CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-249

CORRESPONDENCE

Kos Pharmaceuticals, Inc.
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REPORT

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: NIASPAN® (niacin extended-release tablets) NDA 20-381
Submission of Information Regarding Newly Issued Patent

ORIGINAL

Dear Dr. Orloff:

Please refer to Kos Pharmaceuticals, Inc. NDA 20-381 for NIASPAN® (niacin extended-release tablets), approved for commercial distribution on July 28, 1997. Patent Number 6,129,130 is both a Formulation/Composition and Method of Use patent for treating hyperlipidemia with nicotinic acid without causing treatment-limiting elevations in uric acid or glucose levels or causing liver damage, by dosing once per day in the evening or at night. The patent was issued October 10, 2000. As closely as possible, Kos has prepared this submission in accordance with the format that is posted on the FDA website for submission of time sensitive patent information.

Simultaneously with submission of this supplement to the NDA, Kos is sending a copy by FedEx to the Division of Data Management and Services Information Services Team to facilitate inclusion of the information in the Orange Book.

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

Sincerely,

David H Warnock

David H. Warnock, PhD
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

enclosures

DUPLICATE

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November 13, 2001

ORIG AMENDMENT

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: NDA 21-249: Advicor® (niacin extended-release and lovastatin tablets)
Submission of revised draft labels for bottle containers

Dear Dr. Orloff:

Enclosed are revised draft container-label images for Advicor (niacin extended-release and lovastatin tablets) bottles of 90 tablets. These revised labels are representative of the change in the Advicor logo that will be made for all immediate-container labels. Please note that revised immediate-container labels for the 3-tablet sample packs were submitted to your office on November 09, 2001 and to the Division of Drug Marketing, Advertising and Communications (DDMAC) on November 08, 2001.

Dr. Andrew Haffer of DDMAC indicated in a conversation today between himself and Dr. David Warnock of Kos that the changes in the revised sample pack as submitted November 08 are acceptable to DDMAC. It is our understanding that Dr. Haffer communicated the same information to Mr. William Koch, Project Manager. Mr. Koch advised us today that the Division of Endocrine and Metabolic Drug products needs a representative set of the revised bottle labels to complete the file. Kos believes that the logo is the only change affecting the bottle labels and that the enclosed label images should be adequate to illustrate the logo change for all bottles regardless of tablet-fill number (images of other fill-sizes are not yet available).

Should you have questions, or require additional information, please contact either Valerie Ahmuty or myself at 305-512-7000. Thank you for your help in this matter.

Sincerely,

David H. Warnock, PhD
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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DUPLICATE

October 04, 2001

CENTER FOR DRUG
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HFD-510
EVALUATION AND RESEARCH

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ORIG AMENDMEN

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: NDA 21-249: Advicor® (niacin extended-release and lovastatin tablets)
Submission of sample carton text and patient 'tips' card for comment

Dear Dr. Orloff:

Enclosed are the labeling/packaging materials for Advicor (niacin extended-release and lovastatin tablets) as listed below. These materials were provided to DDMAC in a submission dated September 20, 2001 (copy of the cover letter to DDMAC also enclosed). Submission of these documents to your office for concurrent review was inadvertently overlooked. We apologize for the delay and hope the timing of the review process has not been adversely affected.

An Approvable letter for the Advicor NDA 21-249 was issued July 20, 2001. In a submission dated September 12, Kos provided a complete response to the Approvable letter, and a revised draft package insert. In the submission provided to DDMAC on September 20, Kos included as a reference material the draft package insert that was negotiated with the Division of Endocrine and Metabolic Drug Products and on which issuance of the July 20, 2001 Approvable letter was based. To date, DDMAC has not received from Kos the draft package insert included in our September 12 complete response.

Kos is requesting comments from DDMAC and the Division of Metabolic and Endocrine Drug Products at this time in order to expedite finalization of the labeling for sample packs, as we expect to begin packaging of launch quantities of sample packs in late October 2001. We would appreciate either verbal or written comments.

The following two labeling pieces are provided for review:

1. The outer container (carton) for a three-tablet sample pack for Advicor 500 mg/20 mg tablets (item code 400158, dated 12/01). The carton text is very similar to the text provided in the complete-response submission of September 12, 2001.

[ ]

Should you have questions, or require additional information, please contact either Valerie Ahmuty or myself at 305-512-7000. Thank you for your help in this matter.

Sincerely,

David H. Warnock

David H. Warnock, PhD
Director, Regulatory Affairs

APPEARS THIS WAY
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ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
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HFD-510

N 000 SU
ORIG AMENDMENT

September 27, 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: Advicor™ NDA 21-249 (niacin extended-release and lovastatin tablets)
Submission of Third (12-Month) Safety Update in Accordance with the FDA's NDA Approvable Letter dated July 20, 2001

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Advicor™, an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin. In accordance with the FDA's Approvable letter dated July 20, 2001, we are submitting the Third Safety Update to NDA 21-249.

Like the original NDA and the two previous Safety Updates, this Third Safety Update is an electronic submission. The archival blue folder contains the electronic submission on CD and signed original paper copies of the cover letter and 356h form. Case report forms and case report tabulations are provided only in the electronic files. This Third Safety Update has a stand-alone table of contents (up3toc.pdf) that is hypertext-linked to all sections of the update. Paper review copies of the text of the Safety Update report are provided in the archival blue copy, in a manila folder for the clinical reviewer, and a desk copy (black folder) for the Regulatory Project Manager.

The format of this Third Safety Update has been developed in accordance with the instructions provided in the Approvable letter of July 20. To facilitate review, these instructions are repeated below (bold, italicized text), followed by either a direct response or reference to the location of the information within the submission.

APPEARS THIS WAY
ON ORIGINAL

Safety Update Instructions from July 20 Letter and Kos Response

The Safety Update should be submitted within three months prior to the date that exclusivity will expire. The Safety Update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

The Third Safety Update provided today complies with the requirement for submission within three months prior to the date that exclusivity expires for lovastatin (December 15, 2001). In combination with final study reports and integrated safety summary (ISS) provided in the original NDA, the Third Safety Update includes safety data from all nonclinical and clinical studies of the drug product (see page 10 of the Third Safety Update), regardless of indication, dosage form, or dose level.

New information in the Third Safety Update includes data from the completed long-term open-label studies MA-98-010407 and MA-99-010409, and enrollment estimates and Serious Adverse Events (SAEs) reported for the ———— study, ————

1. ***Describe in detail any significant changes or findings in the safety profile.***

   There have been no significant changes or findings in the safety profile for Advicor. Please see **Section 4.0 – SUMMARY**, beginning on page 6 of the Third Safety Update, for a comprehensive overview.

2. ***When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:***

   - ***Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.***

     The format for presentation of safety data in this Third Safety Update is in accordance with the requests conveyed to Kos after review of the First Safety Update (and provided in the NDA amendment dated February 16, 2001). This format was also used in the presentation of safety data in the Second Safety Update (dated May 18, 2001), and is believed to also be FDA's preference for this update.

   - ***Present tabulations of the new safety data combined with the original NDA data.***

     Discontinuations:
     Table 7 on page 14 of this Third Safety Update summarizes the numbers and reasons for discontinuations in the two long-term studies by individual study and in

combination. Table 8 on page 15 summarizes the numbers and reasons for discontinuations from all safety and efficacy studies and their extensions (except for the ——————— study, for which this information is not yet available). For comparison purposes, data are presented for the original NDA, cumulative through the First, Second, and this Third Safety Update.

SAEs:
A cumulative listing of SAEs by body system and individual event is presented in Table 21 (all safety and efficacy studies except the ——————— study), beginning on page 67 of the Third Safety Update. The two SAEs reported for the ——— ——————— study are presented on page 126.

COMMON AEs:
For the long-term studies, cumulative treatment-emergent adverse events irrespective of causality are presented by study and pooled in Table 22, beginning on page 79 of this Third Safety Update.

Common AE data for the two double-blind studies were presented in Table 1, pages 3 to 15, of the amendment to NDA 21-249 dated February 16, 2001. This was submitted in response to FDA's request for additional information following the review of the NDA ISS and the First Safety Update (submitted January 17, 2001). Common AE data from short-term double-blind studies and from long-term, open-label studies are not usually combined. A paper copy of Table 1 is provided for reference in **Attachment 1** (also electronically provided and linked to the table of contents, up3toc.pdf). A visual review of the AE data does not reveal any notable differences in the types of AEs seen.

- ***Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.***

Please see **Attachment 2** for a comparison table of common adverse events (treatment-emergent irrespective of causality) reported in the original NDA and the pooled cumulative frequencies presented in Table 22 of the Third Safety Update. No data were available for MA-99-010409 and only limited data for MA-98-010407 were available in the original NDA. To facilitate review, tabulations from the addendum to the First Safety Update and tabulations from the Second Safety Update have been included in **Attachment 2**.

Due to the specificity of the requested comparison (i.e., the audience for which it is intended), Kos chose to provide this information as an attachment to this submission

and not integral to the Third Safety Update. The tabulations are provided electronically and in paper form.

- ***For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.***

  No indications other than those proposed in the original NDA have been studied. This request is not applicable to Advicor.

3. ***Present a retabulation of the reasons for premature study discontinuations by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.***

   Please see Tables 7, 8, and 10 (pages 14, 15, and 19, respectively) of the enclosed Third Safety Update. Only four new discontinuations due to adverse events have been reported since the last Safety Update. Table 8 presents the discontinuation statistics from the original NDA, cumulative for the First, Second, and Third Safety Updates. There are no new trends or patterns. Please refer to the discussion in the Safety Update for detail.

4. ***Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.***

   Case report forms (CRFs) for patients who did not complete the study because of an adverse event are provided electronically. Only CRFs for those patients not previously submitted are provided with this submission.

   Narrative summaries are provided in Section 16.1 of the Third Safety Update (electronically and in paper form). There were no new deaths to report. Narratives for serious or significant adverse events begin on page 41. In keeping with reporting during previous Safety Updates, narratives are not provided for patients who discontinue due to adverse events considered "labeled" (from Niaspan®). Narratives are not provided for the four new discontinuations since these were due to labeled adverse events. Discontinuations due to adverse events are discussed in Section 8.3 beginning on page 19 of the Third Safety Update.

5. ***Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.***

   There is no information that suggests a substantial change in the incidence of common, but less serious, adverse events, between the new data and the original NDA data. Please see the discussion included with the tabulation in **Attachment 2.**

6. ***Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.***

   Advicor has not been studied or marketed in any country other than the U.S. This request is not applicable to Advicor.

7. ***Provide English translations of current approved foreign labeling not previously submitted.***

   No foreign labeling of any type has been created. This request is not applicable to Advicor.

Please note that the complete response to the July 20 Approvable letter was also recently submitted (amendment dated September 12, 2001). This submission included minor amendments to the chemistry, manufacturing, and controls section and to the proposed Package Insert.

We believe that all required information has been submitted to the NDA at this time, and we look forward to receiving marketing approval when the period of exclusivity for lovastatin has expired.

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

Review findings entered in DFS 19-Oct-2001. No action required.
151.
19-Oct-2001

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ORIGINAL

N 000 B
ORIG AMENDME

September 12, 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: Advicor™ NDA 21-249 (niacin extended-release and lovastatin) 500mg/20mg, 750mg/20mg, and 1000mg/20mg Tablets

1) **Complete Response to Approvable Letter Dated July 20, 2001**
2) **Updated Chemistry, Manufacturing and Controls (CMC) Information**
3) **Proposed Revisions to the Package Insert (PI)**

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Advicor™, an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin. Subsequent submissions were provided to the application on the following dates: October 09, November 02, and December 05, 2000, January 17, 23, and 31, February 14 (2), 16, and 28, March 20, April 17 (3), May 18, June 26, and July 02, 03, 05, 11, 16, and 19, 2001.

FDA issued an approvable letter for the application on July 20, 2001. Kos responded to that letter on July 27, describing our intent to amend the application to provide the information that was stipulated in the approvable letter as well as additional chemistry, manufacturing, and controls (CMC) information. The enclosed submission is considered a complete response to the approvable letter. In addition, this submission provides updated stability data, copies of revised proposed commercial manufacturing master records, CMC-related changes to the draft package insert (PI), and a correction of an (inconsequential) error in the text of the CMC section of the original NDA. The CMC update is considered a minor amendment that is provided in accordance with our letter of July 27.

In the Kos July 27 response to the approvable letter, we requested agreement from FDA to consider a revision to the ***Dosage and Administration*** section of the draft PI. During a telephone conversation on August 13, Mr. William Koch, FDA Project Manager, advised Kos that FDA would consider such a change also as a minor amendment, and that our proposal should be submitted no later than the complete response to the approvable letter. Accordingly, we are submitting the enclosed revised draft PI. Changes are proposed in the ***Dosage and***

Administration and ***Clinical Studies*** sections to define the dosing transition for this product. These proposed changes are highlighted in the PI text. The rationale and justification for these proposed changes are included within the submission.

Please note that, as agreed, this submission does not include the safety update requested in the approvable letter. In the August 13 telephone conversation, Mr. Koch also advised Kos that the safety update is independent of the other requirements for approval, and therefore should be provided separately from the complete response and no earlier than three months prior to the date that exclusivity will expire (December 15, 2001) for the lovastatin active ingredient.

The complete response, revised draft PI, revised draft container labels, and correction to the CMC text have been provided electronically on a 3" diskette as pdf files as well as in paper format in the archival copy to the NDA. An MS Word file of the revised draft PI is also provided on the diskette. Paper copies of the revised draft PI and main text of this submission are included in each technical review copy (CMC, clinical, and Project Manager desk copy). Paper copies of CMC attachments are provided only in the archival and CMC review copies.

Kos Pharmaceuticals, Inc. certifies that a true copy of the CMC sections of this NDA amendment has been forwarded concurrently to the FDA NJ North Brunswick Resident Post, the FDA district office with jurisdiction over the Edison, NJ manufacturing site.

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

APPEARS THIS WAY
ON ORIGINAL

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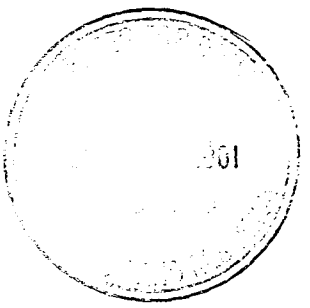
July 27, 2001

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

NEW CORRESP
N-000-C

Re: Advicor™ NDA 21-249 (niacin extended-release and lovastatin)
500mg/20mg, 750mg/20mg, and 1000mg/20mg Tablets
Response to Approvable Letter Dated July 20, 2001

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Advicor™, an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin. Subsequent submissions were provided to the application on the following dates: October 09, November 02, and December 05, 2000, January 17, 23, and 31, February 14 (2), 16, and 28, March 20, April 17 (3), May 18, June 26, and July 02, 03, 05, 11, 16, and 19, 2001.

FDA issued an approvable letter for the application on July 20, 2001. As required, we are providing our response within 10 days of the approvable letter date to notify you that Kos intends to amend the application to provide the information that was stipulated in the approvable letter.

The approvable letter requested that we update the NDA by submitting all available safety information within three months prior to the date that exclusivity will expire (December 15, 2001). Kos agrees to provide this information to FDA by September 18, 2001. Additionally, Kos agrees to provide the safety update in accordance with the seven points regarding format and content as stated in the July 20, 2001 approvable letter.

Our plans for response to the CMC and product package labeling items are described below. For convenience in structuring our response, these have been consecutively numbered (they were not numbered within the approvable letter).

1. The letter noted that, during recent inspections of manufacturing facilities supporting our NDA, a number of deficiencies were noted and conveyed to us and to our suppliers by the investigators. The letter reminded us that satisfactory inspections of these facilities are required before the application may be approved.

   Kos acknowledges that satisfactory inspections of these manufacturing facilities are required before the application can be approved. Kos will ensure that any deficiencies that have been conveyed to us or to our suppliers by the investigators are appropriately addressed. Should relevant documents previously provided for CMC review be affected (e.g., proposed master batch records), updated documents will be submitted to the application.

2. Mock-ups of the immediate container labels for the 90 count presentation in 200cc bottles for all three strengths were requested. Additionally, mock-ups of immediate container labels for all container sizes were requested with the following revisions.

   - Insert the company logo in place of the word "LOGO"
   - Describe the strength of the actives using "mg" after both numbers
   - Express storage temperatures as "C" and "F" instead of the —› and '— ' as submitted in the .pdf file.

   Kos will provide the labels as requested. Additionally, the appropriate logos will be inserted and the strength of the actives will be described using "mg" after each ingredient. The storage temperatures will be expressed as "°C" and "°F". (The presence of the '— with the unit of measure was apparently a conversion error between the Microsoft Word files and the Adobe pdf files for the degree symbol and was not intended as proposed text.)

3. The approvable letter noted that since only 12 months of stability data at 25°C/60% RH were presented for the 30 and 180 count bottles of all three strengths, only an 18-month expiry period would be granted. A 24-month expiry period was granted for 90 count bottles of all three strengths.

   Stability data through 18 months of storage at 25°C/60%RH are now available for the 30 and 180 count bottles of all strengths. Kos plans to amend the NDA by providing the 18-month stability data, and request 24-month expiry dating for all packaging configurations.

Kos agrees to provide the labels and stability data (items 2 and 3, above) to FDA by September 15, 2001. It is hoped that all inspections (item 1) will be completed by that time and that Kos can submit any relevant documents, should there be any, in the CMC response.

Kos acknowledges prior acceptance of the final draft labeling in correspondence dated July 16 and 19, 2001, as noted above. While agreement to all of the labeling was provided in this correspondence, Kos continues to believe that because the *Dosage and Administration* section lacks explicit product-specific dosing instructions, there may be potential safety implications (e.g., medication dispensing errors due to practitioner misunderstanding). If FDA is agreeable, Kos wishes to discuss this consideration further with the Agency during a future meeting that would be supported by the submission of relevant background material.

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

Sincerely,

Karen Bisaro for David Warnock

David H. Warnock, Ph.D.
Director, Regulatory Affairs

Kos Pharmaceuticals, Inc.

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July 19, 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

N 000 BL

ORIG AMEND

Re: Advicor™ NDA 21-249 (formerly known as Nicostatin™)
Submission of Corrected Final Draft Labeling

Dear Dr. Orloff:

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

On July 16, 2001, Kos submitted what we believed to be the final draft labeling, in accordance with the revisions provided by FDA on July 13. In that submission, Kos had fixed what were believed to be non-editorial errors, added the data requested by FDA, and re-inserted the information regarding bottles of 180 in the "How Supplied" section. In one case, Kos fixed what we believed was a "typo" in a notation of tables referencing data from our double-blind study. The text was changed from "Tables 2-4" to "————" in a paragraph on page 9 that made general observations about the results of our long-term study and the double-blind study. On July 17, FDA contacted Kos and informed us that Table — which provided — from the double-blind study, was not included in the reference purposely. Since Kos did not provide — data in the NDA for the long-term study beyond 12 weeks, the ———— should not have been included in the tables referenced. As requested today, the corrected document is being formally provided to the NDA in this submission. Kos apologizes for any inconvenience our error may have caused.

Enclosed in this submission are electronic and paper copies of the corrected PI. The manila clinical review folder and the archival blue folder provide identical materials. As also agreed today, this cover letter and corrected PI have also been provided to Mr. Koch by e-mail on July 19.

If there are any questions regarding this submission or if additional information is required, please contact me at 305-512-7007. Thank you.

Sincerely,

for M. Blanford / Valerie Ahmuty, Mgr of RA

Marvin F. Blanford, PharmD
Vice President of Compliance

Kos Pharmaceuticals, inc.

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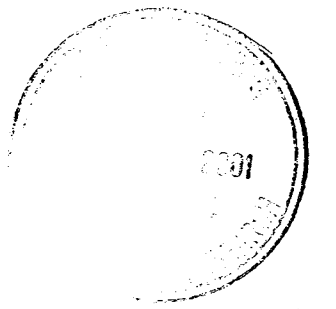
ORIGINAL

July 16, 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



N 000 BL

Re: Advicor™ NDA 21-249 (formerly known as Nicostatin™)
Submission of Final Draft Labeling as Agreed on July 13, 2001

ORIG AMENDMENT

Dear Dr. Orloff:

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

On July 13, 2001, Kos received an e-mail from FDA with revisions to the label previously submitted by Kos on July 11, 2001. FDA noted that no further negotiations for this package insert (PI) would occur prior to the mandated goal date of this application. The Division requested the sponsor's agreement on their draft of the package insert to move the application forward.

Kos verbally accepted FDA's revision to the PI on July 13 in a voicemail to Mr. William Koch, FDA Project Manager. In a later conversation between Ms. Valerie Ahmuty of Kos and Mr. Koch, Mr. Koch indicated that Kos should also submit a "clean" final draft PI to the NDA (paper and electronically by e-mail and diskette). It was agreed that Kos would fix non-editorial errors (e.g., spacing, punctuation), add the data requested by FDA in their highlighted sections, and re-insert the information regarding bottles of 180 in the "How Supplied" section (Kos deleted this in an earlier version by mistake). Enclosed in this submission are electronic and paper copies of the totally "clean" version of the PI and electronic and paper copies highlighting the corrections or information added as noted above (other than commas, spacing or format-only changes). The manila clinical review and archival blue folders provided contain identical materials. Copies of these documents have also been provided to Mr. Koch by e-mail on July 16 as requested.

If there are any questions regarding this submission or if additional information is required, please contact me at 305-512-7007. Thank you.

Sincerely,

Marvin F Blanford

Marvin F. Blanford, PharmD
Vice President of Compliance

Electronic Mail Message

Date: 7/13/01 11:47:07 AM
From: William C. Koch (KOCHW)
To: ahmuty, valerie (vahmuty@kospharm.com)
Cc: Mary Parks (PARKSM)
Cc: Anne Pariser (PARISERA)
Cc: David Orloff (ORLOFFD)
Subject: Division Label for NDA 21-249

Valerie,

Attached is the final draft of the FDA package insert for this action.

No further negotiations for this package insert will occur prior to the mandated goal date of this application.

The Division needs the sponsor's agreement on this draft of the package insert for the application to move forward.

Accordingly the telephone conference with this Division scheduled for 3:00 PM today has been cancelled.

Don't hesitate to contact me with any questions/concerns.

Bill

APPEARS THIS WAY
ON ORIGINAL

Kos Pharmaceuticals, Inc.

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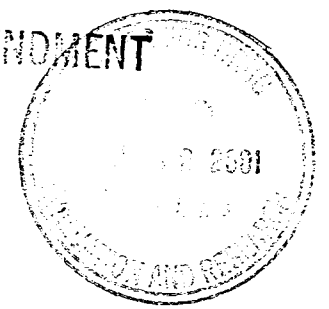
ORIGINAL

July 11, 2001

NDA ORIG AMENDMENT



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: Advicor™ NDA 21-249 (formerly known as Nicostatin™) N-000-BL
Submission of Revised Labeling for Consideration

Dear Dr. Orloff:

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

On July 09, 2001, Kos received an e-mail from FDA with revisions to the label previously proposed by Kos on June 26, 2001. Also on July 09, FDA, Kos, and DuPont representatives participated in a teleconference regarding the proposed labeling for Advicor, using the FDA version as the basis for the discussion. As agreed in that teleconference, Kos is submitting an e-mail response to FDA by close-of-business on July 11, and sending the formal submission (i.e., the archival and review copies) by FedEx. Our response contains the proposed final labeling and a justification document for those sections that differ from FDA's July 09 edited version. In support of this latter document, additional records for review are included for patient 08-005 in study MA-98-010407, whose medical record FDA has considered to possibly suggest a case of drug-induced myopathy.

A paper copy and a diskette with the MicroSoft Word electronic file for the proposed label are provided in a manila folder for the clinical reviewer. The blue archival folder contains a paper copy, PDF files for the justification document and patient information, and a Word file for the proposed label. 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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ORIGINAL

NDA ORIG AMENDMENT
N-000-BM

July 05, 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: Advicor™ NDA 21-249 (formerly known as Nicostatin™)
Submission of Patient Discontinuation Data by Previous Treatment Exposure for Study MA-99-010409 - CORRECTED TABLE

Dear Dr. Orloff:

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

On July 02, 2001, Dr. Anne Pariser of FDA requested that Kos provide the patient discontinuation data for the extension study MA-99-010409, categorized by previous exposure to Advicor and other treatments during participation in either of the two double-blind studies, MA-98-010406 and MA-98-010414. The information was provided by fax and FedEx on July 03. However, several typographic errors were found subsequent to that submission. The corrections are highlighted in the attached document through underlining of the changed information.

Paper review copies (clinical and archival) of this submission are provided in addition to a diskette with PDF (Adobe Acrobat) electronic files in the archival folder. Please note that the enclosed document was also faxed to Dr. Pariser and Mr. Koch on July 05.

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

NAT
07/10/2001

Reviewed
Summarized in
Complete NDA
review -
151
09-July-2001

Kos Pharmaceuticals, Inc.

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ORIGINAL

July 03, 2001

NEW CORRESP
N-000-C

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: Advicor™ NDA 21-249 (formerly known as Nicostatin™)
Submission of Patient Discontinuation Data by Previous Treatment Exposure for Study MA-99-010409

Dear Dr. Orloff:

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

On July 02, 2001, Dr. Anne Pariser of FDA requested that Kos provide the patient discontinuation data for the extension study MA-99-010409, categorized by previous exposure to Advicor and other treatments during participation in either of the two double-blind studies, MA-98-010406 and MA-98-010414. The information is provided in the enclosed document. Data are presented for Advicor vs. the other treatments combined, and for Advicor vs. Lovastatin, vs. Niaspan. The enclosed information also provides a correction to Table 7, page 14, of the second Safety Update to NDA 21-249 dated May 18, 2001. In Table 7, the overall number of discontinuations incorrectly showed ——→ instead of 38 (36%) discontinuations due to a coding error. (However, the number of discontinuations and percentages by category were correctly stated in Table 7.)

Paper review copies (clinical and archival) of this submission are provided in addition to a diskette with PDF (Adobe Acrobat) electronic files in the archival folder. Please note that the enclosed document was faxed to Dr. Pariser on July 03 to expedite fulfillment of her request.

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

Applicant called re errors in Amendment. Will submit corrected Amendment 151
7/05/01

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July 02, 2001

David Orloff, MD
Director, Division of Metabolism and
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Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

N 000 BM

ORIG AMENDMENT

Re: Advicor™ NDA 21-249 (formerly known as Nicostatin™)
Submission of 52-Week Efficacy Data for Study MA-98-010407

Dear Dr. Orloff:

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

On June 28, 2001, Dr. Anne Pariser and Mr. William Koch of FDA contacted Ms. Valerie Ahmuty of Kos to request the final efficacy data for study MA-98-010407. Summary data for LDL-C, HDL-C, total cholesterol and triglycerides through 52 weeks of therapy are provided in the enclosed tables. FDA also requested information regarding the doses received by patients throughout the study. The number of patients by dose is provided in a separate enclosed tabulation.

Paper review copies (clinical and archival) of this submission are provided in addition to a diskette with PDF (Adobe Acrobat) electronic files in the archival folder. Please note that the enclosed documents were faxed to Dr. Pariser on July 02 to expedite fulfillment of her request.

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

Results incorporated into Full NDA review
131
09-July-2001

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ORIGINAL

June 26, 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

NOVO BL
ORIG AMENDMENT

Re: Advicor™ NDA 21-249 (formerly known as Nicostatin™)
Submission of Revised Labeling for Consideration

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Advicor™ (formerly Nicostatin™), an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin. Although this correspondence uses the proposed tradename, Advicor™, the applicant acknowledges that use of this tradename is considered tentative until an approval letter is issued.

On June 06, 2001, Kos received via e-mail FDA's proposed revision to the product labeling that was submitted with the original NDA 21-249. On June 18, Kos e-mailed FDA a counter-proposal that was the basis for discussion between the parties during a teleconference later that afternoon. In the teleconference, Kos agreed to provide a justification for proposed differences in the Kos label version from the FDA's June 06 version. This June 26 (paper) submission contains the justification document and an updated version of the proposed labeling. Please note that the justification and proposed labeling were also provided to FDA by e-mail on June 26. Based on a conversation between Mr. William Koch of FDA and Ms. Valerie Ahmuty of Kos, no other electronic copy of these documents need to be submitted. Paper review copies are provided in a manila folder for the clinical reviewer and a blue archival 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, PhD
Director, Regulatory Affairs

Electronic Mail Message

Date: 6/18/01 4:36:17 PM
From: William C. Koch (KOCHW)
To: ahmuty, valerie (vahmuty@kospharm.com)
Subject: NDA 21-249, Advicor: REQUESTED INFO

Valerie,

I have the second labeling T-CON set up for:

June 26, 2001
12:30 PM
Phone: (301) 827-6379

Any conflicts with this time slot let me know!!

Attached is the infor requested at today's T-CON re:

ONE patient with myopathy

ELEVEN patients with AST, ALT or AST&ALT elevations >3 times ULN

Talk to You Soon!!

ill

APPEARS THIS WAY
ON ORIGINAL

Patient with myopathy:

MA-07 Patient With Myopathy

Week	CPK	Elevation	Dose	Contributing history
Patient 08-005				52 year old male with an extensive medical history, which includes arthromyalgia and muscular aches. At Week 52 the patient was diagnosed with "fibromyalgia". Also at Week 52 the patient was entered in the study extension and Nicostatin 2000/40 was continued. Approximately 1 week into the study extension the patient was discontinued due to an elevated CPK. The patient reported heavy yard work prior to the Week 52 retest, and complained of chest heaviness. An EKG, thallium stress test, and CPK isoenzymes were all normal. The patient's symptoms improved on Ultram, and CPK decreased on retesting.
Baseline	82		None	
Week 4	233	>normal	500/10 X 4 weeks	
Week 8	178		1000/20 X 4 weeks	
Week 8 retest	453	>normal	1500/30 X 2 weeks	
Week 12	149		2000/40 X 1 day	
Week 16	97		2000/40 X 4 weeks	
Week 28	151		2000/40 X 17 weeks	
Week 40	87		2000/40 X 28 weeks	
Week 52	796	>normal	2000/40 X 41 weeks	
Week 52 retest	6700	>10 X ULN	off study drug X 8 days	
Week 52 retest	94		off study drug X 2 weeks	
ET (extension)	108		off study drug X 6 weeks	

Patient (08-005) had CPK elevations 10 X ULN and was discontinued secondary to "fibromyalgia". Per Harrison's textbook of internal medicine, "...there are no laboratory abnormalities." in fibromyalgia. As myopathy was defined in the protocol as "...myalgia with CPK levels >10 X ULN...", patient 08-005 will be considered by this Reviewer as a case of myopathy.

AST and ALT Elevations >3 X ULN

The following patients were found to have AST, ALT, or AST and ALT elevations >3 X ULN:

Study MA-14

MA-14 Patients Experiencing Clinically Significant ALT, AST, or ALT and AST Elevations

Week	AST	ALT	Nicostatin dose	Contributing history
Patient 0414 (Nico/20):				55 year old male, history of colitis, benign prostatic hypertrophy (BPH), gout, and type 2 Diabetes Mellitus (DM). Experienced prostatitis at Week 16. Treated with Cipro X 17 days. Developed severe nausea and vomiting 4 days prior to Week 20, and therapy changed to Floxin. Completed study Week 20, and entered open-label, extension study (MA-09). Study medication was not restarted and patient was discontinued in MA-09.

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Baseline	25	33	None	
Week 4	27	34	500/20 X 4 weeks	
Week 8	25	33	1000/20 X 4 weeks	
Week 12	25	31	1500/20 X 4 weeks	
Week 16	27	32	2000/20 X 4 weeks	
Week 20	218	306	2500/20 X 4 weeks (completed)	
Week 20 retest	58	173	3 days off study medication	
Week 20 retest	30	65	9 days off study medication	
Open-label	20	28	Approx. 1 month off study med	
Patient 1203 (Nic0/20):				51 year old female, history of type 2 DM, suspected cholelithiasis, appendectomy, and tonsillectomy. Developed abdominal pain and was diagnosed with cholelithiasis/cholecystitis after 3 weeks on study medication. Treated with Cipro, Asic, Darvocet and Compazine. Study medication interrupted X 2 days, then resumed. Patient completed the study. The patient had clinically significant elevations in AST and ALT (Week 20) after cholelithiasis/cholecystitis diagnosed.
Baseline	25	35	None	
Week 4	25	29	500/20 X 4 weeks	
Week 8	37	41	1000/20 X 4 weeks	
Week 12	24	28	1500/20 X 4 weeks	
Week 16	25	34	2000/20 X 4 weeks	
Week 20	163	161	2500/20 X 4 weeks (completed)	
Week 20 retest	42	64	16 days off study medication	
Week 20 retest	27	32	5 weeks off study medication	

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Baseline	32	28	None
Week 4	102	118	20 X 4 weeks
Week 4 retest	69	89	20 X 5 weeks
Week 8	76	60	20 X 9 weeks
Week 8 retest	156	207	20 X 10 weeks
Week 8 retest	74	120	20 X 11 weeks
Week 12	55	69	20 X 13 weeks
Week 16	49	77	40 X 4 weeks
Week 20	35	44	40 X 8 weeks
Week 24	33	47	40 X 12 weeks
Week 28	45	53	40 X 16 weeks

APPEARS THIS WAY
ON ORIGINAL

Baseline	11	12	500/10 X 4 weeks	70 year old male, history of PVD, CAD, CABG, HTN and a blood transfusion. After Week 52, the patient continued in the extension study. The patient was discontinued from study medication 2 days later for elevated AST and ALT. Alk phos, LDH, and total and direct bilirubin were also increased. The patient complained of abdominal pain, anorexia, fatigue and dark urine, and a hepatitis panel was positive for hepatitis A. The patient was discontinued from the study.
Week 4	14	20	1000/20 X 4 weeks	
Week 8	20	22	1500/30 X 4 weeks	
Week 12	24	25	2000/40 X 4 weeks	
Week 16	13	21	2000/40 X 8 weeks	
Week 28	16	24	2000/40 X 20 weeks	
Week 40	18	28	2000/40 X 32 weeks	
Week 52	365	330	2000/40 X 44 weeks	
ET/extension	17	24	Off study drug X 3 weeks	

The McGraw-Hill Companies. Chapter 326: Relapsing Polychondritis and Other Arthritides , Fibromyalgia. [2001]. In Harrison's Online. [Online]. <http://www.harrisonsonline.com> ["fibromyalgia"] [2001, June 18].

APPEARS THIS WAY
ON ORIGINAL

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May 18, 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: Advicor™ NDA 21-249 (formerly known as Nicostatin™)
Submission of Second (8-Month) Safety Update and Revised Tabulations for MA-98-010414

Dear Dr. Orloff:

Please refer to our New Drug Application (NDA) Number 21-249, submitted September 21, 2000 for Advicor™ (formerly Nicostatin™), an antidyslipidemic fixed-combination drug product containing extended-release niacin and immediate-release lovastatin. Although this correspondence uses the proposed tradename, Advicor™, the applicant acknowledges that use of this tradename is considered tentative until an approval letter is issued.

Please find enclosed the second safety update to NDA 21-249. Like the original NDA and first (4-month) safety update, this second safety update is an electronic submission. The archival blue folder contains the electronic submission on CD and signed original paper copies of the cover letter and 356h form. Case report forms and case report tabulations are provided only in the electronic files. Paper review copies of the text of the safety update report are provided in a manila folder for the clinical reviewer and a black folder desk copy for the Regulatory Project Manager.

The format of this second safety update has been developed in accordance with requests from the clinical review group. Subsequent to the submission of the 4-month safety update on January 17, 2001, FDA requested additional information related to both the 4-month safety update and the integrated summary of safety in the original NDA (refer to telephone conversations on February 01 and 08 between FDA and Kos). On February 16, Kos submitted additional tabulations of adverse event (AE) and laboratory abnormality data (no data filters) to address FDA's requests. These additional tabulations integrated flushing data with AE data by body system; also, the format of the Serious Adverse Event (SAE) tabulations for individual studies was revised to present SAE terms by body system and not by case relationships. The February 16 submission was electronic and paper; however it was not electronically linked to the NDA.

In addition to incorporating the tabulation and format changes previously requested by FDA, this second safety update includes the following new information.

- Safety data for patients who completed 100 weeks (approximately two years) or terminated early in study MA-98-010407, the long-term, open-label safety and efficacy study

- Safety data for patients who completed 48 weeks (approximately one year) or terminated early in study MA-99-010409, a long-term open-label safety and efficacy study similar in design to the long-term open-label study MA-98-010407. Patients who elected to enroll in this study had participated in either of our two double-blind controlled studies

This submission also contains revised flushing tabulations for the double-blind, controlled study MA-98-010414 as noted in attachment 1, page 5 of our April 17, 2001 correspondence to this NDA regarding the lovastatin dose group for this study.

Since the guidance for electronic NDAs does not address format and structure for a second safety update, Kos consulted Dr. Randy Levin of CDER's electronic submission group. He advised that we structure the safety update into the same categories as provided for in the original NDA. Therefore, this second safety update has a stand-alone table of contents (up2toc.pdf) that is hypertext-linked to all sections of the update.

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

APPEARS THIS WAY
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April 17, 2001

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 18 2001
HFD-510

Re: Nicostatin™ NDA 21-249
Second response to the March 05, 2001 teleconference
1) Investigation into the three patients at center 07, Study MA-98-010414
2) Closure of issues related to the March 05, 2001 teleconference

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. Please also refer to the teleconference held between Kos and FDA on March 05, 2001, at FDA's request. A summary of the FDA comments and discussion was provided by facsimile to your office on March 09, 2001. Additionally, a response concerning the primary topic of discussion during the teleconference, i.e., the efficacy results of the lovastatin-alone group in the MA-98-010414 study, compared to historical results with lovastatin, was provided by fax on March 15 and submitted formally to the NDA on March 20, 2001.

As requested, Kos conducted an investigation regarding possible dispensing issues in Study MA-98-010414. Analysis of unused returned drug for the three patients at site 07 in study MA-98-010414 confirm that all three patients received the appropriate study medications. The full report of our investigation is provided in Attachment 1.

In our March 15/March 20 correspondence, Kos requested a teleconference to discuss any outstanding issues, in particular, any remaining concerns related to the lovastatin-alone group. During subsequent telephone conversations, Mr. William Koch has indicated to us that there do not appear to be any outstanding issues or additional follow-up requirements. This letter also requests confirmation that all issues are now closed and that no further information is required.

If there are any questions regarding this submission or if additional information is required, please contact me at 305-512-7007.

Sincerely,

Marvin F. Blanford

Marvin F. Blanford, PharmD
Vice President, Compliance

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April 17, 2001

David Orloff, MD
Director, Division of Metabolic 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
Response to Request by Dr. Sharon Kelly, Chemistry Reviewer
Stability Data for Lovastatin Reference Product Lot Used in Study MA-98-010414

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. Please also refer to the teleconference held between Kos and FDA on March 05, 2001, at FDA's request. A summary of the FDA comments and discussion was provided by facsimile to your office on March 09, 2001. Additionally, a response concerning the primary topic of discussion during the teleconference, i.e., the efficacy results of the lovastatin-alone group in the MA-98-010414 study, compared to historical results with lovastatin, was provided by fax on March 15 and submitted formally to the NDA on March 20, 2001.

On April 05, 2001, Dr. Sharon Kelly of FDA called Ms. Valerie Ahmuty of Kos to request stability data for the lot(s) used in the lovastatin-alone arm of Study MA-98-010414. The information requested is provided in the Attachment.

Only one lot of tablets was used in the lovastatin-alone arm of Study MA-98-010414. The bulk tablet lot number was 980174; the packaging lot number was 980174A. Tablets were packaged in amber blisters for use in the double-blind study. The tablets were matched in size and color to the Nicostatin 500/10 (mg niacin / mg lovastatin). The 10 mg of lovastatin was [redacted] tablet (P500/10). The report contains the initial release data for the tablets, the stability data, and information concerning the lovastatin raw material lot used.

If there are any questions regarding this submission or if additional information is required, please do not hesitate to contact me at 305-512-7051.

Sincerely,

David H. Warnock

David H. Warnock, PhD
Director, Regulatory Affairs

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ORIGINAL

April 17, 2001

David Orloff, MD
Director, Division of Metabolism and
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Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 18 2001
HFD-510

C
NEW CORRESP
NDA ORIG AMEND

Re: NDA 21-249, Fixed-combination of niacin extended-release and lovastatin
Proposed new tradename: Advicor

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.

Please refer also to the submission dated December 05, 2001, which proposed the new preferred tradename ——— and an alternative tradename, Advicor, to replace the original tradename for the fixed-combination drug that is the subject of this NDA.

Please refer also to the telephone conversation on April 06, 2001 between Mr. William Koch of your Division and myself, and to a subsequent teleconference on April 12, 2001 between representatives of your Division (Mr. Koch and Ms. Enid Galliers) and representatives of Kos (Dr. Marvin Blanford and myself). During these telecommunications Kos was informed that the Office of Postmarketing Drug Risk Assessment (OPDRA) has reviewed the proposed tradenames and has no objections to either name. Ms. Galliers informed Kos that the Division of Marketing, Advertising and Communications (DDMAC) has suggested that the name ——— may be too promotional. She also informed Kos that OPDRA will conduct a 90-day review for similarity to other trade names before an action letter on this NDA and that your Division will make the final decision on tradenames. We understand that the final decision will be communicated to Kos in the action letter for this NDA.

After further consideration of the tradename for the subject fixed-combination drug, Kos has decided to change the preferred tradename from ——— to Advicor. Following approval of the NDA, Kos plans to market the drug under this tradename.

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

Sincerely,

David H Warnock

David H. Warnock, PhD
Director, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

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ORIGINAL

March 20, 2001

David Orloff, MD
Director, Division of Metabolic and
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5600 Fishers Lane
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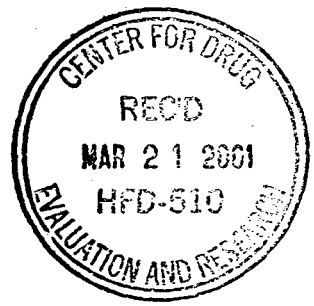

BM

NDA ORIG AMENDM

Re: Nicostatin™ NDA 21-249
Response to the March 05, 2001 Teleconference

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 March 15, 2001, Kos faxed the document enclosed in Attachment 1 of this submission to your office for review and comment. The document addressed the primary topic of discussion during the March 05, 2001 teleconference, i.e., the efficacy results of the lovastatin-alone group in the MA-98-010414 study, compared to historical results with lovastatin.

After the document was faxed to your office, we found a typographical error in Tables I and II and the cover letter, regarding the number of studies reviewed. There were 25 studies in our review, not 24. There are 26 reference articles provided in Attachment 2. These include the 25 studies and an independent meta-analysis by Kong et al. that confirms our findings.

As stated in the previous communications, we would like the opportunity to discuss the enclosed information with you as soon as possible, and request that a teleconference be initiated at your earliest convenience. If there are any questions regarding this submission or if additional information is required, please contact me at 305-512-7007.

Sincerely,

Marvin F. Blanford, PharmD
Vice President, Compliance

1S1
02-APR-2001 to
Corrections noted, to
be included in
full NDA review

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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March 15, 2001

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Re: Nicostatin™ NDA 21-249
Response to the March 05, 2001 Teleconference

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. Please also refer to the teleconference held between Kos and FDA on March 05, 2001, at FDA's request. A summary of the FDA comments and discussion was provided by facsimile to your office on March 09, 2001.

This submission addresses the primary topic of discussion during the teleconference, i.e., the efficacy results of the lovastatin-alone group in the MA-98-010414 study, compared to historical results with lovastatin. In response to this issue, Kos has prepared a detailed summary of study results based upon an extensive literature review of 24 published trials involving once-daily dosing of Mevacor® in nearly 6,000 patients.

Our conclusion from this review is the same as stated in the teleconference: the results from our studies are well within the range of efficacy results to be expected with lovastatin. We believe that you will find our attached review comprehensive and compelling.

In response to FDA's other questions concerning possible dispensing issues, Kos is conducting an investigation of this drug supply (specifically, the three lovastatin-alone patients at Site 7 in the MA-98-010414 study), and it thus far has not revealed any atypical findings. This investigation will be completed shortly and our complete findings will be provided to you at that time.

In the interim, we would like the opportunity to discuss the enclosed information with you as soon as possible, and request that a teleconference be initiated at your earliest convenience. If there are any questions regarding this submission or if additional information is required, please contact me at 305-512-7007.

Sincerely,

Marvin F. Blanford, PharmD
Vice President, Compliance

Kos Pharmaceuticals, Inc.

Attachment

A Comparative Analysis of the Effects of Lovastatin From Kos Nicostatin Protocols MA-98-010414 and MA-98-010406 and Mevacor® on LDL-C

Summary

A broad range of response to lovastatin based on individual study results is well documented in the literature. The reductions in low-density lipoprotein cholesterol (LDL-C) in the lovastatin treatment arms in the Nicostatin double-blind efficacy studies are completely consistent with what has been observed and reported in the literature for Mevacor. Consequently, we continue to believe that our studies demonstrate a superiority of Nicostatin over lovastatin by an amount equal to doubling the dose of lovastatin.

The point estimates for the treatment effect of lovastatin in Kos protocols MA-98-010414 (referred to below as 14) and MA-98-010406 (referred to below as 06) are not significantly different from the point estimates derived from a comprehensive review of published studies with Mevacor undertaken by Kos. The point estimates for the treatment effect on LDL-C of Mevacor administered once-daily in the evening, based on a review of 25 trials involving 5,855 patients are, for 20 mg: -25.3%, and for 40 mg: -29.8%. In the pooled analysis of Kos protocols 14 and 06, the point estimates for the lovastatin arms for these doses are, for 20 mg: -24.4% (95% Confidence Intervals [CI] -22.8, -26.0), and for 40 mg: -28.6% (95% CI -27.0, -30.2).

The treatment effect on LDL-C in the individual Kos studies 14 and 06 for given doses of lovastatin are also not different from what has been observed and reported with Mevacor. Even in the original Mevacor New Drug Application (NDA), a mean value of as low as -21% was reported with once daily in the evening dosing of Mevacor 40 mg. In another study in the original Mevacor NDA, a mean value of as low as -17% was reported with once daily in the evening dosing with 20 mg.

The estimated additional LDL-C reduction obtained when doubling the dose of Mevacor from the literature review in this analysis is 4.5 percentage points. It ranges as low as 2% in published studies with Mevacor. In the pooled analysis of the Kos protocols, this difference is 4.2 percentage points. In the individual studies 14 and 06 themselves, the difference obtained when doubling the dose of lovastatin is within the range reported in the Mevacor literature as well. Furthermore, closer inspection of the results of the 14 study show that both Nicostatin and lovastatin behaved as expected when doubling the dose, showing that the lovastatin formulation was not subpotent relative to Nicostatin.

Point Estimates of the Treatment Effect of Lovastatin 20 mg and 40 mg Once Daily

Numerous studies have evaluated the efficacy and safety of Mevacor administered once-daily in the evening. Following the teleconference of March 5, 2001 between Kos and the Food and Drug Administration, Kos conducted a MEDLINE search for prospective studies published in English in which Mevacor was administered as 20 mg or as 40 mg once daily in the evening for at least 4 weeks in order to ascertain the point estimates of the treatment effect on LDL-C. Both short-term and long-term (ie, up to one year) studies were included, as were both open label and double blind trials. Studies in which the dose was titrated and a result is not reported for either 20 mg or 40 mg (eg, in the Airforce/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS], where the average dose was somewhere between 20 mg and 40 mg) were excluded. In addition, the Mevacor package insert and the Summary Basis of Approval for Mevacor NDA #19-643 were reviewed for relevant study citations. In Mevacor NDA #19-643, three of the four studies evaluated the use of Mevacor given as 20 mg or 40 mg once daily in the evening. The individual studies and results for a total of 25 trials are included in Appendix I. A total of 5,855 patients receiving Mevacor (3,569 treated with 20 mg and 2,730 treated with 40 mg; some patients received both doses in one study) are included among those 25 studies identified and retrieved.

The overall point estimates for the Mevacor 20 mg and 40 mg dosing groups were then summarized by averaging the individual study mean data, weighted for sample size. These results are shown in Table I and

compared to the those reported in the pooled analysis of Nicostatin protocols 14 and 06. The Kos results reported for the pooled analysis are given as the least squares means as described in the Integrated Summary of Efficacy. The Table indicates that in the Kos studies, the point estimates of the treatment effect of lovastatin 20 mg and 40 mg once-daily in the evening are not significantly different from the expected reductions based on the published Mevacor literature.

Table I. Point Estimates of the Treatment Effect of Mevacor and Kos Lovastatin: Mean Percent Change from Baseline in LDL-C

Dose	Literature Review N = 24 Mevacor Studies	Kos Studies Pooled Analysis Protocols 14 and 06 (95% CI)
Lovastatin 20 mg	-25.3%	-24.4% (-22.8, -26.0)
Lovastatin 40 mg	-29.8%	-28.6% (-27.0, -30.2)

CI = Confidence Interval

The results of the literature review cited above for the 20 mg dose are also corroborated by an independent, published meta-analysis of the efficacy of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (Kong et al). In this analysis, summary efficacy results are reported for double-blind clinical trials with at least 25 patients per treatment arm for four HMG CoA reductase inhibitors. For Mevacor 20 mg, the estimated mean percent change in LDL-C in this independent meta-analysis was -24.9%.

Range of Treatment Effects Observed with Mevacor 20 mg and 40 mg Once Daily

There is considerable variability in the treatment effect of lovastatin from study to study (Appendix I). In one of the original Mevacor NDA studies (Lovastatin Study Group II 1986; patients with nonfamilial hypercholesterolemia), the mean reduction in LDL-C with 40 mg once daily in the evening in one treatment arm was -21%. In the other Mevacor NDA study (patients with familial hypercholesterolemia), the mean reduction in LDL-C with 20 mg lovastatin given once daily in the evening in one treatment arm was -17%. The range of results observed in the studies of Mevacor listed in Appendix I is compared in Table II below with the results of the Kos efficacy studies. This table shows that the results of both Kos studies for the mean percent changes from baseline in LDL-C for lovastatin 20 mg and for 40 mg are well within the range of reported values for Mevacor in the literature.

Table II. Range of Treatment Effects Observed With Mevacor and Kos Lovastatin 20 mg and 40 mg Once Daily in The Evening: Mean Percent Change from Baseline in LDL-C

	Literature Review N=24 Mevacor Studies		Kos Protocols 14 and 06	
	Minimum Value Observed	Maximum Value Observed	Minimum Value Observed	Maximum Value Observed
Lova 20 mg	-16.8%	-33%	-21.0%	-29.0%
Lova 40 mg	-21%	-36%	-24.4%	-33.5%

The data for the lovastatin groups in Kos protocols 14 and 06 are also presented below (Tables III, IV) by study visit with the standard error and 95% confidence intervals for the mean percent change from baseline in LDL-C.

In protocol 14, the mean results for lovastatin 20 mg and 40 mg are on the lower side of, but well within the range reported for Mevacor in the literature, as shown in Table II above. For 20 mg of lovastatin in protocol 14, the mean reductions in LDL-C were -21% and -21.9% . Inspection of the studies tabulated in Appendix I shows five Mevacor studies with point estimates of -22% or less with 20 mg, *including two of the original Mevacor NDA studies*. However, the data from protocol 14 are also consistent with a treatment effect of 20 mg of lovastatin of as much as -26.4%, based on the confidence intervals. For 40 mg of

lovastatin in protocol 14, the mean reduction in LDL-C was -24.4%. Inspection of the studies tabulated in Appendix I again shows three Mevacor studies with point estimates of 24% or less and two with a point estimate of 25% for 40 mg; *two of these studies were from the original Mevacor NDA*. The data from protocol 14 are, moreover, consistent with a treatment effect of 40 mg of lovastatin of as much as -28.9%, based on the confidence intervals.

The confidence intervals for the percent change in LDL-C with 20 mg of lovastatin in protocol 14 encompass the point estimates for this same dose of Mevacor shown in Table I. For 40 mg, the upper limit of the confidence interval (-28.9%) is only one percentage point short of the Mevacor point estimate of -29.8%.

Table III. Mean Percent Change From Baseline in LDL-C: Protocol MA-98-010414

Week	N	Dose	Mean % Change	Standard Error	95% CI
Baseline LDL-C	33		195.6 mg/dL		
4	31	10 mg	-18.8%	2.04	-14.6, -23.0
8	29	10 mg	-19.0%	1.56	-15.8, -22.2
12	29	20 mg	-21.9%	2.03	-17.5, -26.3
16	29	20 mg	-21.0%	2.62	-15.6, -26.4
20	29	40 mg	-24.4%	2.41	-19.9, -28.9

In protocol 06, on the other hand, the mean results are actually somewhat greater than anticipated based on the literature. For example, the range of results with 20 mg of lovastatin from protocol 06 is from -25.8% to -29.0%; both values exceed the Mevacor point estimates shown in Table I. For 40 mg of lovastatin, the range of results in protocol 06 is -31% to -33.5%; both values also exceed the Mevacor point estimates derived from the literature and shown in Table I.

Table IV. Mean Percent Change from Baseline in LDL-C: Protocol MA-98-010406

Week	N	Dose	Mean % Change	Standard Error	95% CI
Baseline LDL-C	61		185.6 mg/dL		
4	59	20 mg	-25.8%	1.34	-23, -29
8	58	20 mg	-27.6%	1.33	-25, -30
12	56	20 mg	-29.0%	1.16	-27, -31
16	56	40 mg	-31.0%	1.28	-28, -34
20	54	40 mg	-33.5%	1.32	-31, -36
24	53	40 mg	-32.2%	1.34	-30, -35
28	53	40 mg	-32.3%	1.50	-29, -35

In comparing the two Kos protocols, it should be noted that the confidence intervals for the percent change in LDL-C for both the lovastatin 20 mg and the lovastatin 40 mg doses overlap between the two studies, as can be seen by inspecting Tables III and IV. For example, the confidence intervals for the 20 mg dose in 14 range from -15.6 to -26.4; in 06 they range from -23 to -31. Furthermore, as mentioned above, pooling the Kos lovastatin data together yields point estimates of -24.4% with 20 mg, and -28.6% with 40 mg, which are not significantly different from the point estimates of -25.3% and -29.8% derived from the Mevacor literature (Table I.) The upper limits of the confidence intervals for the Kos lovastatin data in the pooled analysis are -26.0% for 20 mg and -30.2% for 40 mg.

Expected Difference in LDL-C Lowering When Doubling the Dose of Lovastatin

The literature shows that, on average, doubling the dose of lovastatin from 20 mg to 40 mg results in an additional 4.5% lowering of LDL-C (ie, from 25.3% to 29.8%; Table I). However, the range of results for this difference is from 2% to 12% within any given study of Mevacor in which both doses were evaluated. (See Appendix I.) Interestingly, in one of the original Mevacor NDA studies (Lovastatin Study Group II), one of the 40 mg once daily dosing groups produced mean LDL-C lowering (-21%) that was actually 4 percentage points *less* than one of the 20 mg once-daily dosing groups (-25%).

Inspection of Tables III, IV, and V shows that the results of the individual Kos studies, 14 and 06, and especially the pooled analysis, are quite consistent with the findings from the Mevacor literature in this regard.

For example, in protocol 14, the effect of doubling the dose from 10 mg to 20 mg between Weeks 8 and 12 was to decrease LDL-C by 2.9 additional percentage points (-19.0% to -21.9%). As noted in Appendix I, a 3 percentage points or less differential has been observed when doubling the dose of Mevacor in published reports (eg, Lovastatin Study Group II; CURVES 1998; Stein et al 1999). Similarly, the effect of doubling the dose from 20 mg to 40 mg between Weeks 16 to 20 was to decrease LDL-C by 3 additional percentage points (-21.0% to -24.4%).

In protocol 06, the effect of doubling the dose from 20 mg to 40 mg was to decrease LDL-C by 2 additional percentage points (as also reported in the CURVES trial) between Week 12 and 16 (ie, -29% to -31%). However, the difference is as great as 7.7% (comparing -25.8% at Week 4 to -33.5% at Week 20) in the same study.

In the pooled Kos analysis, the effect of doubling the dose of lovastatin from 20 mg to 40 mg was to decrease LDL-C by 4.2 additional percentage points. This value, of 4.2 percentage points, is again a number that is consistent with the figure of 4.5 percentage points derived from published Mevacor reports (ie, the difference between -25.3% and -29.8%. See Table I.).

The suggestion has been made that in Kos protocol 14, Nicostatin behaved as expected when doubling the dose of lovastatin, but that the lovastatin formulation did not. To evaluate this, the data from protocol 14 for the percent change in LDL-C are reproduced below.

Table V. LDL-C Observed Values and Mean % Change from Baseline: MA-98-010414

		Niaspan	Nicostatin/10	Nicostatin/20	Nicostatin/40	Lovastatin
Baseline		201.6 n=31	199.5 n=34	191.4 n=34	204.9 n=32	195.6 n=33
Week 4	Dose	500 198.6 -3.3%	500/10 156.2 -21.6%	500/20 135.5 -29.4%	500/40 134.0 -34.7%	10 157.5 -18.8%
Week 8	Dose	1000 188.8 -6.8%	1000/10 150.2 -24.7%	1000/20 129.2 -31.9%	1000/40 125.9 -37.8%	10 158.8 -19.0%
Week 12	Dose	1500 177.8 -12.2%	1500/10 137.0 -31.0%	1500/20 124.5 -34.9%	1500/40 114.3 -43.3%	20 151.7 -21.9%
Week 16	Dose	2000 171.8 -16.2%	2000/10 131.4 -33.7%	2000/20 117.6 -38.6%	2000/40 109.5 -45.6%	20 153.4 -21.0%
Week 20	Dose	2500 163.0 -19.7%	2500/10 127.4 -36.3%	2500/20 122.0 -36.4%	2500/40 107.2 -46.6%	40 146.4 -24.4%

Inspection of these results shows that when the lovastatin component of Nicostatin is doubled while the Niaspan component is held constant (for example, comparing the results with 1000/20 and 1000/40), comparing across study visits, the average additional reduction in LDL-C in the study is 6%. The range is 0.10% (in the 2500/10 to 2500/20 cells; -36.3% versus -36.4%) to 10.2% (in the 2500/20 to 2500/40 cells; -36.4% to -46.6%). When the lovastatin dose is doubled in the lovastatin arm, the additional reduction in LDL-C is 2.9% from Week 8 to Week 12, and 3.4% from Week 16 to Week 20. These values for the lovastatin group, ie, 2.9% and 3.4% additional reduction in LDL-C, are within the range of observed changes in the Nicostatin groups in the same study, and within the range of observed changes reported in the Mevacor literature. In addition, it should be noted that the comparison for the lovastatin arm is within-group; the comparisons of two Nicostatin doses are between-groups.

Since there are fewer data points with which to evaluate the effect of doubling the dose in the lovastatin group in protocol 14, another way of looking at this is to add the percent change in LDL-C for the lovastatin and Niaspan groups and compare the result to that observed with the equivalent Nicostatin dose at the same study visits. In this case, three independent groups are being compared. The results are almost exactly additive in every case (Table VI), and in two instances the sum of the Niaspan and lovastatin groups is numerically greater than the corresponding Nicostatin dosage strength. Therefore, the findings from the lovastatin group do not appear to be anomalous. The data are also not surprising given the fact that lovastatin from Nicostatin is biocquivalent to Mevacor.

Table VI. Niaspan and Lovastatin Groups and Their Sum Compared to Equivalent Nicostatin Dose

Week	Niaspan	Lovastatin	Sum of Niaspan + Lovastatin	Nicostatin
4	500 mg -3.3%	10 mg -18.8%	-22.1%	500/10 -21.6%
8	1000 mg -6.8%	10 mg -19.0%	-25.8%	1000/10 -24.7%
12	1500 mg -12.2%	20 mg -21.9%	-34.1%	1500/20 -34.9%
16	2000 mg -16.2%	20 mg -21.0%	-37.2%	2000/20 -38.6%
20	2500 mg -19.7%	40 mg -24.4%	-44.1%	2500/40 -46.4%

Conclusion

The point estimates of the treatment effect of lovastatin on LDL-C in the Kos protocols are completely consistent with published reports with Mevacor. There is no evidence that the results are anomalous; in fact, in the pooled analysis of the Kos protocols, the point estimates for the reduction in LDL-C with 20 mg and 40 mg are almost identical to those derived by a comprehensive survey of the literature. The results of the pivotal efficacy studies with Nicostatin clearly demonstrate superiority over lovastatin by an amount equal to doubling the dose of lovastatin.

APPEARS THIS WAY
ON ORIGINAL

Appendix I: Published Lovastatin Studies Using Once-Daily Dosing of 20 mg or 40 mg in the Evening

Study	Study Design	# Pts. On Lovastatin	Mean % change in LDL-C 20 mg QD	40 mg QD	Delta
Mevacor Original NDA Studies or Studies Cited in the Mevacor Package Insert					
Lovastatin Study Group II 1986	Non FH*	20		-21%	
		22	-25%	-31%	
		21	-22%		
Havel et al 1987	FH*	21		-27%	
		20	-17%	-25%	
		20	-19%		
Davignon et al 1986	vs. probucol*	46		-32%	
EXCEL 1991	longterm	1,642/1,645	-24%	-30%	+6
Other Mevacor Studies Evaluating Both 20 mg QD & 40 mg QD in the Evening in the Same Study					
Farmer et al 1992	vs. simvastatin	137/134	-25.4	-31.2	+5.8%
Lovastatin Pravastatin Study Group 1993	vs. pravastatin	339	-28%	-33%	+5%
CRISP 1994	elderly	144/145	-24%	-28%	+4%
Lambert et al 1996	pediatric study	18/15	-24%	-36%	+12%
CURVES 1998	vs. atorvastatin	16/16	-29%	-31%	+2%
Stein et al 1999	pediatric study	63 (Period I) 61 (Period II)	-24%	-27% -25%	+3%

*Original Mevacor NDA studies

Continued....

Appendix I Continued

Study	Study Design	# Pts. On Lovastatin	Mean % change in LDL-C 20 mg QD	40 mg QD	Delta
Studies Evaluating Single Doses of Mevacor, Either 20 mg QD or 40 mg, QD in the Evening					
Pan et al 1990	healthy men	20		-21.6	
Kannel et al 1990	open label	488	-27%		
McPherson et al 1992	vs. pravastatin	67 (Week 4) 67 (Week 8)	-30% -28%		
Wallace et al 1995	open label	36 (Week 6) 36 (1 Year)	-33% -31%		
Vacek et al 1995	vs. niacin	25	-25%		
Weir et al 1996	vs. pravastatin	210		-27.9%	
Berger et al 1996	vs. fluvastatin	134	-27.6%		
Martinez et al 1996	FH	14 (Week4) 14 (Week 12)		-22.1% -30.3%	
Davidson et al 1997	vs. atorvastatin	191	-27%		
Hanes et al 1997	organ transplant	18	-22.7%		
Fong et al 1997	African Amer	22	-20%		
Gholami et al 1998	vs. fenofibrate	16 (Month 1) 16 (Month 3)	-29.5% -25%		
Crespo et al 1999	vs. policosanol	26	-16.8%		
Herrington et al 1999	post menopause	24	-30%		
Gentile et al 2000	vs. other statins	80	-21%		

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APPEARS THIS WAY
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FAX TRANSMISSION COVER SHEET

Date: *March 09, 2001*

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

Fax: *301-443-9282*

Re: *Bullet Point Summary of Teleconference held on March 05, 2001*

Sender: *Valerie Ahmuty*

THIS FAX CONSISTS OF 4 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 of the teleconference held on March 05, 2001 regarding the current review status of the Nicostatin™ NDA 21-249.

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

APPEARS THIS WAY
ON ORIGINAL

Teleconference Bullet-Point Summary

Type of Meeting: Teleconference requested by FDA - see faxed confirmation of teleconference dated February 28, 2001

Product: Nicostatin™ NDA 21-249

Date and Time of Call: Monday, March 05, 2001, approximately 1:00 to 1:45 PM

FDA Participants and Titles: (Alphabetical)
Hae-Young Ahn, PhD, Biopharmaceutics Team Leader
Indra Antonipillai, PhD, Pharmacology Reviewer
Sang Chung, PhD, Biopharmaceutics Reviewer
Sharon Kelly, PhD, Chemistry Reviewer
William Koch, RPh, Regulatory Project Manager
Joy Mele, MS, Mathematical Statistician, Biometrics 2
David Orloff, MD, Division Director
Mary Parks, MD, Acting Clinical Team Leader
Anne Pariser, MD, Clinical Reviewer

Kos Participants and Titles: (Alphabetical)
Marijke Adams, Director of Clinical Pharmacology
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
Rosemary Evans, MD, Director of Clinical Research
Mark McGovern, MD, Vice President of Medical Affairs
Phillip Simmons, MS, Associate Director of Biostatistics
David Warnock, PhD, Director of Regulatory Affairs

DuPont Attendee and Title: Kim Gilchrist, MD, MBA, Executive Director of Health Outcomes Research

Meeting Objectives:

The stated purpose of the meeting was "clarification of general biopharmaceutics issues" (see FDA fax confirming the teleconference, dated February 28, 2001).

Summary of FDA Comments:

1. Dr. Orloff noted that their review has resulted in concerns relating to the results of the lovastatin control arms in the clinical studies, in particular, study MA-98-010414, referred to as the -14 study.

2. The stated criteria for approval of the Nicostatin NDA was that a 5 to 7% increase in LDL lowering should be seen with the combination product over the same lovastatin-alone dose, that is, the same as doubling a statin dose. (Note: While concurring with the statement in principle, Kos added that the reported values for this range are variable. This is the reason to include a lovastatin-only group as an internal control in the studies.)

3. However, the lovastatin-alone arms of the two pivotal studies did not produce LDL lowering levels as predicted historically, especially in the -14 study. Additionally, the LDL lowering effects did not increase as expected with lovastatin dose and were "flat" as the dose increased from 10 to 40 mg of lovastatin. FDA acknowledged that Kos also made this observation in the Integrated Summary of Efficacy.

4. The Nicostatin results "behaved" as expected, i.e., the difference between two Nicostatin doses where the Niaspan component is held constant and the lovastatin dose is doubled, gives a LDL result as expected. However, the lovastatin-alone results for LDL were lower than expected. In addition, the results for three patients in the lovastatin arm of the -14 study at Site 07 appeared to be more in-line with results expected from administration of Nicostatin than lovastatin-alone. FDA requested Kos look to see if a dispensing problem may have occurred.

5. Dr. Orloff concluded by stating that the Company needs to provide the Agency with a basis for resolving its concerns about the lovastatin-alone treatment arms. He noted that a dissolution comparison alone would not suffice.

Summary of Discussion

1. Kos agreed that the lovastatin-alone LDL lowering results seen in the -14 study are slightly less than would have been expected based on typical or average experience from historical reports/literature. However, the data from the MA-98-010406 study are slightly more than expected, and in the pooled analysis they come out exactly as expected. FDA noted that they had not reviewed the pooled efficacy data, and would need to look further at these.

2. Dr. McGovern briefly reviewed his experience with both pravastatin and lovastatin, which are equipotent. He considers the data from the -14 study to be within the scope of what occurs in clinical trials of this nature and that there was nothing anomalous about the results from the -14 study based on his experience and knowledge of the literature.

3. Kos agreed to look in detail at the records for the three patients in the -14 study, Site 7, that FDA cited as possibly involved in a dispensing problem, and report the findings back to FDA.

4. Kos agreed to address the concerns expressed by FDA in this conference call and respond as soon as possible.

APPEARS THIS WAY
ON ORIGINAL

Kos Pharmaceuticals, Inc.

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February 28, 2001

David Orloff, MD
Director, Division of Metabolic 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 Dissolution Information

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 February 27, 2001, Dr. Sang Chung, the Biopharmaceutics Reviewer, called to request additional information regarding the review of the biopharmaceutics section of the NDA. His requests followed by our responses are provided below and in the enclosures with this correspondence.

1. **Dr. Chung requested the raw data that were used to create Figures 1 and 2 on page 29 of the 97/07 report (volume 2 of the Biopharmaceutics section paper review copy). These figures present comparative dissolution data for niacin from 'Niaspan®' (niacin ER) tablets and Nicostatin tablets, and lovastatin from Mevacor and Nicostatin tablets.**

   The requested data are provided in the enclosed tabulations.

2. **Dr. Chung noted that the dissolution method for lovastatin in Nicostatin tablets, which is USP apparatus 1 at — RPM, is different from the Mevacor® dissolution method (apparatus 2 at 50 RPM). He asked for the rationale for not using the lovastatin tablets USP method.**

   The composition of Nicostatin, which is ——————— (——————— was the major factor in determining the dissolution method for lovastatin. The ——— caused adhesion of tablets to the paddles during attempts to use the USP lovastatin tables method (apparatus 2). Thus, the USP apparatus 1 (basket) method was selected to test the dissolution of lovastatin from Nicostatin. The proposed dissolution method for lovastatin was briefly discussed with Dr. Hae Young Ahn immediately following the Nicostatin pre-NDA meeting; Dr. Ahn agreed

that the apparatus 1 method is appropriate for Nicostatin.

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

Sincerely,

David H Warnock

David H. Warnock, PhD
Director, Regulatory Affairs

APPEARS THIS WAY
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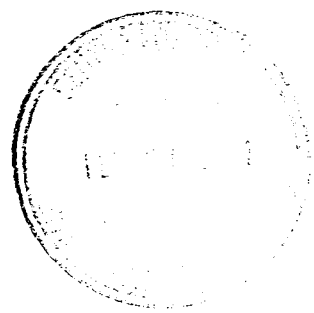
February 16, 2001



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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
Response to Dr. Anne Pariser's request for additional data presentations and table format changes for safety information

Dear Dr. Orloff:

Please refer to Kos Pharmaceuticals, Inc.'s 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 telephone conversations on February 01 and 08, 2001, additional tabular presentations of safety data and changes in table format related to information presented in the NDA Integrated Summary of Safety and/or the 4-Month Safety Update were requested by Dr. Anne Pariser, the lead clinical reviewer. We believe the enclosed tabulations provided fully address her requests. Introductory information regarding the tabulations is provided immediately before the List of Tables; the tables are otherwise self-explanatory.

A CD containing the electronic documents (Adobe PDF files) is provided in the archival copy (blue jacket). The List of Tables for this submission is linked to the tabular presentations in this submission. We believe this submission does not require changes to the overall NDA table of contents at this time and therefore a new electronic NDA table of contents is not included with the CD. Paper copies of the cover letter, 356h form, and tabular presentations are provided in the clinical review copy (manila jacket) as well as the archival copy. A paper desk copy (black folder) is also provided for Mr. William Koch, the Regulatory Project Manager.

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE