, 2000

Discussion Points and Agreements (by Review Discipline):

Chemistry, Manufacturing and Controls (CMC) Section

1. Submission of the CMC section as paper for archival and technical review copies is acceptable, supplemented by Microsoft® Word files for all text and reports.

2. A claim for a Categorical Exclusion from the Environmental Assessment will be included in the forthcoming NDA.

3. There are no issues with the drug master files (DMFs) for the ——————— at this time. Copies of the open DMFs provided by the vendors should not be included in the NDA. Kos should notify FDA if a ——————— will need to be evaluated.

4. Data supporting the proposed dissolution specification for lovastatin should be included in the NDA, since our proposed specification differs somewhat from the specification for Lovastatin Tablets USP.

5. There are no issues at this time with the proposed Regulatory Specifications, commercial stability protocol, expiry date, or amount of stability data planned for initial submission and a later update.

6. The proposed reports to be included in the NDA should be sufficient to allow in-depth review; no additional reports were identified as required for filing.

7. The order of presentation and table of contents for the CMC section will be modified as suggested by Dr. Kelly after the conclusion of the main meeting. A revised table of contents will be provided for review as the submission progresses.

8. As agreed with Dr. Kelly after the conclusion of the main meeting, a table listing all manufacturing, testing, and packaging sites, with their responsibilities clearly delineated, will be included in the NDA to facilitate assigning the required pre-approval inspections. The table will include the Central File Number, location of the facility, and dates of the most recent FDA inspection, if available.

Nonclinical Pharmacology and Toxicology Section

1. There are no issues with the amount and source of data planned for inclusion in the NDA.

2. Dr. Steigerwalt requested that the data extracted from the literature be summarized and organized in the order required for the labeling.

3. Each subsection of the nonclinical pharmacology and toxicology section must be appropriately supported and referenced for each of the two active ingredients. A compilation of reference papers alone would not be considered acceptable.

4. The calculation of safety margins for our highest doses should be supported by appropriately referenced information.

Human Pharmacology and Bioavailability/Bioequivalence Section

1. There are no issues with the extent of studies planned for inclusion in the NDA.

2. There are no issues with the submission format. Previously reviewed Niaspan® reports will be provided directly to the reviewer as paper desk copies for reference purposes. Proposed dataset formats are acceptable. Listings of terminations due to adverse events will be provided for each study and case report forms will be provided upon request.

Clinical/Statistical Section

1. There are no filing issues for the clinical and statistical sections. The number of studies and the amount of exposure data that will be included in the NDA are acceptable.

2. There are no issues with the planned electronic format and content. The electronic NDA documents will be supplemented by paper in accordance with the IT-3 guidance and MS Word files as previously agreed.

3. The question of a first-line therapy indication for Nicostatin is not a filing issue. At this time, the FDA position remains that the combination product does not meet agency guidelines for first-line therapy, since the two agents address different aspects of the metabolic profile and are not dose-sparing for the same effect. The sponsor may provide additional background information in the NDA to support this claim; however, further discussion will be deferred until the negotiating process for the labeling is underway.

4. The requirements for adding ——— are also not a filing issue and should be addressed at a later time. With respect to the clinical outcomes claims in general, the sponsor should provide a detailed rationale for granting these indications to the combination product.

5. The plan for safety updates during NDA review is acceptable. Dr. Jenkins noted that a standard review is expected for this NDA. Dr. Orloff commented that the safety summaries should enumerate the duration of exposure by dose.

6. The documentation plan for SAS data sets and the organization of this section are acceptable to the FDA statistical reviewer. There are no statistical issues at this time.

7. Domain profiles only for case report tabulations are acceptable. This agreement will be stated in the NDA documents as a waiver from the requirement to submit patient profiles.

8. The Kos request for a pediatric waiver is being addressed. FDA does not believe that pediatric studies are appropriate for this combination product.

This concludes the major discussion points and agreements reached at the June 21 meeting. There are no unresolved filing issues although some follow-up on minor format and organizational questions is expected to occur. There are no action items as a result of this meeting.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-249

Kos Pharmaceuticals, Inc
Attention: David H. Warnock, Ph.D.
Director, Regulatory Affairs
1001 South Bayshore Drive
Suite 2502
Miami, Florida 33131

Dear Dr. Warnock:

Reference is made to your correspondence dated October 9, 2000, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver of the requirement for pediatric studies is justified for Advicor (extended release niacin and lovastatin) Tablets as a convenience product for the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb) in:

- Patients treated with lovastatin who require further TG lowering or HDL raising who may benefit from having niacin added to their regimen.
- Patients treated with niacin who require further LDL lowering who may benefit from having lovastatin added to their regimen.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have questions, please contact William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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
8/27/01 10:22:34 AM

APPEARS THIS WAY
ON ORIGINAL

KOS Pharmaceuticals, Inc.
Laboratory:
Two Oakwood Boulevard
Suite 140
Hollywood, Florida 33020
Phone (954) 920-7200
Fax (954) 920-7272

Corporate Office:
1001 South Bayshore Drive
Suite 2502
Miami, Florida 33131
Phone (305) 577-3464
Fax (305) 577-4596

October 09, 2000

David Orloff, MD
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Request for Pediatric Waiver for Nicostatin™ NDA 21-249 under §314.55

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Nicostatin™, an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin. We have received the acknowledgement letter from FDA dated September 29, 2000. This letter noted the requirement to either submit plans for pediatric drug development or to request a waiver with supporting information and documentation in accordance with the provisions of 21 CFR §314.55 within 60 days from the date of the letter.

On March 21, 2000, we had been advised by FDA to submit a request for a Pediatric Waiver under §314.55 to our Nicostatin™ IND —— as an amendment. The request for waiver was submitted to the IND as serial number 054, dated March 28, 2000. However, we did not make reference to this specific IND submission in the NDA cover letter or in other sections of the NDA. The waiver request is provided to NDA 21-249 with this letter. We look forward to your review and approval of our request for a Pediatric Waiver.

If there are any questions regarding this submission or if additional information is required, please contact either Valerie Ahmuty, Manager of Regulatory Affairs, or myself at 305-512-7000. Thank you.

Sincerely,

David H Warnock

APPEARS THIS WAY
ON ORIGINAL

David H. Warnock, PhD
Director, Regulatory Affairs

Request for Pediatric Waiver

Kos Pharmaceuticals, Inc. requests a full waiver of the requirements of paragraph (a) of 21 CFR § 314.55 for a pediatric-use assessment for Nicostatin™.

As directed under paragraph (c), Kos certifies that:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are highly impractical because the number of such patients is so small and geographically dispersed.

Justification

The Nicostatin product is a combination of two already marketed drug substances, niacin and lovastatin. The niacin component of Nicostatin is identical in formulation to Niaspan®, our commercially available extended-release product. In a letter dated October 28, 1999, approving NDA 20-381 Supplement S-006 (indication for Niaspan to increase HDL cholesterol), FDA waived the requirement for pediatric studies of Niaspan based on their assessment of the risks and benefits of pediatric use of this drug for the approved indications. (A copy of the letter is attached for reference.) It is our belief that the same risks and benefits of pediatric use apply to the combination product, Nicostatin.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

APR 13 2001

Leo Kent Smith, M.D.
Arizona Heart Institute
2632 North 20th Street
Phoenix, Arizona 85006

Dear Dr. Smith:

Between January 16 and January 23, 2001, Ms. Valerie Whipp, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol # MA-98-010406) of the investigational drug Nicostatin, performed for Kos Pharmaceuticals, Inc. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Whipp during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Kaan

John R. Crouse, M.D.
Wake Forest School of Medicine
Clinical Lipid Center
Medical Center Boulevard
Winston-Salem, North Carolina 27157

APR 13 2001

Dear Dr. Crouse:

Between January 23 and January 30, 2001, Ms. Michelle Haamid, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol ——) of the investigational drug, Niastatin® (niacin extended-release/lovastatin immediate release) performed for Kos Pharmaceuticals, Inc. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and your letter of February 1, 2001, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We accept your February 1, 2001, response regarding responsibility for drug disposition records, which is consistent with 21 CFR 312.62(a).

We appreciate the cooperation shown Investigator Haamid during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

———————— ws,

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research,
7520 Standish Place
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB - 6 2001

Ronald L. Brazg, M.D.
4033 Talbot Road South, Suite 500
Renton, Washington 98055

Dear Dr. Brazg:

Between January 2 and January 11, 2001, Ms. Astrida Mattson, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol ———) of the investigational drug, Niastatin® (niacin extended-release/lovastatin immediate release) performed for Kos Pharmaceuticals, Inc. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Mattson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research,
7520 Standish Place
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

Kos Pharmaceuticals, Inc.
Research Office:
14875 Northwest 77th Avenue
Suite 100
Miami Lakes, Florida 33014
Phone (305) 512-7000
Fax (305) 512-0337

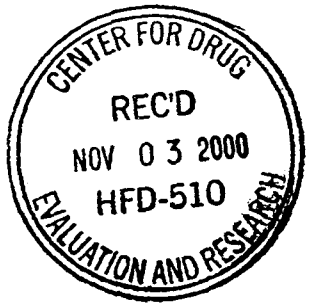
Corporate Office:
1001 Brickell Bay Drive
25th Floor
Miami, Florida 33131
Tel (305) 507-3600
Fax (305) 577-4596

November 02, 2000

DUPLICATE

David Orloff, MD
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

C
REPORT



RE: Correspondence to Nicostatin™ NDA 21-249

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Nicostatin™, an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin.

It is our understanding that the NDA has been determined fileable and is currently under active review. Roy Blay, PhD, of the Division of Scientific Investigations, requested the attached information on November 01, 2000, to use in the selection of clinical sites from our pivotal studies for audit. The information was provided to Dr. Blay on November 01 by fax. Dr. Blay suggested that we send the review division a copy of the correspondence for the NDA file. There is no new information in the materials provided to Dr. Blay. Many of the pages are taken directly from the clinical reports submitted to the NDA.

If there are any questions regarding this submission or if additional information is required, please contact either Valerie Ahmuty, Manager of Regulatory Affairs, or myself at 305-512-7000. Thank you.

Sincerely,

David H. Warnock

David H. Warnock, PhD
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

All sites are ready for inspection.

Commercial Establishment	Role in Manufacture of Nicostatin Drug Product	Central File Number
[redacted]	[redacted]	[redacted]
[redacted]		
Kos Pharmaceuticals, Inc. 18 Mayfield Avenue Edison, NJ 08837 732-225-2930 *Contact: Barbara Falco* *Director of Quality Assurance*	1) Manufacturer of Niacin ER [redacted] Tablets 2) Tablet [redacted] 3) Quality Control Laboratory and Stability Testing	2248571
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Kos Pharmaceuticals, Inc. 2 Oakwood Blvd., Suite 140 and 200 Oakwood Lane, Suite 100 Hollywood, FL 33020 *Contact: Marvin Blanford, PharmD* *Vice President of Compliance*	Quality Control Laboratory and Stability Testing	1054801
[redacted]	[redacted]	[redacted]

WITHHOLD 1 PAGE (S)

(NDA-98-010414)

16.1.4 List and Description of Investigators and Documentation of Training and Experience

Site Number	Investigator(s)	Affiliation[b]
01	Stephen D. Nash, MD	Cholesterol Control Center 600 East Genesee St.,Suite 204 Syracuse, NY 13202-3108
02	William Castelli, MD	Framingham Cardiovascular Institute MetroWest Medical Center 115 Lincoln Street Framingham, MA 01702-9167
03	John Corbelli, MD	Buffalo Cardiology & Pulmonary Assoc.. PC 5305 Main Street Williamsville, NY 14221
04	John R. Crouse, MD	Wake Forest University School of Medicine Department of Medicine/ Endocrinology Medical Center Boulevard Winston-Salem, NC 27157-1047
05	Stephen DeVries, MD	University of Illinois Section of Cardiology 1801 West Taylor, Room 3C Chicago, IL 60612-7323
06	Henry Ginsberg, MD	Columbia Presbyterian Medical Center Arteriosclerosis Research Center Harkness Pavillion, Room 956 180 Fort Washington Avenue New York, NY 10032
07	Norman Castellano, MD Peter Alagona, MD	Florida West Coast Clinical Research Group 2727 Martin Luther King Jr. Blvd., Suite 460 Tampa, FL 33607
08	Mark Goodman, MD	Cardiovascular Medical Associates 975 Stewart Avenue Garden City, NY 11530
09	William Insull, MD	Baylor College of Medicine Lipid Research Clinic 6565 Fannin, MS B120 Houston, TX 77030
10	Leonard Keilson, MD	Maine Medical Center Center for Lipid & Cardiovascular Health 48 Gilman Street Portland, ME 04102
11	Ronald Krauss, MD	Cholesterol Research Center 3101 Telegraph Avenue Berkley, CA 94705

MA-98-010414)

Site Number	Investigator(s)	Affiliation[b]
12	Mary McGowan, MD	New England Heart Institute Cholesterol Management Center 88 McGregor Street, Suite 301 Manchester, NH 03102
14	Helmut G. Schrott, MD Howard R. Knapp, MD, PhD	University of Iowa Lipid Research Clinic 2190 Westlawn S. Iowa City, IA 52242
15[a]	Donald Smith, MD	Mount Sinai Medical Center Box 1014 One Gustave Levy Place New York, NY 10029
16	Paul Thompson, MD	Hartford Hospital – Cardiology Research 80 Seymour Street Hartford, CT 06102-5037
17	Franklin Zieve, MD	McGuire VA Medical Center 1201 Broad Rock Blvd. Richmond, VA 23249
18	Michael Koren, MD	Jacksonville Center Clinical Research 4004 University Blvd. South Jacksonville, FL 32216

[a]Information not included for Site 15. The site was IRB approved but never screened patients
[b]Curriculum vitae attached
Comment: Site 13 is not assigned.

APPEARS THIS WAY
ON ORIGINAL

Kos Pharmaceuticals, Inc.
FAX TRANSMISSION COVER SHEET

14875 NW 77th Avenue, Suite 100
Miami Lakes, FL 33014
(305) 512-7000
Fax: (305) 512-0337

Date:	*November 01, 2000*	
To:	*Roy Blay, PhD*	*FDA - DSI (301-827-7378)*
Fax:	*301-827-5290*	
Re:	*Information Request*	
Sender:	*Valerie Ahmuty, Manager of Regulatory Affairs*	

THIS FAX CONSISTS OF 19 PAGES, INCLUDING THIS COVER SHEET.
PLEASE CALL (305) 512-7002 IF THIS TRANSMISSION IS IMPROPERLY RECEIVED.

Dear Dr. Blay:

It was a pleasure to speak with you this morning. The attached pages should provide the information that you requested regarding investigators, enrollment, and serious adverse events. As you suggested, I will send a copy of this correspondence to the Division of Metabolism and Endocrine Drugs for the NDA file as soon as I am sure that all of your needs have been met.

Kos conducted two pivotal double-blind controlled studies that support Nicostatin NDA 21-249. The study identifiers are MA-98-010406 and MA-98-010414. To provide some relevant background information on each study, I have included certain pages from the study synopses and used them as an introductory section preceding the list of investigators, patient enrollment, and serious adverse event information for each of the studies. The page numbers seen are from the study reports. In addition to the pages directly taken from the study reports, I have provided some explanatory text regarding the information presented in the tables (summarized from the study report).

The lists of investigators that were included in the study reports do not include telephone numbers. If you need telephone numbers, please let me know. Additionally, I can provide you with names and telephone numbers of study site coordinators, since these may be of value to you in coordinating your inspections.

If you have any questions or need any additional information, please do not hesitate to call David Warnock, PhD, Director of Regulatory Affairs (305-512-7051), or myself. I hope you find these materials helpful and look forward to hearing from you soon.

Sincerely,

Valerie Ahmuty

Valerie Ahmuty

Kos Pharmaceuticals, Inc.
Research Office:
14875 Northwest 77th Avenue
Suite 100
Miami Lakes, Florida 33014
Tel (305) 512-7000
Fax (305) 512-0337

Corporate Office:
1001 Brickell Bay Drive
25th Floor
Miami, Florida 33131
Tel (305) 577-3464
Fax (305) 577-4596

March 10, 2000

John Jenkins, M.D., Acting Director,
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Nicostatin™ IND —— Submission Serial #051
Claim of Categorical Exclusion from the Requirement to Submit an Environmental Assessment with Nicostatin™ NDA

Dear Dr. Jenkins:

Please refer to our Investigational New Drug Application (IND) Number —— for Nicostatin™ (niacin extended-release and lovastatin), an antidyslipidemic combination drug product for reducing total (TC) and low-density lipoprotein serum cholesterol levels (LDL-C), reducing triglycerides (TG), and increasing high-density lipoprotein cholesterol (HDL-C). Studies that were designed to establish the safety and efficacy of Nicostatin are being completed and technical sections for a Nicostatin new drug application (NDA) are being prepared. Kos anticipates submission of the Nicostatin NDA during the second half of 2000.

Kos believes that the Nicostatin™ NDA will qualify for a categorical exclusion from the requirement to submit an Environmental Assessment for the following reason:

> Nicostatin™ is a combination drug which will substitute for two approved products (Niaspan® NDA 20-381 and Mevacor® NDA 19-643) without an increase in the use of its active moieties. As provided for by 21 CFR 25.31(a) FDA's approval of an NDA that does not result in an increased use of the active moieties in the drug product is an action that ordinarily qualifies for a categorical exclusion from the requirement to submit an Environmental Assessment. **Attachment A: No Increased Use** of the FDA's Guidance Document *Environmental Assessment of Human Drug and Biologics Applications* (July 1998, CMC 6, Revision 1) lists actions that are not considered to result in increased use of an active moiety if approved by the Agency. One of these actions is approval of "combination drugs in which the single product substitutes directly for two approved products that would be administered separately."

By this letter we are requesting your opinion on our position that a claim of categorical exclusion from the requirement to submit an Environmental Assessment is appropriate for the Nicostatin™ NDA. Please let us know as soon as conveniently possible if you concur with our position on this matter.

If there are any questions regarding this submission or if additional information is required, please contact either Karen DiStefano, Associate Director, Regulatory Affairs, or myself at 305-512-7000.

Sincerely,

David H Warnock

David H. Warnock, PhD
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 7/19/01 3:32:16 PM
From: Sammie Beam (BEAMS)
To: William C. Koch (KOCHW)
Subject: OPDRA consul#01-0165

Hi,

NDA 21-249 final proposed proprietary name review has been assigned the number above.

Thanks,
Trade name team

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 7/19/01 12:13:12 PM
From: William C. Koch (KOCHW)
To: Account OPDRA Request (OPDRAREQUEST)
Subject: NDA 21-249, 90-day review request

Trade name Team,

NDA 21-249

Advicor

September 22, 2001

Bill

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 1/19/01 4:15:54 PM
From: Sammie Beam (BEAMS)
To: William C. Koch (KOCHW)
Subject: OPDRA consult #01-0015

Hello,

This is to inform you that NDA 21-249 has been assigned the above consult number for proposed proprietary name review.
As a reminder we will need the carton/container labels to complete the review.

Thanks,
Sammie Beam
7-3231

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-249 / _____ _____

Drug Advicor (extended release niacin and lovastatin) Tablets Applicant Kos Pharmaceuticals, Inc.

RPM William C. Koch Phone (301) 827-6412

☐505(b)(1)
X505(b)(2) Reference listed drugs Niaspan & Mevacor

☐Fast Track ☐Rolling Review Review priority: 2-month resubmission

Pivotal IND(s) —

Application classifications:
Chem Class 4
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary November 17, 2001
Secondary _____

Arrange package in the following order:

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

GENERAL INFORMATION:

- User Fee Information: ☐User Fee Paid — **N/A**
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption
- Action Letter..... ☐AP ☐AE X TA
- Labeling & Labels
  - FDA revised labeling and reviews..... **X**
  - Original proposed labeling (package insert, patient package insert) ..... **X**
  - Other labeling in class (most recent 3) or class labeling..... N/A
  - Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☐ No
  - Immediate container and carton labels ..... **X**
  - Nomenclature review ..... **X**
- Application Integrity Policy (AIP) — This application is not on the AIP.
  - Exception for review (Center Director's memo)..... N/A
  - OC Clearance for approval.....

Continued ⇨

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

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

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

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

- Exclusivity Summary X

- Debarment Statement X

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

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings X
  - Date of EOP2 Meeting January 26, 1999 — X
  - Date of pre NDA Meeting June 21, 2000 — X
  - Date of pre-AP Safety Conference _____ — NN

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

- Federal Register Notices, DESI documents ..... NA

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

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) .....

- Clinical review(s) and memoranda X

Continued ⇨

- ♦ Safety Update review(s) X

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

- ♦ Statistical review(s) and memoranda ..... _____

- ♦ Biopharmaceutical review(s) and memoranda..... N/A

- ♦ Abuse Liability review(s) ..... NN
  Recommendation for scheduling ..... _____

- ♦ Microbiology (efficacy) review(s) and memoranda ..... NN

- ♦ DSI Audits ..... N/A
  XClinical studies ☐ bioequivalence studies ..... _____

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

- ♦ CMC review(s) and memoranda X

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

- ♦ DMF review(s) ..... N/A

- ♦ Environmental Assessment review/FONSI/Categorical exemption ..... NN

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

- ♦ Facilities Inspection (include EES report)
  Date completed _____ ..... X Acceptable ☐ Not Acceptable

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

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

- ♦ Pharm/Tox review(s) and memoranda ..... N/A

- ♦ Memo from DSI regarding GLP inspection (if any) ..... NN

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... NN
- CAC/ECAC report ..... NN

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-249 / ____ _____

Drug Advicor (extended release niacin and lovastatin) Tablets Applicant Kos Pharmaceuticals, Inc.

RPM William C. Koch Phone (301) 827-6412

☐505(b)(1)
X505(b)(2) Reference listed drugs Niaspan & Mevacor

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

Pivotal IND(s) ____

Application classifications:
Chem Class 4
Other (e.g., orphan, OTC) ____

PDUFA Goal Dates:
Primary July 22, 2001
Secondary Sept. 22, 2001

Arrange package in the following order:

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

GENERAL INFORMATION:

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

- Action Letter..... ☐AP X AE ☐NA

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

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

  Exception for review (Center Director's memo)..... N/A
  OC Clearance for approval.....

Continued ⇨

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

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

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

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

- Exclusivity Summary X

- Debarment Statement X

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

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings X
  - Date of EOP2 Meeting January 26, 1999 X
  - Date of pre NDA Meeting June 21, 2000 X
  - Date of pre-AP Safety Conference NN

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

- Federal Register Notices, DESI documents ..... NA

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

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X

- Clinical review(s) and memoranda X

Continued ⇨

- Safety Update review(s) X

- Pediatric Information
  X Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... X
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- Statistical review(s) and memoranda X

- Biopharmaceutical review(s) and memoranda..... X

- Abuse Liability review(s) ..... NN
  Recommendation for scheduling ..... _____

- Microbiology (efficacy) review(s) and memoranda ..... NN

- DSI Audits X
  X Clinical studies ☐ bioequivalence studies ..... _____

CMC INFORMATION:

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

- CMC review(s) and memoranda X

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

- DMF review(s) ..... N/A

- Environmental Assessment review/FONSI/Categorical exemption ..... NN

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

- Facilities Inspection (include EES report)
  Date completed _____ ..... ☐ Acceptable X Not Acceptable

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

PRECLINICAL PHARM/TOX INFORMATION:

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

- Pharm/Tox review(s) and memoranda X

- Memo from DSI regarding GLP inspection (if any) ..... NN

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... NN
- CAC/ECAC report ..... NN

NO

FEDERAL REGISTER NOTICES

or

DESI DOCUMENTS

REQUIRED

APPEARS THIS WAY
ON ORIGINAL

MICROBIOLOGY REVIEW
NOT REQUIRED