CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-406/S044

Trade Name: Prevacid Delayed Release Capsules

Generic Name: (lansoprazole)

Sponsor: TAP Holdings Inc

Approval Date: December 5, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-406/S041

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APPLICATION NUMBER:

NDA 20-406/S044

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-406/S-044

TAP Pharmaceutical Products, Inc.
Attention: Nancianne Knipfer, Ph.D.
Senior Regulatory Affairs Specialist
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

Please refer to your supplemental new drug application dated July 13, 2001, received July 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

We acknowledge receipt of your submission dated November 30, 2001.

This supplemental new drug application provides for a new manufacturing site for lansoprazole delayed-release granules [redacted] b(4)

We note your November 30, 2001 facsimile in which you confirmed that the [redacted] facility located in [redacted] b(4) b(4)

We have completed the review of this supplemental application, and it is approved.

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 Cheryl Perry, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
12/5/01 12:53:47 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-406/S044

CHEMISTRY REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls Supplement

NDA #:20-406 **SUPPLEMENT #:**SCS-044 **CHEM REVIEW #:**1 **REVIEW DATE:**Nov 15, 2001

SUBMISSION TYPE	**DOCUMENT**	**CDER**	**ASSIGNED**
ORIGINAL	13-Jul-2001	16-Jul-2001	17-Jul-2001

SUPPLEMENT PROVIDES FOR: addition of new manufacturing facility for the delayed-release granules [redacted] b(4)

NAME & ADDRESS OF APPLICANT: TAP Holdings, Inc.
2355 Waukegan Road
Deerfield, IL 60015

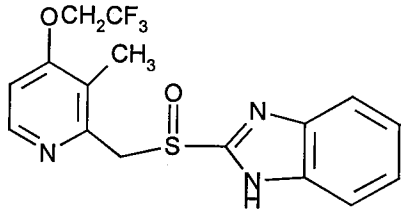
DRUG PRODUCT NAME: Proprietary: Prevacid Nonproprietary/USAN: lansoprazole

PHARMACOLOGICAL CATEGORY: proton pump inhibitor **INDICATION:** treatment of ulcers

DOSAGE FORM: CAPSULE, DELAYED RELEASE PELLETS **STRENGTH:** 15 and 30 mg

ROUTE OF ADMINISTRATION: oral **HOW DISPENSED:** X **Rx** ___ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
2-[[[3-methyl-4-(2,2,-trifluoroethoxy)-2-pyridyl-]methyl]-sulfinyl]benzimidazole



SUPPORTING DOCUMENTS: N/A **RELATED DOCUMENTS: N/A** **CONSULTS:** Biopharm

REMARKS/COMMENTS: All aspects of the manufacturing and quality criteria are identical between the currently approved site [redacted] and the proposed new site [redacted] b(4) An inspection has been scheduled but will not be performed until December 26, 2001

CONCLUSIONS & RECOMMENDATIONS: The supplement is approvable (AE) pending an acceptable inspection.

Arthur B. Shaw, Ph.D.,
Review Chemist, HFD-180

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

R/D Init by: LZhou 15-Nov-2001
ABS**ABS F/T/15-Nov-2001** D:\My Documents Back\Word\F\20-406 Prevacid SCS-044 Review 1.doc

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-20-406
S044
Chem Rec Ltr

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/s/

Arthur B. Shaw
11/15/01 03:00:45 PM
CHEMIST
Approvable but inspection not done yet

Liang Zhou
11/16/01 02:15:35 PM
CHEMIST

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/s/

Arthur B. Shaw
11/15/01 03:00:45 PM
CHEMIST
Approvable but inspection not done yet

Liang Zhou
11/16/01 02:15:35 PM
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CHEMIST

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls Supplement

NDA #:20-406 **SUPPLEMENT #:**SCS-044 **CHEM REVIEW #:**2**REVIEW DATE:**Nov 202001

SUBMISSION TYPE	**DOCUMENT**	**CDER**	**ASSIGNED**
ORIGINAL	13-Jul-2001	16-Jul-2001	17-Jul-2001

SUPPLEMENT PROVIDES FOR: addition of new manufacturing facility for the delayed-release granules b(4) [redacted]

NAME & ADDRESS OF APPLICANT: TAP Holdings, Inc.
2355 Waukegan Road
Deerfield, IL 60015

DRUG PRODUCT NAME: Proprietary: Prevacid Nonproprietary/USAN: lansoprazole

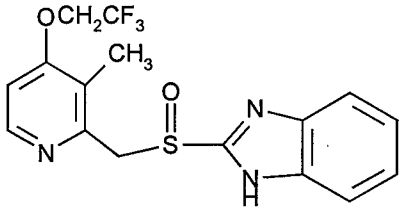
PHARMACOLOGICAL CATEGORY: proton pump inhibitor **INDICATION:** treatment of ulcers

DOSAGE FORM: CAPSULE, DELAYED RELEASE PELLETS **STRENGTH:** 15 and 30 mg

ROUTE OF ADMINISTRATION: oral **HOW DISPENSED:** X **Rx** ___**OTC**

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

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



SUPPORTING DOCUMENTS: N/A **RELATED DOCUMENTS: N/A** **CONSULTS:** Biopharm

REMARKS/COMMENTS: All aspects of the manufacturing and quality criteria are identical between the currently approved site b(4) [redacted] and the proposed new site b(4) [redacted] An inspection has been scheduled but will not be performed until November 26, 2001. However, on Nov 16, the Office of Compliance recommended approval.

CONCLUSIONS & RECOMMENDATIONS: The supplement may be approved.

Arthur B. Shaw, Ph.D.,
Review Chemist, HFD-180

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

R/D Init by: LZhou 20-Nov-2001
ABS**ABS F/T/20-Nov-2001** D:\My Documents Back\Word\F\20-406 Prevacid SCS-044 Review 1.doc

20-NOV-2001 FDA CDER EES Page 1 of 1
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 20406/044	Action Goal:	
Stamp:	16-JUL-2001	District Goal:	12-OCT-2001
Regulatory Due:	16-NOV-2001	Brand Name:	PREVACID
Applicant:	TAP PHARM	Estab. Name:	
	675 NORTH FIELD DR	Generic Name:	LANSOPRAZOLE
	LAKE FOREST, IL 60045		
Priority:	1S	Dosage Form:	(DELAYED RELEASE CAPSULE
Org Code:	180	Strength:	15 & 30MG

Application Comment:

FDA Contacts:	C. PERRY	(HFD-180)	301-827-7310	, Project Manager
	A. SHAW	(HFD-180)	301-827-7310	, Review Chemist
	L. ZHOU	(HFD-180)	301-827-7471	, Team Leader

Overall Recommendation: ACCEPTABLE on 16-NOV-2001by M. GARCIA(HFD-322)301-594-0095

Establishment: CFN [redacted] b(4) b(4)

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: CTR OAI Status: NONE

Estab. Comment: SUPPLEMENT PROVIDES FOR MANUFACTURE OF DELAYED RELEASE GRANULES AT NEW SITE. [redacted] b(4)
(on 19-JUL-2001 by A. SHAW (HFD-180) 301-827-7310)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-JUL-2001				SHAWA
SUBMITTED TO DO	23-JUL-2001	10D			DAMBROGIOJ
ASSIGNED INSPECTION T	27-JUL-2001	GMP			EGASM
INSPECTION SCHEDULED	16-OCT-2001		27-NOV-2001		GARCIAM
DO RECOMMENDATION	14-NOV-2001			ACCEPTABLE BASED ON FILE REVIEW	GARCIAM
ASSIGN FOR POST APPROVAL					
OC RECOMMENDATION	16-NOV-2001			ACCEPTABLE DISTRICT RECOMMENDATION	GARCIAM

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/s/

Arthur B. Shaw
11/20/01 02:40:46 PM
CHEMIST

Liang Zhou
11/20/01 02:58:59 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-406/S044

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-406 (S-044) SUBMISSION DATE: 07/13/01

LANSOPRAZOLE DELAYED RELEASE
CAPSULES CITRATE (PREVACID®)

TAP PHARMACEUTICALS, INC.
675 NORTH FILED DRIVE
LAKE FOREST, IL 60045 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: SUPPLEMENT

CONTENT PAGE

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1. SYNOPSIS/BACKGROUND

Supplement S-044 was submitted to NDA 20-406 for lansoprazole delayed release capsule (Prevacid®), by the sponsor, on July 13, 2001. Lansoprazole delayed release capsule is an approved drug for use in adult patients for the treatment of duodenal ulcers, gastric ulcers, erosive esophagitis, symptomatic gastroesophageal reflux disease (GERD) and pathological hypersecretory conditions including Zollinger-Ellison syndrome. It is also approved for use in adult patients for the maintenance of healing of duodenal ulcers and erosive esophagitis and for H. *pylori* eradication to reduce the risk of reoccurrence of duodenal ulcer. The dosage recommended for each of these indications is specified in the drug product labeling.

In this supplement, the sponsor submits one bioequivalence study evaluating the 30 mg lansoprazole delayed release capsule manufactured at a new site located [redacted] b(4) b(4)
[redacted] 30 mg lansoprazole delayed release capsule manufactured at the approved manufacturing site locate[redacted]
b(4)

II. REVIEW OF BIOEQUIVALENCE STUDY

1. Bioequivalence Study: The bioequivalence of lansoprazole 30 mg capsule manufactured at a new site located in [redacted] with lansoprazole 30 mg capsule manufactured at the approved site located ir[redacted] was assessed in 36 healthy subjects (27 Caucasians, 7 Blacks and 2 Asians consisting of 28 males aged 22-53 years, weighing 67-97 kg and 8 females aged 19-46 years, weighing 55-88 kg) (Protocol M00-239). The body weight specification of ±15% of the ideal body weight b(4) b(4)

ranges based on height, gender and body frame and ≥ 54.4 kg for women and ≥ 61.2 kg for men were met.

Protocol M00-239 was a randomized, open-label, two-period, single dose, crossover study conducted at a single center. During each treatment period, each subject was treated orally with one 30 mg lansoprazole capsule (Lot #01524) manufactured at a new site located [redacted] (Treatment A [Test]) or 30 mg lansoprazole capsule (Lot #671692E21) manufactured at the approved site located in [redacted] (Treatment B [Reference) under fasting conditions. The duration of blood sampling was 12 h for each treatment period. The washout period between treatments was seven days. Pharmacokinetic analysis utilized a non-compartmental method. The mean plasma concentration profiles of lansoprazole for both treatments are presented in Fig. 1. The pharmacokinetic parameters are summarized in Table 1.

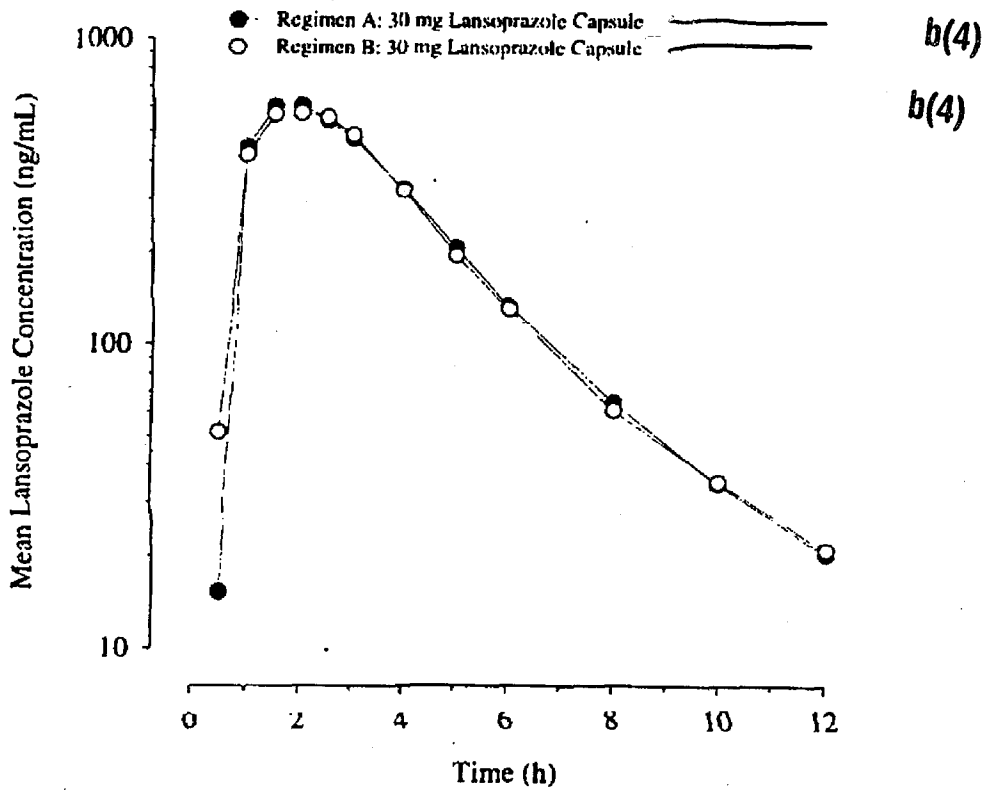
b(4)

b(4)

Fig. 1. Plots of Mean Plasma Lansoprazole Concentration in Healthy Adult Subjects Versus Time Following a 30 mg Oral Dose of Lansoprazole Capsule Manufactured in [redacted] (darkened circle) or in [redacted] (open circle).

b(4)

b(4)



b(4)

b(4)

b(4)

Table 1. Mean ± SD of Lansoprazole Pharmacokinetic Parameters in Healthy Adult Subjects Following Oral Dose of 30 mg of Lansoprazole Capsule Manufactured in [redacted] and Oral Dose of 30 mg of Lansoprazole Capsule Manufactured in [redacted]

b(4)

Pharmacokinetic Parameter	30-mg lansoprazole capsule manufactured [redacted] (test) (N=35)	30-mg lansoprazole capsule manufactured a [redacted] (reference) (N=35)
T_{max} (h)	1.8 ± 0.8	1.8 ± 0.7
C_{max} (ng/mL)	925.7 ± 423.0	893.4 ± 387.2
AUC_t (ng•h/mL)	2404 ± 1759	2379 ± 1832
AUC_∞ (ng•h/mL)	2527 ± 2211	2533 ± 2486
$t_{½}$ (h)‡,$	1.14 ± 0.38†	1.09 ± 0.37
CL/F (L/h)+	23.5 ± 39.6	18.0 ± 10.5

b(4)

‡ Harmonic mean ± pseudo-standard deviation.
$ Evaluations of $t_{½}$ were based on statistical tests for λ.
† N=34.
+ Parameter was not tested statistically.

b(4) The bioequivalence of lansoprazole 30 mg capsule manufactured at a new site located in [redacted] Treatment A [Test]) with lansoprazole 30 mg capsule manufactured at the approved site located in [redacted] (Treatment B [Reference]) was assessed by the two one-sided t-tests procedure at the 90% confidence level using log-transformed values of C_{max} and AUC. The results are summarized in Table 2.

b(4)

b(4)

Table 2. Bioequivalence Summary of a 30 mg Oral Dose of Lansoprazole Capsule Manufactured in [redacted] with a 30 mg Oral Dose of Lansoprazole Capsule Manufactured in [redacted]

Regimens[a] Test *vs.* Reference	Pharmacokinetic Parameters	Central Values[b] Test	Central Values[b] Reference	Relative Bioavailability Point Estimate[c]	Relative Bioavailability 90% Confidence Interval
A *vs.* B	C_{max}	802.6	818.9	0.980	0.853 – 1.126
	AUC_t	1889	1953	0.967	0.868 – 1.077
	AUC_∞	1932	1995	0.968	0.872 – 1.075

b(4)

a Regimen A: One 30-mg lansoprazole capsule manufactured at [redacted] administered orally (test).
Regimen B: One 30-mg lansoprazole capsule manufactured [redacted] administered orally (reference).

b(4)

b Antilogarithm of the least squares means for logarithms.
c *Antilogarithm of the difference (test minus reference) between the least squares means for logarithms.*

b(4)

The confidence intervals of the ratios (test/reference) of the mean, log-transformed $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were within the interval of 0.80 – 1.25 required for bioequivalence. Accordingly, lansoprazole 30 mg capsule manufactured at a new site located in [redacted] is considered bioequivalent with lansoprazole 30 mg capsule manufactured at the approved site located in [redacted]

b(4)

2. Method of Sample Analysis: Analysis of lansoprazole in plasma samples was performed at [redacted] using mainly quality control samples. The LC/MS/MS analytical procedures were utilized. The linearity range of the assay method was [redacted] ng/mL. The limit of quantification was [redacted] ng/mL. The precision and accuracy of the analytical method were assessed for lansoprazole concentrations of [redacted] and [redacted] ng/mL. Inter-day precision and intra-day precision (CV%) ranged from 4.0% to 5.0% (n=18) and 4.5% to 7.2% (n=6), respectively. Inter-day accuracy and intra-day accuracy ranged from 99.7% to 103.4% (n=18) and 101.8% to 106.8% (n=6), respectively. Lansoprazole peak eluted without significant interference by other substances indicating good specificity of the analytical method for lansoprazole.

Bench-top stability of lansoprazole (spiked plasma samples containing [redacted] and [redacted] ng/mL of lansoprazole stored on bench under conditions [redacted]) ranged from [redacted] to [redacted] (n=6 per concentration). Freeze-thaw stability (lansoprazole concentrations of [redacted] and [redacted] ng/ml [redacted] eeze-thaw cycles per concentration]) ranged from [redacted] to [redacted] (n=6 per concentration per cycle). Long-term stability (lansoprazole concentrations of [redacted] ng/mL stored at [redacted] for ≥ [redacted] years [redacted] months) ranged from [redacted] to [redacted] % (n=6 per concentration).

The analytical method and validation data are considered acceptable.

3. Acid Resistance and Drug Release (Dissolution) Testing: The acid resistance and drug testing was performed using [redacted] operated at [redacted] rpm. The other aspects of the testing procedures were as follows:

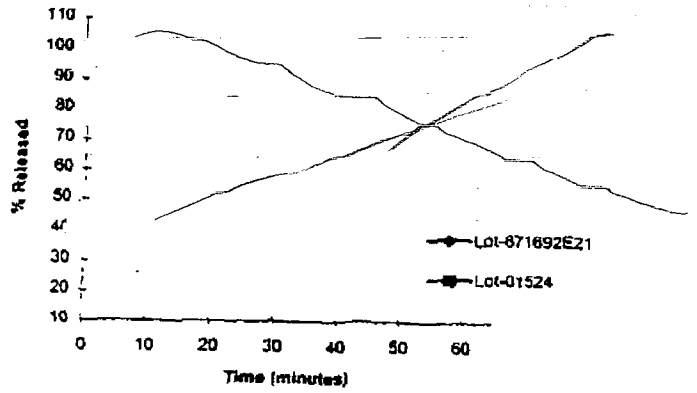
	Acid Resistance Test	Drug Release Test
Medium:	[redacted]	[redacted]
Assay method:	UV absorbance at [redacted] nm	UV absorbance at [redacted] nm and [redacted] nm

The summary of acid resistance and drug release testing results for capsule Lot #01524 manufactured in [redacted] (Test) and Lot #671692E21 manufactured in [redacted] (Reference) (n=12 capsules per lot) are presented below.

Lot	Acid Resistance (%)	Mean % Released (sd)
671692E21		
01524		

b(4)
b(4)
b(4)

Mean Dissolution Profiles for Lansoprazole, 30 mg Delayed Release Capsules



b(4)

Based on these results, the sponsor proposes the following acid resistance and dissolution specifications:

Acid Resistance: Q ≤ / % i / min b(4)
Dissolution: Q ≥ / % in / min. b(4)

b(4) At the / min time point, the mean ± SD Q value is —— % for the test formulation b(4)
and — % for the reference formulation. It appears that a dissolution specification of
b(4) Q ≥ % in / min would be more appropriate (see Overall Comment [page 6]).

III. OVERALL COMMENT

1. If the 15 mg lansoprazole capsule will also be produced at the proposed new site, comparative acid resistance and dissolution information for the old site and the new site needs to be provided if the 15 mg and the 30 mg capsules are composition proportional. The bioequivalence of the 15 mg capsules produced at the new site and the old site needs to be established if the 15 mg and the 30 mg capsules are not composition proportional.

b(4)

2. In this supplement, the proposed drug release (dissolution) specification is Q ≥ /% in /min. However, at the / min dissolution testing time point, the mean ± SD percentage drug release is —% for the test formulation and — % for the reference formulation. Please revise the drug release specification to Q ≥ /% in / min.

b(4) b(4) b(4) b(4)

IV. RECOMMENDATION

Supplement S-044 submitted to NDA 20-406 for lansoprazole delayed release capsule (Prevacid®), by the sponsor, on July 13, 2001, has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. Prior to supplement approval, the sponsor needs to satisfactorily address the issues raised in Overall Comment 1 above and those raised in the Overall Comment 2 above if the reviewing chemist concurs.

Please convey this Recommendation and Overall Comment 1 above, as appropriate, to the sponsor. Overall Comment 2 above needs to be brought to the attention of the reviewing chemist and should be conveyed to the sponsor if he concurs.

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D. _____

cc: NDA 20-406, HFD-180, HFD-180 (Perry), HFD-870 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

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/s/

David Udo
11/16/01 11:18:46 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/16/01 11:51:12 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-406/S044

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-406/S-044

PRIOR APPROVAL SUPPLEMENT

TAP Pharmaceutical Products, Inc.
Attention: Nancianne Knipfer, Ph.D.
Senior Regulatory Affairs Specialist
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Prevacid® (lansoprazole) Delayed-Release Capsules
NDA Number:	20-406
Supplement Number:	044
Date of Supplement:	July 13, 2001
Date of Receipt:	July 16, 2001

This supplement proposes the following change: a new manufacturing site for lansoprazole delayed-release granules at [redacted] b(4)

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 13, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 16, 2001 and the secondary user fee goal date will be January 16, 2002.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at (301) 827-7475.

Sincerely,

{See appended electronic signature page}

Cheryl Perry
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Cheryl Perry
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