CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-249

APPROVAL LETTER

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:

Please refer to your new drug application (NDA) dated September 21, 2000, received September 22, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advicor (niacin extended-release and lovastatin) Tablets, 500mg/20mg, 750mg/20mg, and 1000mg/20mg.

We also refer to the Division letter of November 16, 2001, granting a tentative approval of this application subject to a period of exclusivity protection for the listed reference product which expires December 15, 2001.

This new drug application provides for the use of Advicor (extended-release niacin and lovastatin) Tablets as a convenience product for the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson 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.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. The period of exclusivity protection for the listed reference product upon which you based your application has expired. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted September 12, 2001, immediate container and carton labels submitted November 13, 2001). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-249." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call 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

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/s/

David Orloff
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-249

APPROVABLE LETTER

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
14875 Northwest 77th Avenue
Suite 100
Miami Lakes, Florida 33014

Dear Dr. Warnock:

Please refer to your new drug application (NDA) dated September 21, 2000, received September 22, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advicor (niacin extended release and lovastatin) Tablets, 500mg/20mg, 750mg/20mg, and 1000mg/20mg.

We acknowledge receipt of your submissions dated October 9, November 2, and December 5, 2000, and January 17, 23, and 31, February 14 (2), 16, and 28, March 20, April 17 (3), May 18, June 26, and July 2, 3, 5, 11, 16, and 19, 2001.

This new drug application provides for the use of Advicor 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.

We have completed the review of this application, as amended, and it is approvable. During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections of the manufacturing facilities are required before this application may be approved.

In addition, please submit mock-ups of immediate container labels for all container sizes with the following revisions:

- insert an image of the company logo in place of the word "LOGO."

- describe strength using "mg" after both numbers; i.e., 500mg/20mg, 750mg/20mg, and 1000mg/20mg.

- express storage temperature as "°C" and "°F" instead of [redacted] and [redacted]" as was originally submitted in the *.pdf* file.

- provide mock-ups of the immediate container labels for the 90 count presentation in 200 cc bottles for all three strengths.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you have regarding your new drug. 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.

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

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.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

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

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.

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.

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.

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

Please note that since only 12 months of stability data at 25°C/60%RH were presented for the following package configurations, an eighteen-month expiry period is granted:

- 30 count in a 90 cc bottle for all three strengths
- 180 count in a 200 cc bottle for the 500mg/20mg strength
- 180 count in a 325 cc bottle for the 750mg/20mg and the 1000mg/20mg strengths.

Twenty-four months expiry is granted for the 90 count presentation in 200 cc bottles for all three strengths.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

One of the listed reference drug products upon which you base your application is subject to a period of exclusivity protection, therefore, under section 505(c)(3) of the Act we cannot approve your application until the exclusivity period has expired, i.e., on December 15, 2001.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call 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

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/s/

David Orloff
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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:

Please refer to your new drug application (NDA) dated September 21, 2000, received September 22, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advicor (niacin extended-release and lovastatin) Tablets, 500mg/20mg, 750mg/20mg, and 1000mg/20mg.

We acknowledge receipt of your submissions dated September 12 and 27, October 4 and November 9, 2001. Your submission of September 12, 2001, constituted a complete response to our July 20, 2001, action letter.

This new drug application provides for the use of Advicor (niacin extended-release 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.

We have completed the review of this application, as amended, and have concluded that based upon the information you have presented to date, the drug product is safe and effective for use as recommended in the agreed upon draft labeling (enclosed text of package insert submitted September 12, 2001, and submitted November 9, 2001, text for immediate container and carton labels). Accordingly, the application is tentatively approved under 21 CFR 314.105. This determination is contingent upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in manufacturing and testing of the drug product) and is, therefore, subject to change on the basis of new information that may come to our attention.

The listed reference drug product upon which you base your application is subject to a period of exclusivity protection and therefore final approval of your application under section 505(c)(3) of the Act (21 U.S.C. 355(c)(3)) may not be made effective until the period has expired, i.e., December 15, 2001.

Upon agency request, submit an amendment to this application identifying changes, if any, in the conditions under which your product was tentatively approved. This information should include updated labeling, chemistry, manufacturing and controls data and a safety update.

Failure to submit any such amendment requested by the Agency will prompt a review of the application that may result in rescission of the tentative approval letter.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

An expiry period of 24 months is granted for all packaging configurations.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Any significant change in the conditions outlined in this new drug application requires Agency review before final approval may be granted.

Prior to the issuance of a final approval letter by the Agency, your product is not deemed approved and will not be included in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list published by the Agency. If you believe that there are grounds for issuing the final approval letters prior to December 15, 2001, you should amend your application accordingly.

The drug product may not be legally marketed until you have been notified in writing that the application is finally approved.

If you have any questions, call 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

ENCLOSURE

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/s/

David Orloff
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