CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-249

CHEMISTRY REVIEW(S)

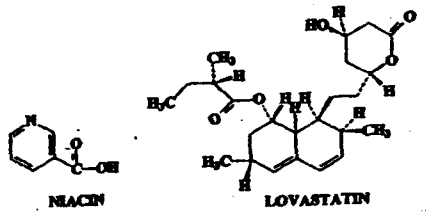
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 21-249
CHEMISTRY REVIEW #: 1 DATE REVIEWED: 07-19-01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	09-21-00	09-22-00	10-02-00
AMENDMENT	02-14-01	02-15-01	
AMENDMENT	04-17-01	04-18-01	
AMENDMENT	07-16-01	07-17-01	

NAME & ADDRESS OF APPLICANT: Kos Pharmaceuticals, Inc.
1001 Brickell Bay Drive
25th Floor
Miami, FL 33131

DRUG PRODUCT NAME
Proprietary: Nicostatin (tentative) / Advicor
Nonproprietary/Established/USAN: Niacin/Lovastatin
Code Name/#: Nicostatin
Chem.Type/Ther.Class: Vitamin, HMG-CoA Red. Inhibitor
ANDA Suitability Petition / DESI / Patent Status: N/A
PHARMACOLOGICAL CATEGORY/INDICATION: Lipid lowering agent
DOSAGE FORM: Tablets, ER Niacin — IR Lovastatin —
STRENGTHS: 500/20, 750/20, 1000/20 mg (Niacin/Lovastatin)
ROUTE OF ADMINISTRATION: Oral DISPENSED: Rx
SPECIAL PRODUCTS: NO
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:



Nicotinic acid: $C_6H_5NO_2$; Mol.Wt. 123.11, pyridine-3-carboxylic acid, niacin.
Lovastatin: $C_{24}H_{36}O_5$; Mol.Wt. 404.55; mevinolin, monacolinK, 6α methyl compactin.

CONCLUSIONS & RECOMMENDATIONS:
From the Chemistry perspective, the application is Not Approvable. EES issued an overall Withhold decision for this application based on numerous FDA 483 issues. Minor deficiencies in this review are noted. See Draft Deficiencies Letter.

cc:
Org. NDA 21-249
HFD-510/Division File
HFD-510/SKelly, SMoore
HFD-510/WKoch

APPEARS THIS WAY
ON ORIGINAL

Sharon Kelly, Review Chemist

NA

SUPPORTING DOCUMENTS: DMF

DMF	Subject	Holder	Status	Rev. Date	Letter Date
[redacted]			Adequate	May 4, 2000	May 17, 2000
			Adequate	March 6, 2000	May 10, 2000
			USP Product		May 26, 1999
			Adequate	July 16, 2001	March 3, 1999
			Adequate	July 16, 2001	March 3, 1999
			Adequate	May 29, 2001	March 3, 1999
			Adequate	Feb. 10, 2000	May 6, 1998
			Adequate	Sept. 12, 2000	August 16, 1999
			Adequate	Sept. 10, 1997	February 12, 1999
			Adequate	July 19, 2001	August 31, 1999
			Adequate	Dec. 4, 2000	August 27, 1999
			Adequate	Aug. 11, 2000	June 12, 2000
			Adequate	May 24, 2000	February 5, 1999
			Adequate	Sept. 29, 1994	November 1, 1999

SUPPORTING DOCUMENTS: NDA

20-381	Niaspan	Kos Pharmaceticals, Inc.	Approved July 29, 1997

RELATED DOCUMENTS (if applicable):
IND —— for Nicostatin

CONSULTS: Biopharm (for dissolution specifications); OPDRA (for labeling); EER

REMARKS/COMMENTS:
The applicant proposed a two year expiry period on all packaging configurations, and to support this expiry period, updated stability data was received on February 14, 2001.
N 000 BC.
Two years is granted for tablets packaged into ———— since 18 months of stability data at 25°C/60%RH is presented.
Two years is granted for the 90 count in the 200 cc bottle size, since 18 months of stability data at 25°C/60%RH is presented.
Eighteen months is granted for the following packaging configurations- 30 count in 90 cc, 180 count in 200 cc, 180 count in 325 cc since only 12 months of stability data at 25°C/60%RH is presented.

This NDA application received an NA due to a withhold recommendation from EES. Most of the CMC site deficiencies observed in the FDA-483 were not evident in the NDA submission. When the applicant adequately responds to the FDA-483, this application can receive an AP recommendation based on CMC issues.

SUMMARY:

Kos Pharmaceuticals, Inc. (Kos) has developed a single-tablet, oral solid-dose, fixed-combination product comprised of a niacin extended-release (ER) [redacted] with immediate-release lovastatin. The working name of the product is Nicostatin for the treatment of dyslipidemia. The niacin [redacted] in Nicostatin are equivalent to Niaspan, niacin ER tablets (NDA 20-381, approved July 28, 1997). The niacin ER [redacted] Four different tablet strengths of Nicostatin were formulated for use in clinical development: 500/10, 500/20, 750/20, and 1000/20. The Nicostatin 500/20, 750/20, and 1000/20 tablet strengths are proposed for commercial use.

The Niacin USP [redacted]; and the Lovastatin USP [redacted] The niacin [redacted] tablets are manufactured by Kos in Edison, NJ, and [redacted] at either Kos in Edison, NJ or [redacted] There are no unsatisfactory CMC issues regarding the two drug substances. There are no unsatisfactory CMC issues regarding the manufacture of the drug product; however, cGMP issues were identified by EES and an FDA 483 was issued.

Appropriate stability studies are being performed on large-scale batches of Nicostatin tablets from the [redacted] proposed [redacted] sites and [redacted] at the proposed [redacted] The initial proposed expiry period is [redacted] months, however, insufficient stability data is available to grant [redacted] months for all strengths.

filename: 21249#00

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/s/

Sharon Kelly
7/20/01 10:53:26 AM
CHEMIST

Paper copy signed 7/20/01

Stephen Moore
7/20/01 11:01:19 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 21-249
CHEMISTRY REVIEW #: 2 DATE REVIEWED: 10-30-01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	09-21-00	09-22-00	10-02-00
AMENDMENT	02-14-01	02-15-01	
AMENDMENT	04-17-01	04-18-01	
AMENDMENT	07-16-01	07-17-01	
AMENDMENT	09-12-01	09-17-01	

NAME & ADDRESS OF APPLICANT: Kos Pharmaceuticals, Inc.
1001 Brickell Bay Drive
25th Floor
Miami, FL 33131

DRUG PRODUCT NAME
Proprietary: Advicor
Nonproprietary/Established/USAN: Niacin/Lovastatin
Code Name/#: Nicostatin
Chem.Type/Ther.Class: Vitamin, HMG-CoA Red. Inhibitor
ANDA Suitability Petition / DESI / Patent Status: N/A
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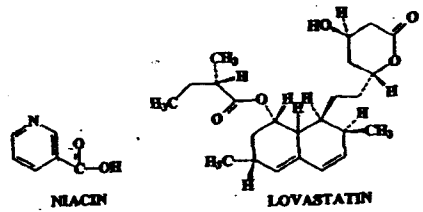
ROUTE OF ADMINISTRATION: Oral DISPENSED: Rx
SPECIAL PRODUCTS: NO
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:



Nicotinic acid: $C_6H_5NO_2$; Mol.Wt. 123.11, pyridine-3-carboxylic acid, niacin.
Lovastatin: $C_{24}H_{36}O_5$; Mol.Wt. 404.55; mevinolin, monacolinK, 6α methyl compactin.

CONCLUSIONS & RECOMMENDATIONS:
The September 12, 2001 amendment N 000 AZ supplies satisfactory updated stability information for all bottle configurations. From the Chemistry perspective, this NDA can be approved. See comment to be communicated to the sponsor in the stability section.

cc:
Org. NDA 21-249
HFD-510/Division File
HFD-510/SKelly, SMoore
HFD-510/WKoch

Sharon Kelly, Review Chemist

AP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Kelly
10/30/01 05:42:57 PM
CHEMIST

paper copy signed Oct. 30, 2001.

Stephen Moore
10/30/01 06:10:45 PM
CHEMIST

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21249/000** Priority: **4S** Org Code: **510**
Stamp: **22-SEP-2000** Regulatory Due: **17-NOV-2001** Action Goal: District Goal: **23-MAY-2001**
Applicant: **KOS PHARMS**
801 BRICKELL AVE STE 1006
MIAMI, FL 33131

Brand Name: **ADVICOR (NIACIN ER/LOVASTATIN)**
Established Name:
Generic Name: **NIACIN ER/LOVASTATIN**
Dosage Form: **EXT (EXTENDED-RELEASE TABLET)**
Strength: **500/20, 750/20, 1000/20**

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

Overall Recommendation:
ACCEPTABLE on 06-AUG-2001by J. D AMBROGIO(HFD-324)301-827-0062
WITHHOLD on 19-JUL-2001by J. D AMBROGIO(HFD-324)301-827-0062

Establishment: [redacted] DMF No:
AADA No:

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

Establishment: [redacted] DMF No:
AADA No:

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

Establishment: [redacted] DMF No:
AADA No:

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

ESTABLISHMENT EVALUATION REQUEST

Reason: **DISTRICT RECOMMENDATION**

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

DMF No:
AADA No:

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

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

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

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-AUG-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: [redacted]

DMF No:
AADA No:

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

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**

Responsibilities: [redacted]

ESTABLISHMENT EVALUATION REQUEST

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment [redacted] DMF No:
AADA No:

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

Establishment: [redacted] DMF No:
AADA No:

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

Establishment: [redacted] DMF No:
AADA No:

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

Establishment: [redacted] DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities:

ESTABLISHMENT EVALUATION REQUEST

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

APPEARS THIS WAY
ON ORIGINAL