

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-281

CHEMISTRY REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
 Review of Chemistry, Manufacturing, and Controls

NDA #: 21-281 **CHEM REVIEW #:** 1 **REVIEW DATE:** March 29, 2001

SUBMISSION TYPE	DOCUMENT	DATES	
		CDER	ASSIGNED
ORIGINAL	30-JUN-2000	03-JUL-2000	12-JUL-2000
AMENDMENT	BC 22-SEP-2000	25-SEP-2000	02-OCT-2000
	BC-18-OCT-2000	19-OCT-2000	22-OCT-2000
	BB 30-NOV-2000	01-DEC-2000	05-MAR-2001
	BC 06-MAR-2001	07-MAR-2001	08-MAR-2001
	BC 07-MAR-2001	13-MAR-2001	14-MAR-2001

NAME & ADDRESS OF APPLICANT: TAP Pharmaceutical Products Inc.
 675 North Field Drive Lake Forest, IL 60045

DRUG PRODUCT NAME:

Proprietary: Prevacid Sachet for Suspension
Nonproprietary/USAN: Lansoprazole
Code Name/ #: AG-1749, A-65006
Chem. Type/Ther. Class: 3S
CAS Registry Number: 103577-45-3

PHARMACOLOGICAL CATEGORY: Inhibits gastric acid secretion.

INDICATION: Erosive Esophagitis, Duodend ulcer, H.pylori, Zollinger-Ellison Syndrome and GERD.

DOSAGE FORM: Sachet for Suspension

STRENGTH: 15 and 30 mg/ sachet

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: xxx Rx OTC

SPECIAL PRODUCT: —Yes xxx-No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

See NDA 20-406 and NDA 21-281 Vol. 3.1

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
[Redacted]					
[Redacted]					

RELATED DOCUMENTS (if applicable): A. (Cross Referenced) NDA 20-406 Prevacid (Lansoprazole) Capsules, 15 & 30 mg

B. (WD: 2/21/01) NDA 21-331 Prevacid Injection
Submitted: December 22, 2000.

CONSULTS: Microbiological Review: Assigned 02/08/01
OPDRA Consult sent to Carol Pamer, CDER/ORM

REMARKS/COMMENTS:

Remarks:

1. DS: Lansoprazole exists in two polymorphic forms (A and B). Form B is metastable, and the ethanol-water solvate (Form V) are both converted to Form A in water (part of the current manufacturing process.) Form A is manufactured for the drug product.

Optical Rotation: None (stable racemate)

2. ~~_____~~
3. Biopharmaceutics has one outstanding issue on the pH ~~---~~ buffer for the drug release test. (07-Mar-2001)
4. Microbiology has completed the consult on TAP's microbiological testing of the sachet formulation. (26-Mar-2001) Micro deficiencies conveyed to TAP, 27-Mar-2001.
5. ~~_____~~
6. See ADDENDUM after Review Item H.

CONCLUSIONS & RECOMMENDATIONS:

Issue an IR letter to the Applicant (issued on 14-Mar-2001) and if the chemistry responses are acceptable along with a satisfactory response to Biopharmaceutics and Microbiology issues, the application is approvable. Additionally, see ADDENDUM at the end of the review for one more IR item and note that compliance issues have not been completely resolved (see item 5 above).

Joseph Sieczkowski
Review Chemist, HFD-180

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

Cc:
NDA # 21-281
HFD-180/Division Director/L. Talarico
HFD-180/Div File/NDA # 21-281
HFD-180/Chemistry Team Leader/L. Zhou
HFD-180/Chemistry Reviewer/J.Sieczkowski
HFD-181/CSO/C.Perry
R/D Init by:

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS HFD-180
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-281 **CHEM REVIEW #:** 2 **REVIEW DATE:** 13-APR-2001

APR 16 2001

SUBMISSION TYPE	DOCUMENT	DATES	
		CDER	ASSIGNED
ORIGINAL	30-JUN-2000	03-JUL-2000	12-JUL-2000
AMENDMENT	BC 22-SEP-2000	25-SEP-2000	02-OCT-2000
	BC-18-OCT-2000	19-OCT-2000	22-OCT-2000
	BB 30-NOV-2000	01-DEC-2000	05-MAR-2001
	BC 06-MAR-2001	07-MAR-2001	08-MAR-2001
	BC 07-MAR-2001	13-MAR-2001	14-MAR-2001
	*BL 15-MAR-2001	16-MAR-2001	20-MAR-2001
	*BB 28-MAR-2001	29-MAR-2001	30-MAR-2001
	*BC 30-MAR-2001	02-APR-2001	02-APR-2001
	*BZ 06-APR-2001	09-APR-2001	10-APR-2001
	*BC 06-APR-2001	09-APR-2001	10-APR-2001

* Amendments reviewed in Chem. Rev. 2

NAME & ADDRESS OF APPLICANT: TAP Pharmaceutical Products Inc.
675 North Field Drive Lake Forest, IL 60045

DRUG PRODUCT NAME:

Proprietary: Prevacid Sachet for Suspension
Nonproprietary/USAN: Lansoprazole
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Chem. Type/Ther. Class: 3S
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PHARMACOLOGICAL CATEGORY: Inhibits gastric acid secretion.

INDICATION: Erosive Esophagitis, Duodenal ulcer, H.pylori, Zollinger-Ellison Syndrome and GERD.

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HOW DISPENSED: xxx Rx ___ OTC

SPECIAL PRODUCT: --Yes xxx-No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

See NDA 20-406 and NDA 21-281 Vol. 3.1

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date

RELATED DOCUMENTS (if applicable): A. (Cross Referenced) NDA 20-406 Prevacid (Lansoprazole) Capsules, 15 & 30 mg

CONSULTS: Microbiological Review: ONDC, Microbiologist Review #1, 26-MAR-2001; IR letter sent OPDRA Consult sent to Carol Pamer, CDER/ORM: Consultation Response, OPDRA, HFD-400, 29-MAR-2001; No objection to names, Prevacid and Prevacid Sachet.

REMARKS/COMMENTS:

Remarks:

1. **DS: Lansoprazole exists in two polymorphic forms (A and B). Form B is metastable, and the ethanol-water solvate (Form V) are both converted to Form A in water (part of the current manufacturing process.) Form A is manufactured for the drug product.**
Optical Rotation: None (stable racemate)
2.

3. **Biopharmaceutics has one outstanding issue on the pH buffer for the drug substance release, from enteric coated granules, test (07-Mar-2001). Review of last amendment not entered in DFS.**
4. **Microbiology has completed the consult on TAP's microbiological testing of the sachet formulation. (26-Mar-2001) Micro deficiencies conveyed to TAP, 27-Mar-2001. Review of last Amendment not entered in DFS.**
5.

6. **See compiled chemistry review comments at the end of the April 6, 2001 BC Amendment/30-MAR-2001 review.**
April 6, 2001-CONCLUSIONS : The chemistry review cannot be completed pending the resolution of issues with Microbiology and Biopharmaceutics, and due to an incomplete response to the chemistry IR letter (see BC 30-Mar-2001). Other issues pending are with Field/Compliance, and the drug product name. Additionally, one more chemistry issue arose after the IR letter to the company was sent (see Chem. Rev. #1 comment under the BC Amendment Comments). [Note: The chemistry review of the labeling (BL 15-Mar-2001) and biopharmaceutic's (BB 30-Mar-2001) amendments was placed after the chemistry amendment review.] After the April 6, 2001 review, two additional amendments were submitted by TAP, BZ 06-APR-2001 and BC 06-APR-2001.
7. **Dan Boring, by E-Mail on 4/12/01, suggested the following established name for the new Prevacid dosage form, (lansoprazole for delayed release oral suspension). This name is acceptable to this Review Chemist.**

CONCLUSIONS AN RECOMMENDATIONS: The Methods Validation Package is deficient but not an impediment to approval and can be completed at a later date. No other major chemistry deficiencies remain and the application is approvable contingent on the completion of the microbiologist's and biopharmaceutic's reviews, and a response to the Field's 483. (See H. COMMENTS AND LIST OF DEFICIENCES at the end of the review for more details and comments on labeling and degradants.)

**APPEARS THIS WAY
ON ORIGINAL**

**Joseph Sieczkowski, PhD
Review Chemist, HFD-180**

**Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180**

Cc:
NDA # 21-281
HFD-180/Div File/NDA # 21-281
HFD-180/Division Director/L. Talarico
HFD-180/Chemistry Team Leader/L. Zhou
HFD-180/Chemistry Reviewer/J.Sieczkowski
HFD-181/CSO/C.Perry
R/D Init by:

**APPEARS THIS WAY
ON ORIGINAL**

MAY - 1 2001

NDA 21-281

1

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS HFD-180
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-281 CHEM REVIEW #: 3 REVIEW DATE: 01-MAY-2001

SUBMISSION TYPE	DOCUMENT	DATES	
		CDER	ASSIGNED
ORIGINAL	30-JUN-2000	03-JUL-2000	12-JUL-2000
AMENDMENT	BC 22-SEP-2000	25-SEP-2000	02-OCT-2000
	BC-18-OCT-2000	19-OCT-2000	22-OCT-2000
	BB 30-NOV-2000	01-DEC-2000	05-MAR-2001
	BC 06-MAR-2001	07-MAR-2001	08-MAR-2001
	BC 07-MAR-2001	13-MAR-2001	14-MAR-2001
	*BL 15-MAR-2001	16-MAR-2001	20-MAR-2001
	*BB 28-MAR-2001	29-MAR-2001	30-MAR-2001
	*BC 30-MAR-2001	02-APR-2001	02-APR-2001
	*BZ 06-APR-2001	09-APR-2001	10-APR-2001
	*BC 06-APR-2001	09-APR-2001	10-APR-2001

* Amendments reviewed in Chem. Rev. 2

NAME & ADDRESS OF APPLICANT: TAP Pharmaceutical Products Inc.
675 North Field Drive Lake Forest, IL 60045

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HOW DISPENSED: xxx Rx ___ OTC

SPECIAL PRODUCT: --Yes xxx-No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

See NDA 20-406 and NDA 21-281 Vol. 3.1

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
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RELATED DOCUMENTS (if applicable): A. (Cross Referenced) NDA 20-406 Prevacid (Lansoprazole) Capsules, 15 & 30 mg

CONSULTS: Microbiological Review: See Remarks #4.
OPDRA Consult sent to Carol Pamer, CDER/ORM: Consultation Response, OPDRA, HFD-400, 29-MAR-2001; No objection to names, Prevacid and Prevacid Sachet.
Consult to Drug Product Nomenclature committee: See Remarks #7.

REMARKS/COMMENTS:

1. **DS: Lansoprazole exists in two polymorphic forms (A and B). Form B is metastable, and the ethanol-water solvate (Form V) are both converted to Form A in water (part of the current manufacturing process.) Form A is manufactured for the drug product.**
Optical Rotation: None (stable racemate)
2.

3. **Biopharmaceutics had one outstanding issue on the pH buffer for the drug substance release, from enteric coated granules, test (07-Mar-2001). Biopharmaceutics Review (04/26/01) of BB Amendment (08/03/01) recommends approval.**
4. **Microbiology completed the consult on TAP's microbiological testing of the sachet formulation. (26-Mar-2001) Micro deficiencies conveyed to TAP, 27-Mar-2001. Microbiologist's Review #2 (04/24/01) of BZ Amendment (04/06/01) recommends approval.**
5.

6. **Dan Boring, by E-Mail on 4/12/01, suggested the following established name for the new Prevacid dosage form, (lansoprazole for delayed release oral suspension). This name is acceptable to this Review Chemist.**

**APPEARS THIS WAY
ON ORIGINAL**

CONCLUSIONS AND RECOMMENDATIONS: The Methods Validation Package is deficient but is not an impediment to approval and can be completed at a later date (see Chem. Rev. #2). No major chemistry deficiencies remain and no other deficiencies remain with respect to microbiology, biopharmaceutics and the Field. The application is recommended for approval with respect to chemistry.

**APPEARS THIS WAY
ON ORIGINAL**

**Joseph Sieczkowski, PhD
Review Chemist, HFD-180**

**Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180**

**Cc:
NDA # 21-281
HFD-180/Div File/NDA # 21-281
HFD-180/Division Director/L. Talarico
HFD-180/Chemistry Team Leader/L. Zhou
HFD-180/Chemistry Reviewer/J.Sieczkowski
HFD-181/CSO/C.Perry**

**APPEARS 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/

Joe Sieczkowski
5/1/01 04:44:38 PM
CHEMIST

Liang Zhou
5/1/01 05:01:24 PM
CHEMIST

I concurred the chemist's approval recommendation. We recommended to have the chemist's recommendation for the established name [see Chem. Review #2] if we didn't receive Yana's recommendation by 5/2/01.