

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-507

CHEMISTRY REVIEW(S)

09/23/03



CHEMISTRY REVIEW



NDA/ANDA 21-507

**NAPROSYN/PREVACID
Combination Package**

TAP Pharmaceuticals Inc.

**Ramesh Raghavachari, Ph.D.
Division of Gastrointestinal and Drug Coagulation Products**



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Chemistry Review Data Sheet

1. NDA 21-507
2. REVIEW #: 3
3. REVIEW DATE: September 23, 2003
4. REVIEWER: Ramesh Raghavachari, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents:
NDA 20-406
NDA 17-581

Document Date
Approved April 14, 1995
Approved March 11, 1976

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original
BC
BZ
BZ
BC
N 000 AZ
N 000 BC

Document Date
May 20, 2003
November 1, 2002
November 29, 2002
January 15, 2003
March 31, 2003
July 25, 2003
September 04, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: TAP Pharmaceutical Products Inc.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Address: 675 North Field Drive
Representative: Lake Forest, IL 60045
Telephone: 847-582-2557

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: _____

(review pending)

b) Non-Proprietary Name (USAN): Naproxen /Lansoprazole

c) Code Name/# (ONDC only): N/A

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

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

This application was filed under the provisions of section 505(b) Federal Food, Drug and Cosmetic Act and 21 CFR 314.50.

10. PHARMACOL. CATEGORY:

Non steroidal anti-inflammatory and proton pump inhibitor drug combination.

11. DOSAGE FORM: Naprosyn- tablets and Prevacid-delayed-release capsules.

12. STRENGTH/POTENCY:

15 mg Prevacid with either 250 mg, 350 mg or 500 mg of Naprosyn

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

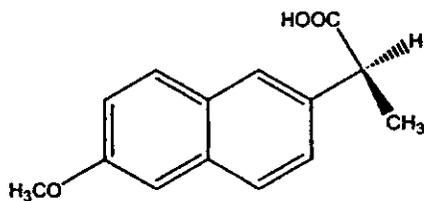
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

___X Not a SPOTS product

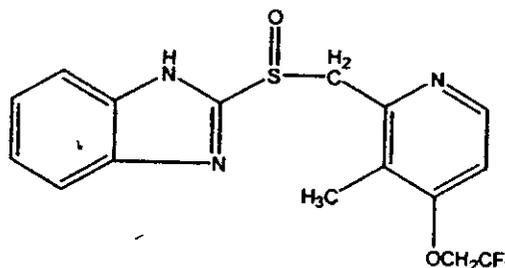
Chemistry Review Data Sheet

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



Naprosyn
MF: C₁₄H₁₄O₃
MW: 230.26

(S)-6-methoxy-(alpha)-methyl-
2-naphthaleneacetic acid



Prevacid
MF: C₁₆H₁₄F₃N₃O₂S
MW: 369.3

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	III			1	Adequate	Feb. 03, 2003 (review # 1)	----
	III			1	Adequate	Jan. 29, 2003 (review # 4)	----

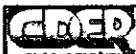
¹ Action codes for DMF Table:

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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- 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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-406	Approved NDA
NDA	17-581	Approved NDA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	---	---
EES	Acceptable by EES	09/10/2003	N/A
Pharm/Tox	N/A	---	---
Biopharm	N/A	---	---
LNC	Consult done	05/09/2003	Also see attached email consult from Dan Boring
Methods Validation	N/A	---	---
DMETS	Pending review	03/31/2003	HFD-400
EA	N/A	---	See review comments page 21
Microbiology	N/A	---	---

OGD: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical	N/A		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

19. ORDER OF REVIEW (OGD Only): N/A

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

APPENDIX
ON ORDER

The Chemistry Review for NDA 21-507

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

dated September 4, 2003. The applicant will use _____ facility for the drug product stability testing and additional testing and release. _____ was inspected and found acceptable by the Office of Compliance. _____ the overall recommendation from the EER was found to be "Acceptable" on September 10, 2003. Hence, this NDA is recommended for "Approval".

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

During the pre-NDA meetings, FDA required the applicant to provide 12-month stability data for the combination package of the drug product. FDA agreed to an accelerated three month stability data within ninety days after filing the NDA. The three-month normal and accelerated stability study tests for the individual drugs the combination package has been provided by the applicant as agreed in the pre NDA meeting.

The applicant has requested a _____ expiration date for the combination drug product in the NDA application, however has provided with only three month stability data for this packaging material. In the course of next year long-term stability data must be made available to the FDA (by Annual reports) for the individual drug components in the combination package, to extend the expiration date to _____

Due to the historical data available already for the approved products and based on the stability data provided, a two year expiry date is acceptable for this combination package.

II. Summary of Chemistry Assessments

Summary and all other review details are the same as in Review #1 of NDA 21-507.



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

III. Attachments:

None.

APPROVED FOR USE

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

/s/

Ramesh Raghavachari
9/23/03 01:24:33 PM
CHEMIST

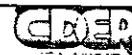
Liang Zhou
9/23/03 01:59:01 PM
CHEMIST

APPENDIX
ON 09/23/03

07/08/03



CHEMISTRY REVIEW



NDA/ANDA 21-507

**NAPROSYN/PREVACID
Combination Package**

TAP Pharmaceuticals Inc.

**Ramesh Raghavachari, Ph.D.
Division of Gastrointestinal and Drug Coagulation Products**

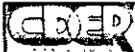
APPROVED TO STAY
ON ORIGINAL



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APPLIES THIS WAY
ON ORIGINAL



Chemistry Review Data Sheet

1. NDA 21-507
2. REVIEW #: 2
3. REVIEW DATE: July 07, 2003
4. REVIEWER: Ramesh Raghavachari, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents:

NDA 20-406
NDA 17-581

Document Date

Approved April 14, 1995
Approved March 11, 1976

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original
BC
BZ
BZ
BC

Document Date

May 20, 2003
November 1, 2002
November 29, 2002
January 15, 2003
March 31, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: TAP Pharmaceutical Products Inc.
Address: 675 North Field Drive
Representative: Lake Forest, IL 60045



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Telephone:

847-582-2557

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: _____
_____ (review pending)

b) Non-Proprietary Name (USAN): Naproxen /Lansoprazole

c) Code Name/# (ONDC only): N/A

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- Submission Priority: S

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12. STRENGTH/POTENCY:

15 mg Prevacid with either 250 mg, 350 mg or 500 mg of Naprosyn

13. ROUTE OF ADMINISTRATION: Oral

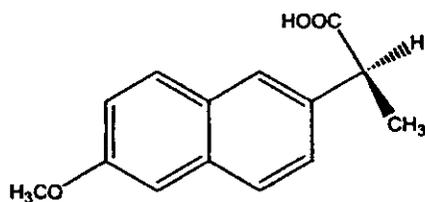
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

_____ SPOTS product – Form Completed

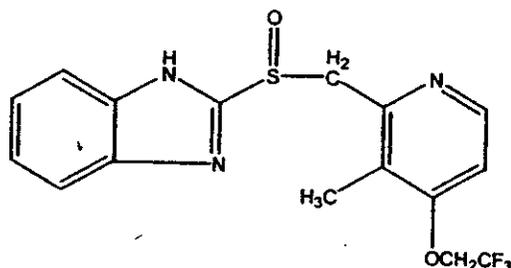
____X Not a SPOTS product

Chemistry Review Data Sheet

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


Naprosyn
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 MW: 230.26

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 MF: C₁₆H₁₄F₃N₃O₂S
 MW: 369.36

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
 pyridyl] methyl] sulfinyl] benzimidazole

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	III			1	Adequate	Feb. 03, 2003 (review # 1)	---
1	III			1	Adequate	Jan. 29, 2003 (review # 4)	---

¹ Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type I DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-406	Approved NDA
NDA	17-581	Approved NDA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	---	---
EES	"WITHHOLD" Recommended by EES	07/07/2003	See email attached from Randy Woods
Pharm/Tox	N/A	---	---
Biopharm	N/A	---	---
LNC	Consult done	05/09/2003	Also see attached email consult from Dan Boring
Methods Validation	N/A	---	---
DMETS	Pending review	03/31/2003	HFD-400
EA	N/A	---	See review comments page 21
Microbiology	N/A	---	---

OGD: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical	N/A		



CHEMISTRY REVIEW

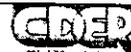
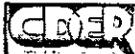


Chemistry Review Data Sheet

19. ORDER OF REVIEW (OGD Only): N/A

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

APR 11 2011
ORIGINAL



The Chemistry Review for NDA 21-507

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The EER recommends _____
_____. Hence, this application is
approvable. _____

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

During the pre-NDA meetings, FDA required the applicant to provide 12-month stability data for the combination package of the drug product. After many debates, FDA agreed to an accelerated three month stability data within ninety days after filing the NDA. The three-month normal and accelerated stability study tests for the individual drugs the combination package has been provided by the applicant as agreed in the pre NDA meeting.

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II. Summary of Chemistry Assessments

Summary and all other review details are the same as in Review #1 of NDA 21-507.



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

III. Attachments:

From: Woods, Randy L
Sent: Monday, July 07, 2003 1:58 PM
To: Raghavachari, Ramesh; Zhou, Liang; Kowblansky, Marie
Cc: Ysem, Maria E; Duffy, Eric P; Wu, Duu Gong; Rivera Martinez, Edwin; Justice, Robert; Korvick, Joyce A; Furness, Melissa; Blumenschein, Frederick W; Dietrick, John M; Davis Lopez, Mary; Strongin, Brian K; Moore, Diane V; Dubeau, Julieann; Uratani, Brenda W
Subject: NDA 21-507 - CDER/OC overall withhold recommendation for _____

Hello to Everyone,

Today, I placed an overall CDER/OC withhold recommendation into EES for the subject application.

Since another CDER/OC Compliance Officer has been reviewing the EIR for consideration of issuance of a _____, it was necessary to wait until all reviews were sufficiently complete prior to issuing our recommendation.

Briefly, CHI-DO's January - March '03 EI revealed serious CGMP deficiencies in the Quality Assurance and Laboratory systems. The CGMP deficiencies could affect the subject product. We await CHI-DO's reinspection to confirm corrections promised by Our memo summarizing our review will follow in the next couple of days.

Randall Woods, CSO HFD-322

Tel 7-9011

APPROVED THIS WAY
ON ORIGINAL

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

/s/

Ramesh Raghavachari
7/7/03 05:24:37 PM
CHEMIST

Liang Zhou
7/8/03 12:55:27 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL



NDA/ANDA 21-507

**NAPROSYN/PREVACID
Combination Package**

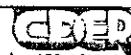
TAP Pharmaceuticals Inc.

**Ramesh Raghavachari, Ph.D.
Division of Gastrointestinal and Drug Coagulation Products**



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A. Labeling & Package Insert.....	18
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III. List Of Deficiencies To Be Communicated	21
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Chemistry Review Data Sheet

1. NDA 21-507
2. REVIEW #: 1
3. REVIEW DATE: May 20, 2003
4. REVIEWER: Ramesh Raghavachari, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents:

NDA 20-406
NDA 17-581

Document Date

Approved April 14, 1995
Approved March 11, 1976

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original
BC
BZ
BZ
BC

Document Date

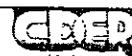
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CHEMISTRY REVIEW



Chemistry Review Data Sheet

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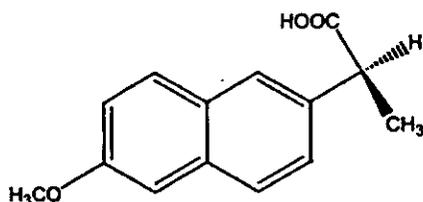
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_____ X Not a SPOTS product

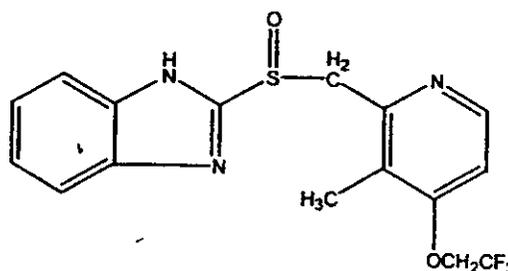
Chemistry Review Data Sheet

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2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole

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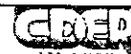
4 – Sufficient information in application

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CHEMISTRY REVIEW



Chemistry Review Data Sheet

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)

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NDA	17-581	Approved NDA

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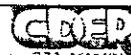
CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	---	---
EES	Inspection requested- Pending	Request date 09/09/2002	
Pharm/Tox	N/A	---	---
Biopharm	N/A	---	---
LNC	Consult done	05/09/2003	Also see attached email consult from Dan Boring
Methods Validation	N/A	---	---
DMETS	Pending review	03/31/2003	HFD-400
EA	N/A	---	See review comments page 21
Microbiology	N/A	---	---

OGD: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical	N/A		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

19. ORDER OF REVIEW (OGD Only): N/A

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

APR 11 2007
6:00 PM

The Chemistry Review for NDA 21-507

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) point of view, NDA 21-507 is recommended for approval.

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

During the pre-NDA meetings, FDA required the applicant to provide 12-month stability data for the combination package of the drug product. After many debates, FDA agreed to an accelerated three month stability data within ninety days after filing the NDA. The three-month normal and accelerated stability study tests for the individual drugs the combination package has been provided by the applicant as agreed in the pre NDA meeting.

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Due to the historical data available already for the approved products and based on the stability data provided, a two year expiry date is acceptable for this combination package.

II. Summary of Chemistry Assessments

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

The combination drug package has two approved drugs, which have been in the market for years.

1. Naprosyn- Naproxen as the drug substance formulated into tablets of 250 mg, 375 mg and 500 mg as the drug product.
2. Prevacid- Lansoprazole as the drug substance as delayed-release capsules 15 mg per capsule as the drug product.



Executive Summary Section

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

The drug will be packaged for a four seven day (for 28 days) dosage with one 15 mg Prevacid and one 250 mg or 375 mg or 500 mg Naprosyn in the morning and one Naprosyn in the evening. Each seven-day package will contain seven 15 mg Prevacid delayed release capsules and 14 Naprosyn (250 mg or 375 mg or 500 mg) tablets. This product is indicated for patients with arthritis, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis treatment as a non-steroidal anti-inflammatory drug with a history of documented gastric ulcer. The drug is stored and dispensed in its original container and must be stored at 20-25 °C (68-77° F), excursions permitted to 15-30 °C (50 -86°F) [see USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

The two drug products in the combination package are approved. (NDA 17-581 and NDA 20-406)

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS by Ramesh Raghavachari, Ph.D. Review Chemist, HFD-180

B. Endorsement Block

Signed electronically in DFS by Liang Zhou, Ph.D., Chemistry Team Leader, HFD-180

Ramesh Raghavachari /Date: Same date as draft review
Liang Zhou, Ph.D./Date
Melissa Furness /Date

C. CC Block

NDA 21-507
HFD-180/Chemistry Reviewer/raghavachari
HFD-180/Chemistry Team Leader/lzhou
HFD-180/Project Manager/mfurness
HFD-180/Div File/NDA 21-507

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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling