CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-078

CHEMISTRY REVIEW(S)

2/12/08

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
CDER, Office of New Drug Quality Assessment
Mail Room 2562
10903 New Hampshire Ave.
Silver Spring, Maryland 20993
(301) 796-1679
(301) 796-9747 (FAX)

MEMORANDUM

DATE: 11-FEB-2008

FROM: John C. Hill, Ph.D., CMC Reviewer

THROUGH: Ali Al-Hakim, Ph.D., Chief, Division II, DPA-I

TO: Kati Johnson, NDA 22-078 File

SUBJECT: NDA 22-078; Establishment Inspection Results and Recommendation on Approvability

Establishment Evaluation

The establishment inspection was completed after Chemistry Review #2 was signed-off in DFS. The overall recommendation from the Office of Compliance remained "pending" at that time. Since then, the Establishment Evaluation Report (EER) has been issued. Per the Establishment Evaluation Summary Report dated February 11, 2008, the overall recommendation form the Office of Compliance is "acceptable".

Recommendation and Conclusion on Approvability of NDA 22-078

There are no outstanding CMC concerns for NDA 22-078. From a Chemistry standpoint, the overall recommendation for NDA 22-078 is "approval".

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT Application: NDA 22078/000 Action Goal:
Stamp: 17-APR-2007 District Goal: 19-DEC-2007
Regulatory Due: 17-FEB-2008 Brand Name: SIMCOR
Applicant: ABBOTT LABORATORIES Estab. Name: NO
CITY, , XX Generic Name: NIACIN/SIMVASTATIN
4S Priority: 510 Dosage Form: (TABLET)
Org Code: Strength:
500/20,750/20,1000/20 Application Comment: FDA Contacts: S. GOLDIE
301-796-2055 , Project Manager J. HILL
301-796-1679 , Review Chemist S. MOORE
301-796-1718 , Team Leader ----------
---------- Overall Recommendation:
ACCEPTABLE on 11-FEB-2008by S. ADAMS (HFD-325)301-796-3193 ----------
---

Establishment: CFN [redacted] FEI [redacted]

[redacted] DMF No: AADA:
Responsibilities: [redacted]
[redacted] Profile: CTL
OAI Status: NONE EMilestone Name Date Type Insp. Date
Decision & Reason Creator ---------- ---------- ------ ---
---------- ---------- --------- SUBMITTED TO OC 09-MAY-
2007
MOOREST OC
RECOMMENDATION 10-MAY-2007 ACCEPTABLE
FERGUSONS BASED ON
PROFILE ----------
---------- Establishment: CFN [redacted] FEI
[redacted] DMF No:
AADA: Responsibilities:
Profile: CSN
OAI Status: NONE Estab. Comment: ADDRESS GIVEN FOR SITE 1:

DETAIL REPORT (on 09-MAY-2007 by S. MOORE () 301-796-1718) Milestone Name Date Type Insp. Date Decision & Reason Creator

SUBMITTED TO OC 09-MAY-2007
MOOREST OC RECOMMENDATION 10-MAY-2007 ACCEPTABLE
ADAMSS BASED ON PROFILE

Establishment: CFN [redacted] FEI [redacted]

[redacted] DMF No: [redacted]

AADA: Responsibilities: [redacted]

[redacted] Profile: CTL OAI Status: NONE EMilestone Name Date Type Insp. Date Decision & Reason Creator

SUBMITTED TO OC 09-MAY-2007
MOOREST SUBMITTED TO DO 10-MAY-2007 10D
FERGUSONS DO RECOMMENDATION 17-MAY-2007
ACCEPTABLE MWOLESKE
INSPECTION A GMP INSPECTION WAS CONDUCTED 5/7-9/2007. THE INSPECTION COVERED THE QUALITY AND LABORATORY SYSTEMS. THE INSPECTION FOUND NO SIGNIFICANT OBJECTIONABLE CONDITIONS AND AN FDA 483 WAS NOT ISSUED HOWEVER THE INVESTIGATOR DID VERBALLY RELAY CONCERNS REGARDINGA METHOD TRANSFER AND DOCUMENTATION OF THEIR ROORT CAUSE ANALYSIS FOR INVESTIGATIONS OF UNEXPECTED EVENTS. THE INSPECTION WILL BE CLASSIFIED AS NO ACTION INDICATED (NAI)AND PROFILE CLASS CTL WILL BE JUDGED ACCEPTABLE. THE DISTRICT'S RECOMMENDATION IS ACCEPTABLE. OC RECOMMENDATION 17-MAY-2007
ACCEPTABLE FERGUSONS
DISTRICT RECOMMENDATION

Establishment: CFN [redacted]
FEI [redacted]

[redacted] DMF No:
AADA: Responsibilities: [redacted] Profile:
TTR OAI Status: NONE EMilestone Name
Date Type Insp. Date Decision & Reason Creator

- SUBMITTED TO OC 09-MAY-2007
MOOREST OC RECOMMENDATION 10-MAY-2007 ACCEPTABLE
FERGUSONS

APPEARS THIS WAY
ON ORIGINAL

DETAIL REPORT BASED
ON PROFILE ----------
---------- Establishment: CFN [redacted] FEI
[redacted]
[redacted] [redacted] DMF No:
AADA: Responsibilities: [redacted]
[redacted] Profile: CTL
OAI Status: NONE EMilestone Name Date Type Insp. Date
Decision & Reason Creator ---------- ---------- ---------- ------ ---
---------- ---------- SUBMITTED TO OC 09-MAY-
2007 MOOREST OC
RECOMMENDATION 10-MAY-2007 ACCEPTABLE
FERGUSONS BASED ON
PROFILE ----------
---------- Establishment: CFN 1054801 FEI
1000114176 KOS PHARMACEUTICALS INC 2
OAKWOOD BLVD HOLLYWOOD, FL 33020 DMF No:
AADA: Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER Profile: CTL
OAI Status: NONE Estab. Comment: ADDRESS GIVEN: 200 OAKWOOD BLVD.,
SUITE 140, HOLLYWOOD, FL 33020 (on 09-MAY-2007 by S.
MOORE () 301-796-1718) Milestone Name Date Type Insp. Date
Decision & Reason Creator ---------- ---------- ---------- ------ ---
---------- ---------- SUBMITTED TO OC 09-MAY-
2007 MOOREST SUBMITTED TO DO
10-MAY-2007 GMP FERGUSONS DO
RECOMMENDATION 25-JUN-2007 ACCEPTABLE
STURCOVS BASED ON
FILE REVIEW EI ON 12/16/05 CLASSED VAI; COVERED QUALITY, FACILITY AND LAB
SYSTEMS; ACCEPTABLE PROFILE OC RECOMMENDATION 26-JUN-2007
ACCEPTABLE FERGUSONS
DISTRICT RECOMMENDATION ----------
---------- Establishment: CFN 2248571
FEI 3000206320 KOS PHARMACEUTICALS INC
18 MAYFIELD AVE

APPEARS THIS WAY
ON ORIGINAL

DETAIL REPORT EDISON, NJ 08837 DMF No:
AADA: Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE RELEASE
TESTER Profile: TTR OAI Status:
NONE EMilestone Name Date Type Insp. Date Decision &
Reason Creator ---------- ---------- ------ ----------
---------- --------- SUBMITTED TO OC 09-MAY-2007
MOOREST SUBMITTED TO DO 10-MAY-2007 10D
FERGUSONS DO RECOMMENDATION 11-MAY-2007
ACCEPTABLE NROLLI
BASED ON FILE REVIEW GMP INSPECTION CONDUCTED IN APRIL 2006, CLASSIFIED
"VAI". OC RECOMMENDATION 15-MAY-2007 ACCEPTABLE
FERGUSONS DISTRICT
RECOMMENDATION ----------
---------- Establishment: CFN
FEI

DMF No:
AADA: Responsibilities:

Profile: CTL
OAI Status: NONE EMilestone Name Date Type Insp. Date
Decision & Reason Creator ---------- ---------- ------ ---
---------- ---------- --------- SUBMITTED TO OC 09-MAY-
2007 MOOREST OC
RECOMMENDATION 10-MAY-2007 ACCEPTABLE
FERGUSONS BASED ON
PROFILE ----------
---------- Establishment: CFN FEI

DMF No:
AADA: Responsibilities: Profile:
CSN OAI Status: NONE Estab. Comment:
ADDRESS GIVEN:
(on 09-MAY-2007 by S. MOORE () 301-796-1718) Milestone Name Date
Type Insp. Date Decision & Reason Creator

APPEARS THIS WAY
ON ORIGINAL

DETAIL REPORT SUBMITTED TO OC 09-MAY-2007
MOOREST OC RECOMMENDATION 10-MAY-2007 ACCEPTABLE
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CTL OAI Status: NONE EMilestone Name
Date Type Insp. Date Decision & Reason Creator ----------
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MOOREST OC RECOMMENDATION 10-MAY-2007 ACCEPTABLE
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PROFILE ----------
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PROFILE ----------
---------- Establishment: CFN FEI
DMF No:
AADA: Responsibilities:

APPEARS THIS WAY
ON ORIGINAL

DETAIL REPORT Profile: CSN OAI
Status: NONE Estab. Comment: ADDRESS GIVEN:
(on 09-MAY-2007 by S. MOORE () 301-796-1718)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-MAY-2007				MOOREST
SUBMITTED TO DO	10-MAY-2007	GMP			ADAMSS
ASSIGNED INSPECTION T	17-MAY-2007	GMP			ADAMSS
INSPECTION SCHEDULED	28-SEP-2007		31-OCT-2007		ADAMSS
INSPECTION PERFORMED	31-OCT-2007		31-OCT-2007		ADAMSS
DO RECOMMENDATION	11-FEB-2008			ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	11-FEB-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

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

/s/

John C. Hill
2/11/2008 11:50:52 AM
CHEMIST

Ali Al-Hakim
2/12/2008 09:30:10 AM
CHEMIST

1/28/08

CHEMISTRY REVIEW

NDA/ANDA 22-078

SIMCOR
(simvastatin and niacin extended-release tablets)

Abbott Laboratories

John C. Hill, Ph.D.
ONDQA/DPMA-I and DMEP

Chemistry Review #2

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-078

2. REVIEW #2

3. REVIEW DATE: January 16, 2008

4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
(N) Original NDA Filing	17-APR-2007
(C) Trade name update	22-AUG-2007
(C)Clinical site information	13-AUG-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Response to CMC DR Letter (BC)	08-NOV-2007
CMC/Labeling Update (BZ)	12-OCT-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Abbott Laboratories
Address:	PA76, Building AP30-1E 200 Abbott Park Road Abbott Park, IL 60064-6157
Representative:	Jeanne M. Fox, Sr. Director Global Pharmaceutical Regulatory Affairs
Telephone:	Tel. 847-937-5533 FAX 847-937-8002

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SIMCOR
b) Non-Proprietary Name (USAN): niacin extended-release & simvastatin tablets NS tablets
c) Code Name/# (ONDC only):

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

Listed Drugs:

Zocor NDA 19-766 for Simvastatin, Merck
Niaspan NDA 20-381 for Niacin, Kos Life Sciences

10. PHARMACOL. CATEGORY:
Niacin – Lipid lowering
Simvastatin: 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitor

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500/20, 750/20 and 1000/20 mg/mg

13. ROUTE OF ADMINISTRATION: Oral

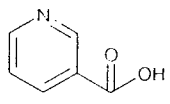
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed

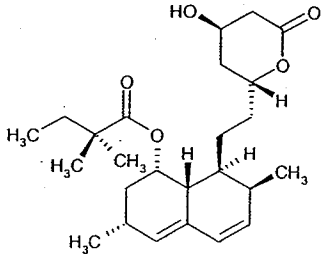
__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Niacin: Niacin is nicotinic acid, or 3-pyridinecarboxylic acid. The empirical formula of niacin is $C_6H_5NO_2$ and its molecular weight is 123.11.



Simvastatin: Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3-7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2Hpyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3 α,7β,8β(2S*4S*),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1,4	Adequate	15-DEC-2003	LOA: 21-AUG-2005
	II			1,4	Adequate	13-JUN-2007	LOA: 08-JUL-2006
	II			1,4	Adequate	24-OCT-2006	LOA: 04-AUG-2006
	IV		s	1,4	Adequate	28-FEB-2003 and 24-FEB-1994)	LOA: 14-SEP-2006
	III			1,4	Adequate	Review Not Needed*	LOA: 16-MAR-2007 Complies with CGMP for
	III			1,4	Adequate	Review Not Needed*	LOA: 30-MAR-2004
	III			1,4	Adequate	Review Not Needed*	LOA: 02-NOV-2005
	III			1,4	Adequate	Review Not Needed*	LOA: 07-MAR-2007
	III			1,4	Adequate	Review Not Needed*	LOA: 08-MAR-2007
	III			1,4	Adequate	Review Not Needed*	LOA: 23-MAR-2007
	III			1,4	Adequate	Review Not Needed*	LOA: 22-MAR-2007
	III			1,4	Adequate	Review Not Needed*	LOA: 13-APR-2007
	III			1,4	Adequate	Review Not Needed*	LOA: 13-APR-2007

—	III	—	[redacted]	1,4	Adequate	Review Not Needed*	LOA: 13-APR-2007

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

* Review not needed in accordance with review policy for [redacted], for solid oral dosage forms.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,187	KOS/Abbott SIMCOR
IND	34,613	KOS Niaspan
NDA	20-381	KOS Niaspan
IND	56,027	KOS Advicor
NDA	21-249	KOS Advicor

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending	28-Jan-2008	
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not Requested		
OPDRA			
EA	Acceptable	27-SEP-2007	John C. Hill, Ph.D.
Microbiology	N/A		

Executive Summary Section

The Chemistry Review for NDA 22-078

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC perspective, this application is approvable pending:

1. Completion of the EES evaluation.

Based on the updated stability data, an expiry period of 18-months when stored at (25°C/60% RH) is granted.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

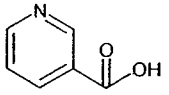
None

II. Summary of Chemistry Assessments

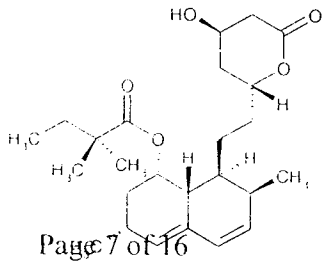
A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

Niacin is nicotinic acid, or 3-pyridinecarboxylic acid. Niacin is a white, nonhygroscopic crystalline powder that is very soluble in water, boiling ethanol and propylene glycol. It is insoluble in ethyl ether. The empirical formula of niacin is $C_6H_5NO_2$ and its molecular weight is 123.11. Niacin has been reported to be a Biopharmaceutical Classification System (BCS), Class 1 drug, i.e., a highly soluble, highly permeable drug. Niacin is manufactured by the DMF supplier, [redacted]. Niacin has the following structural formula:



Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3-7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2Hpyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3 α,7β,8β(2S*4S*),-8aβ]]. Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water and freely soluble in chloroform, methanol and ethanol. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Simvastatin has been reported to be a BCS Class 4 drug, i.e., a low solubility, low permeability drug. Simvastatin is manufactured by two DMF suppliers [redacted]. Simvastatin has the following structural formula:



2. Drug Product

Niacin ER/simvastatin tablets are intended for oral use and are composed of an extended-release (ER) niacin [redacted] immediate-release (IR) simvastatin [redacted] color coat, and a clear [redacted] coat. The niacin [redacted] is identical in formulation to Kos' Niaspan® (niacin ER tablets, NDA #20-381, approved July 28, 1997) and the niacin ER [redacted] in Advicor® (niacin ER/lovastatin tablets, NDA #21-249, approved December 17, 2001).

Niacin ER/simvastatin tablets are available in three strengths (expressed as mg niacin/mg simvastatin) – 500 mg/20 mg, 750 mg/20 mg, and 1000 mg/20 mg. Each caplet contains the following inactive ingredients: hypromellose, povidone, stearic acid, polyethylene glycol, and a Blue Opadry II 32K-10858 color coat. Butylated hydroxyanisole (BHA) is added

Based on the updated stability data, it is safe to grant an expiry period of 18-months when stored at (25°C/60% RH). This expiry period will be updated via the annual report, following the stability protocol submitted in the NDA.

B. Description of How the Drug Product is Intended to be Used

Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles: SIMCOR is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, non-HDL-C, Apo B, TG, [redacted] levels and to increase HDL-C in patients with primary hypercholesterolemia [redacted], mixed dyslipidemia, and hypertriglyceridemia.

[redacted]

The dosage range is 500/20 mg/day-2000/40 mg/day. The recommended initial dose is 500/20 mg/day [redacted] SIMCOR dose should be increased based upon desired lipid effects and the individual's tolerability. Doses of SIMCOR greater than 2000/40 mg daily are not recommended.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable (AE) from a CMC viewpoint. This recommendation is based on the evaluation of the drug substance characterization data, the current and acceptable status of cross-referenced Drug Master Files, the drug product pharmaceutical and manufacturing development report, available real-time, accelerated and stressed stability data, and demonstrated lot-to-lot final drug product quality.

A meaningful CGMP facility inspection report remains pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.D., Review Chemist, DPA-I: Same date as electronic review
Ali Al-Hakim, Chief, Branch II, DPA-I: Same data as electronic review

C. CC Block

Kati Johnson, CSO, DMEP, ODE II, OND

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

John C. Hill
1/28/2008 07:33:46 AM
CHEMIST

Ali Al-Hakim
1/28/2008 11:57:52 AM
CHEMIST

10/4/07

CHEMISTRY REVIEW

NDA/ANDA 22-078

SIMCOR
(simvastatin and niacin extended-release tablets)

Abbott Laboratories

John C. Hill, Ph.D.
ONDQA/DPMA-I and DMEP

DRAFT
Chemistry Review #1

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-078

2. REVIEW #: 1

3. REVIEW DATE: September 27, 2007

4. REVIEWER: John C. Hill, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
(N) Original NDA Filing	17-APR-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Abbott Laboratories
Address:	PA76, Building AP30-1E 200 Abbott Park Road Abbott Park, IL 60064-6157
Representative:	Jeanne M. Fox, Sr. Director Global Pharmaceutical Regulatory Affairs
Telephone:	Tel. 847-937-5533 FAX 847-937-8002

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SIMCOR
b) Non-Proprietary Name (USAN): niacin extended-release & simvastatin tablets NS tablets
c) Code Name/# (ONDC only):
d) Chem. Type Submission Priority (ONDC only):

- Chem. Type: 3

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

Listed Drugs:

Zocor NDA 19-766 for Simvastatin, Merck
Niaspan NDA 20-381 for Niacin, Kos Life Sciences

10. PHARMACOL. CATEGORY:
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Simvastatin: 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitor

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13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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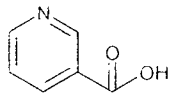

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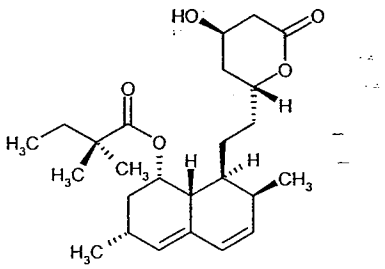

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A. DMFs:

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	II			1,4	Adequate	13-JUN-2007	LOA: 08-JUL-2006
	II			1,4	Adequate	24-OCT-2006	LOA: 04-AUG-2006
	IV			1,4	Adequate	, 28-FEB-2003 and 24-FEB-1994)	LOA: 14-SEP-2006
	III			1,4	Adequate	Review Not Needed*	LOA: 16-MAR-2007 Complies with CGMP for indirect food additives.
	III			1,4	Adequate	Review Not Needed*	LOA: 30-MAR-2004
	III			1,4	Adequate	Review Not Needed*	LOA: 02-NOV-2005
	III			1,4	Adequate	Review Not Needed*	LOA: 07-MAR-2007
	III			1,4	Adequate	Review Not Needed*	LOA: 08-MAR-2007
	III			1,4	Adequate	Review Not Needed*	LOA: 23-MAR-2007
	III			1,4	Adequate	Review Not Needed*	LOA: 22-MAR-2007
	III			1,4	Adequate	Review Not Needed*	LOA: 13-APR-2007
	III			1,4	Adequate	Review Not Needed*	LOA: 13-APR-2007

III		1,4	Adequate	Review Not Needed*	LOA: 13-APR-2007

[1] Action codes for DMF Table:
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

* Review not needed in accordance with review policy for container-closure systems for solid oral dosage forms.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,187	KOS/Abbott SIMCOR
IND	34,613	KOS Niaspan
NDA	20-381	KOS Niaspan
IND	56,027	KOS Advicor
NDA	21-249	KOS Advicor

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending	04-OCT-2007	
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not Requested		
OPDRA			
EA	Acceptable	27-SEP-2007	John C. Hill, Ph.D.
Microbiology	N A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			

Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 22-078

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

At this stage of CMC review, this drug is approvable pending:

1. Completion of the EES evaluation.
2. Submission and review of revised labeling.
3. Additional stability data to support proposed expiry period.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

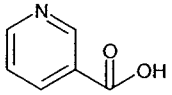
None

II. Summary of Chemistry Assessments

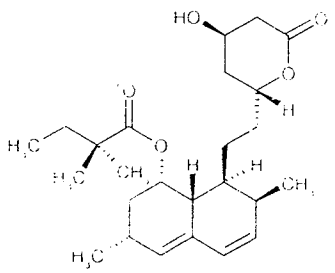
A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

Niacin is nicotinic acid, or 3-pyridinecarboxylic acid. Niacin is a white, nonhygroscopic crystalline powder that is very soluble in water, boiling ethanol and propylene glycol. It is insoluble in ethyl ether. The empirical formula of niacin is $C_6H_5NO_2$ and its molecular weight is 123.11. Niacin has been reported to be a Biopharmaceutical Classification System (BCS), Class 1 drug, i.e., a highly soluble, highly permeable drug. Niacin is manufactured by the DMF supplier, Nicain has the following structural formula:



Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3-7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2Hpyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3 α,7β,8β(2S*4S*),-8aβ]]. Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water and freely soluble in chloroform, methanol and ethanol. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Simvastatin has been reported to be a BCS Class 4 drug, i.e., a low solubility, low permeability drug. Simvastatin is manufactured by two DMF suppliers, . Simvastatin has the following structural formula:



2. Drug Product

Niacin ER/simvastatin tablets are intended for oral use and are composed of an extended-release (ER) niacin [redacted] an immediate-release (IR) simvastatin [redacted] color coat, and a clear [redacted] coat. The niacin [redacted] is identical in formulation to Kos' Niaspan® (niacin ER tablets, NDA #20-381, approved July 28, 1997) and the niacin ER [redacted] in Advicor® (niacin ER/lovastatin tablets, NDA #21-249, approved December 17, 2001).

Niacin ER/simvastatin tablets are available in three strengths (expressed as mg niacin/mg simvastatin) – 500 mg/20 mg, 750 mg/20 mg, and 1000 mg/20 mg. Each caplet contains the following inactive ingredients: hypromellose, povidone, stearic acid, polyethylene glycol, and a Blue Opadry II 32K-10858 color coat. Butylated hydroxyanisole (BHA) is added [redacted]

B. Description of How the Drug Product is Intended to be Used

Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles: SIMCOR is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, non-HDL-C, Apo B, TG, [redacted] levels and to increase HDL-C in patients with primary hypercholesterolemia [redacted], mixed dyslipidemia, and hypertriglyceridemia.

[redacted]

The dosage range is 500/20 mg/day-2000/40 mg/day. The recommended initial dose is 500/20 mg/day [redacted] SIMCOR dose should be increased based upon desired lipid effects and the individual's tolerability. Doses of SIMCOR greater than 2000/40 mg daily are not recommended.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable (AE) from a CMC viewpoint. This recommendation is based on the evaluation of the drug substance characterization data, the current and acceptable status of cross-referenced Drug Master Files, the drug product pharmaceutical and manufacturing development report, available real-time, accelerated and stressed stability data, and demonstrated lot-to-lot final drug product quality.

Consultative reviews, stability update, revision to proposed name, final container/closure labeling and CGMP facility inspections are currently pending.

III. Administrative

Executive Summary Section

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.D., Review Chemist, DPA-I: Same date as electronic review
Ali Al-Hakim, Chief, Branch II, DPA-I: Same data as electronic review

C. CC Block

Kati Johnson, CSO, DMEP, ODE II, OND

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/s/

John C. Hill
10/4/2007 01:18:24 PM
CHEMIST

Ali Al-Hakim
10/4/2007 04:14:21 PM
CHEMIST

5/14/07

INITIAL QUALITY ASSESSMENT
Office of New Drug Quality Assessment
Division of Metabolism and Endocrinology Products
NDA 22-078

APPLICANT INFORMATION :

Applicant: Abbott Laboratories
PA76, Building AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157
Tel. 847-937-5533
FAX 847-937-8002

Date of Submission: Letter date 17-APR-2007 (Stamp date: 17-APR-2007)

PRODUCT DESCRIPTION:

Proprietary Name: SIMCOR®

Established Name: Niacin extended-release and simvastatin tablets

Dosage Form: Tablets (Caplets)

Strength/Potency: 500/20, 750/20 and 1000/20 mg/mg

Route of Administration: Oral

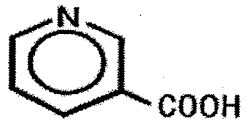
Pharmacological Category: Niacin (nicotinic acid) has distinctive lipid-altering properties when used at gram dosages. Niacin acts as an antihyperlipidemic agent on a broad range of lipid particles and was the first extensively used lipid altering medication. Niacin is the most potent agent available for increasing high-density lipoprotein cholesterol (HDL-C) levels. It also lowers levels of Apolipoprotein B (Apo B) containing lipoproteins including low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C), triglycerides (TG) and lipoprotein a (Lp[a]). Simvastatin is a widely prescribed 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitor (also called a statin) that has a potent effect on LDL-C levels and has been proven to reduce the risk of coronary heart disease (CHD) mortality and cardiovascular (CV) events in patients at high risk of coronary events.

Indication(s): Treatment of primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia

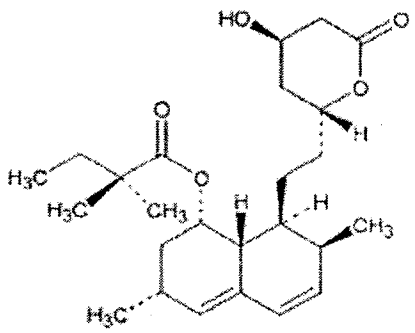
Drug Product Summary: SIMCOR® is for oral use as caplets containing 500 mg of extended-release niacin and 20 mg simvastatin (SIMCOR 500/20), 750 mg of extended- release niacin and 20 mg simvastatin (SIMCOR 750/20), and 1000 mg of extended-release niacin and 20 mg simvastatin (SIMCOR 1000/20). Each caplet contains the following inactive ingredients: hypromellose, povidone, stearic acid, polyethylene glycol, and a Blue Opadry II 32K-10858 color coat. Butylated hydroxyanisole (BHA) is added as —— The tablets are a combination of two approved drugs, niacin ER tablets and simvastatin. (see IQA Notes for additional information).

Drug Substance Summary: The drug substances are niacin and simvastatin.

Niacin is nicotinic acid, or 3-pyridinecarboxylic acid. Niacin is a white, nonhygroscopic crystalline powder that is very soluble in water, boiling ethanol and propylene glycol. It is insoluble in ethyl ether. The empirical formula of niacin is $C_6H_5NO_2$ and its molecular weight is 123.11. Niacin has been reported to be a Biopharmaceutical Classification System (BCS), Class 1 drug, i.e., a highly soluble, highly permeable drug. Niacin is manufactured by the DMF supplier, —— — Nicain has the following structural formula:



Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3-7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3 α,7β,8β(2S*4S*),-8aβ]]. Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water and freely soluble in chloroform, methanol and ethanol. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Simvastatin has been reported to be a BCS Class 4 drug, i.e., a low solubility, low permeability drug. Simvastatin is manufactured by two DMF suppliers, [redacted]. Simvastatin has the following structural formula:



Neither niacin nor simvastatin is a new chemical entity (NCE). (see IQA Notes for additional information).

Description of How the Drug Product is Intended to be Used: The clinical indication(s) being sought are as follow:

Patients with Hypercholesterolemia Requiring Modifications of Linid Profiles: SIMCOR is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, non-HDL-C, Apo B, TG, [redacted] levels and to increase HDL-C in patients with primary hypercholesterolemia [redacted], mixed dyslipidemia, and hypertriglyceridemia.

The dosage range is 500/20 mg/day-2000/40 mg/day. The recommended initial dose is 500/20 mg/day [redacted] SIMCOR dose should be increased based upon desired lipid effects and the individual's tolerability. Doses of SIMCOR greater than 2000/40 mg daily are not recommended.

Pre-submission CMC issues and/or agreements:

1. KOS proposed to add butylated hydroxyanisole (BHA) to the formulation [redacted]. Six months of primary stability was agreed acceptable for initial filing (with addition of BHA) and 12 months of data submitted during review (FDA Advice Letter 01-JUN-2006).

2. Because [redacted] ([redacted]) stability study should be performed for the bottle packaging (FDA Advice Letter 01-JUN-2006). An in-use stability study was performed.

3. Similar dissolution profiles between the formulations without BHA and with BHA may be used to waive a BE study (FDA Advice Letter 01-JUN-2006). Simvastatin dissolution data across tablet strengths is provided in the NDA.

4. There are two API manufacturers for simvastatin. Two separate drug substance sections will be included in the NDA, with cross-reference as appropriate (26-SEP-2006 Pre-NDA meeting).

5. A categorical exclusion from an environmental assessment is being sought. A calculation for the estimated concentration of each active moiety at the entry point into the aquatic environment should be included in the NDA (26-SEP-2006 Pre-NDA meeting).

6. The niacin active DMF has been reviewed under t
. Kos plans to refer to the DMF and those applications for the niacin active. The following information on niacin will be sufficient: references to the DMF and approved NDAs, a brief section on the general properties of niacin, the regulatory specification(s), and a list of all manufacturing and testing facilities with a readiness statement for FDA's GMP inspections (26-SEP-2006 Pre-NDA meeting).

7. Since KOS will be relying on the DMFs, only summary information as per the proposed reports below on the drug substance will be included:
   - Simvastatin characterization report (both vendors)
   - Summary of data for all simvastatin lots received to date
   - Rely upon DMFs for active substance stability
   - Methods validation reports not required as the active meets USP requirements

   This is acceptable provided the following is also included in the NDA: the regulatory specification(s) and a list of all manufacturing and testing facilities with a readiness statement for FDA's GMP inspections (26-SEP-2006 Pre-NDA meeting).

8. KOS proposed the following drug product reports to be included in the NDA.
   - Stability report for clinical study lots
   - Registration batches stability report (6 months of accelerated and controlled room temperature data)
   - Photostability report
   - In-Use Stability Study Report
   - Method Validation for Simvastatin Assay and Impurities/Degradants
   - Method Validation for Simvastatin Dissolution
   - Method Validation for BHA Assay
   - Validation Test Report
   - Comparison of simvastatin dissolution profiles with and withou
   - Comparison of niacin dissolution

   The proposed list of drug product reports is acceptable, as long as comparative niacin dissolution supports testing in-process material rather than finished product (26-SEP-2006 Pre-NDA meeting).

Initial Evaluation: All Pre-submission CMC issues and/or agreements are addressed in the NDA. As noted in the NDA, a shelf life for the drug product(s) will be proposed when additional stability data are available.

APPLICATION INFORMATION:

Type of Submission: 505(b)(2) NDA

Proposed marketing status: Rx

Cross-references: IND 65,187 for SIMCOR; NDA 20-381 and IND 34,613 for Niaspan; NDA 21-249 and IND 56,027 for Advicor; DMF for niacin DMF for simvastatin DMF for simvastatin , DMF

Other: SIMCOR® (niacin extended-release and simvastatin) tablets was originally developed by Kos Life Sciences, Inc. under IND 65,187. In December 2006, Kos Life Sciences, Inc. became a wholly owned subsidiary of Abbott

Laboratories. IND 65,187 and NDA 22-078 were transferred to Abbott Laboratories. The listed drugs for this 505(b)(2) NDA are: Zocor® NDA 19-766 for simvastatin, Merck and Niaspan® NDA 20-381 for niacin, Kos Life Sciences, Inc.

RECOMMENDATIONS:

Time goals:

Initial Quality Assessment in DFS: 17-MAY-2007
CMC-related consults initiated (see table below): 17-MAY-2007
CMC filing memo in DFS (see table below): 17-JUN-2007
Filing date ("Day 60"): 17-JUN-2007
Filing review issues letter ("Day 74"): 01-JUL-2007
Chemistry Review (DR/IR) letter ("Month 5"): 17-SEP-2007
Mid-cycle meeting ("Month 5"): TBD
Final Chemistry Review in DFS ("Month 8"): 17-DEC-2007
PDUFA date ("Month 10"): 17-FEB-2008

Filability: Acceptable for filing from CMC perspective.

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?			N/A

Comment: The application was submitted in electronic copies. A conventional CMC summary is included in the application.

Drug Master Files (DMFs):

DMF	TYPE	HOLDER	ITEM REFERENCED	LOA	PREVIOUS REVIEW(S)	RECOMMENDATION
	IV			14-SEP-2006	Similar materials have been reviewed, but not these particular materials; Adequate qualitative information in NDA	Review deferred to discretion of primary CMC reviewer
	III			16-MAR-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*
	III			30-MAR-2004	DMF previously reviewed; Adequate information in NDA	Review not needed*
	III			11-FEB-2005	DMF previously reviewed; Adequate information in NDA	Review not needed*
	III			13-APR-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*
	III			13-APR-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*
	III			13-APR-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*

	III		23-MAR-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*
	III		22-MAR-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*
	III		08-MAR-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*
	III		07-MAR-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*
	II		21-AUG-2005	DMF previously reviewed 08-APR-2003; Adequate.	Review of updates, if any, deferred to discretion of primary CMC reviewer
	II		08-JUL-2006	DMF previously reviewed 19-SEP-2005; Adequate.	Review not needed*
	II		04-AUG-2006	DMF previously reviewed 13-OCT-2007; Adequate.	Review not needed*

*Review not needed in accordance with review policy for for solid oral dosage forms.

Consults:

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	To be assessed by Biopharm/ClinPharm reviewer.
CDRH	N/A
EA	Claim for Categorical Exclusion (< 1 PPB). To be assessed by primary CMC reviewer.
EES	EER submitted to Office of Compliance on 08-MAY-2007.
OSE/DMETS	Labeling consult request to be sent by DMEP
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	N/A
Pharm/Tox	To be assessed by Pharm/Tox reviewer.

Recommendation for Primary CMC Reviewer(s): John Hill, Ph.D. is recommended as the primary CMC reviewer. If Dr. Hill's current workload changes in a manner that would not permit him to review this NDA, then another CMC reviewer in DPAI, Branch 2 can be recommended.

Identification of Critical CMC Review Issues: See IQA notes and list of critical CMC review issues.

Endorsement block (see appended electronic signature page):

Stephen Moore, Ph.D., Pharmaceutical Assessment Lead (PAL), Branch II/DPA I/ONDQA

Init. by: Blair Fraser, Ph.D., Division Director, Branch II/DPA I/ONDQA

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/s/

Stephen Moore
5/11/2007 06:26:51 PM
CHEMIST

Blair Fraser
5/14/2007 05:15:48 AM
CHEMIST