CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-428

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-428
SUPPL # N/A
Trade Name PREVACID SoluTab Delayed-Release Orally Disintegrating Tablet
Generic Name lansoprazole
Applicant Name TAP Pharmaceuticals, Inc.
HFD- 180
Approval Date August 30, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /_ _/

   b) Is it an effectiveness supplement? YES /___/ NO /_X /

      If yes, what type(SE1, SE2, etc.)? N/A

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /__/ NO /_x_/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      This application is supported by data from 9 bioequivalence studies and contains no clinical data. The sponsor calls the studies bioequivalence studies and does not claim that they are clinical studies.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:
      _N/A

d) Did the applicant request exclusivity?

YES /__/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-406 Prevacid Delayed-Release Capsules

NDA # 21-281 Prevacid Delayed Release Oral Suspension

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X__/

APPEARS THIS WAY
ON ORIGINAL

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS

{See appended electronic signature page}

Signature of Preparer Date
Title:

{See appended electronic signature page}

Signature of Office or Division Director Date

cc:
Archival NDA 21-428
HFD-180/M.Furness
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Joyce Korvick
8/30/02 02:34:57 PM
for Victor Raczkowski

Brian Strongin
8/30/02 11:42:00 AM
Please sign for Victor.

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-428 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: October, 30, 2001 Action Date: August 30, 2002

HFD- 180 Trade and generic names/dosage form: PREVACID SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablet

Applicant: TAP Pharmaceuticals, Inc. Therapeutic Class: Proton Pump Inhibitor

Indication(s) previously approved:

None. This is a new NDA.

Indication(s)approved in this application:

1. H. pylori Eradication to reduce the risk of duodenal ulcer recurrence.
2. Short-Term Treatment of Active Duodenal Ulcer
3. Maintenance of Healed Duodenal Ulcers
4. Short-Term Treatment of Active Benign Gastric Ulcer
5. Healing of NSAID-Associated Gastric Ulcer
6. Risk Reduction of NSAID-Associated Gastric Ulcer
7. Gastroesphageal Reflux Disease
8. Maintenance of Healing of Erosive Esophagitis
9. Pathological Hyper Secretory Conditions Including Zollinger-Ellison Syndrome

A pediatric plan was not submitted. A plan was requested in the approval letter within three months of approval.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 9

Indication #1: ___

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
  Too few children with disease to study
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

Products in this class for this indication have been studied/labeled for pediatric population

- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is com plete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments: The applicant has requested deferral until after the adult PONV supplement is approved.

If there are additional indications, please proceed to Attachm ent A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

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/s/

Brian Strongin
8/30/02 02:38:55 PM
CSO

Joyce Korvick
8/30/02 04:04:17 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 8/30/02

FROM: Joyce A Korvick, MD, MPH

DGCDP/ODE III

SUBJECT: **Director (Deputy) Summary Approval Comments**
NDA 21-428

APPLICANT: TAP Pharmaceutical Products, INC.

DRUG: Prevacid® SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablets.

DIVISION RECOMMENDATION:

The Division recommends approval of Prevacid® SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablets. The approval letter was accompanied by agreed upon labeling (package insert) changes that will be discussed below.

Comments:
This new drug application (NDA 21-428) provides for a new dosage form of Prevacid, Prevacid SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablets. It is formulated to disintegrate in the mouth without chewing while retaining the enteric coating of the granules.

The currently approved lansoprazole label includes both the Delayed-Release Capsule and Delayed Release Oral Suspension dosage forms approved for the following indications:

- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence,
- Short-term treatment of active duodenal ulcer,
- Maintenance of healed duodenal ulcers,
- Short-term treatment of active benign gastric ulcer,
- Healing of NSAID-associated gastric ulcer,
- Gastroesophageal reflux disease,
- Maintenance of healing of erosive esophagitis,
- Pathological hyper-secretory conditions including Zollinger-Ellison Syndrome.

This dosage form was demonstrated to be bioequivalent to the capsule. Therefore, this new dosage form is acceptable for use in the currently approved indications. There are

no concerns regarding the use of this dosage form in pediatric patients from 1 to 11 years of age.

Labeling issues that were negotiated within this review cycle centered on the Dosage and Administration, Alternative Administration Options Section and the Precautions, Information for Patients, Alternative Administration Options. Specifically for patients who have difficulty swallowing the capsules.

This was the subject of a Discipline Review Letter sent to the applicant during this review cycle.

Joyce Korvick, MD, MPH
Deputy Division Director
Division of Gastrointestinal and Coagulation Drug Products
CDER/FDA

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/s/

Joyce Korvick
8/30/02 04:16:29 PM
MEDICAL OFFICER

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TAP PHARMACEUTICAL PRODUCTS INC.

'5 North Field Drive
Lake Forest, IL 60045

NDA Amendment
Labeling

August 29, 2002

Electronic Media for Archive

Victor Raczkowski, M.D.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Document Control Room 6B-45
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: PREVACID® SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablets
NDA 21-428/Amendment 014
Labeling

Dr. Raczkowski:

The sponsor, TAP Pharmaceutical Products Inc. (TAP), submits this amendment to a New Drug Application under the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.60. The purpose of this amendment is to submit revised labeling.

In reference to the pending NDA listed above and the teleconference held with representatives of the Division and TAP on August 28, 2002, TAP has revised the package insert as follows:

- Removed the hyphen between [redacted] and [redacted] throughout the package insert.
- Under the PRECAUTIONS [redacted] Per the Agency's request, this information will only appear under the DOSAGE AND ADMINISTRATION section.
- The following changes were made under both the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections:
    - The spelling of "CLINICALLY" was corrected.

- Per the Agency's request, the following statement was removed:

- Replaced the word "disperse" with "disintegrate" under the directions for administering PREVACID SoluTab.

- Per the Agency's request, the following statement was removed:

- Apple juice was included as a juice suitable for use with the capsule granules. *In vivo* bioavailability data was previously submitted (6/3/96) and approved (12/24/96) for NDA 20-406 for PREVACID® (lansoprazole) Delayed-Release Capsules (S-012).

Per the verbal agreement with the Agency, the statement re will be removed from all promotional and advertising material at the time of next printing or revision.

The enclosed submission consists of 1 paper volume and a CD-ROM that includes the *proposed.pdf* file. All differences from the package insert approved for NDA 20-406/S-045 and NDA 21-281/S-002 on May 3, 2002 are highlighted. A word file is included as a review aid. All electronic files and media provided in this submission have been scanned for computer viruses using McAfee VirusScan version 4.5.0.534 (Network Associates, Inc.).

Any questions or comments on this submission can be delivered to my attention.

Sincerely,

Nancianne Knipfer

Nancianne Knipfer, Ph.D.
Project Manager, Regulatory Affairs
847-236-2193
847-236-2880 (fax)

Attachment
CC: Melissa Furness, Regulatory Project Manager

TAP Pharmaceutical Products Inc.
675 North Field Drive
Lake Forest, Illinois 60045

Facsimile Cover Sheet

To: Melissa Furness
Company: FDA
Phone:
Fax: 1-301-443-9285

From: Nancianne Knipfer
Project Manager Regulatory Affairs
Phone: (847) 236-2193
Fax: (847) 236-2880

Date: August 21, 2002
Pages including this cover page: 26

Melissa,

Attached please find our response to the Agency's Discipline Review Letter dated August 14, 2002. This fax does not include the supporting attachments. These will be submitted today.

Please feel free to call me if you have any questions.

Sincerely,

Nancianne Knipfer

Nancianne Knipfer, Ph.D.
Project Manager, Regulatory Affairs

TAP PHARMACEUTICAL PRODUCTS INC.

Field Drive
ke Forest, IL 60045

NDA Amendment
Response to Discipline Review Letter

August 21, 2002

Victor Raczkowski, M.D.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Document Control Room 6B-45
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: PREVACID® SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablets
NDA 21-428/Amendment 012
Response to Discipline Review Letter dated August 14, 2002

Dr. Raczkowski:

The sponsor, TAP Pharmaceutical Products Inc. (TAP), submits this amendment to a New Drug Application under the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.60. The purpose of this amendment is to respond to the Agency's Discipline Review Letter dated August 14, 2002.

Response Approved by:

Ashraf Youssef, M.D., Ph.D., DABT
Senior Toxicology Investigator
Drug Safety

8/21/02
Date

Shuyen Huang, Ph.D.
Project Leader
Pharmaceutical Development

8/21/2002
Date

D.R. Vishwasrao
Dilip Vishwasrao, Ph.D.
Senior Research Investigator
Pharmaceutical Development

8/21/2002
Date

Dean Shaffer, Ph.D.
Program Manager
Pharmaceutical Development

8/21/02
Date

FDA Comment:

The environmental assessment is considered deficient for this application. The following items need to be addressed:

1. **Provide the specific citation for the categorical exclusion, for example 21 CFR 25.31 a, b, c.**
2. **Calculate the total number of kilograms of lansoprazole based upon the total lansoprazole use for all of your applications.**
3. **Calculate the level of lansoprazole use by using a timeframe that is based upon the highest quantity of lansoprazole use in any of the next five years**

Note: Additional information on the environmental assessment calculation may be obtained from the Environmental Assessment Guidance in section III.A.2 (http://www.fda.gov\cder\guidance\index.htm).

TAP Response:

The following are TAP's answers regarding deficiencies in the environmental assessment (EA) requests and include:

1. Specific citations of 21 CFR 25.31 (a), (b) and (d) as appropriate.
2. The calculated total number of kilograms of lansoprazole for all applications.
3. The calculated highest quantity for lansoprazole in the next five years

TAP Pharmaceutical Products Inc. has filed two NDAs (NDA 20-406 and NDA ———) pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act. Each included an EA, arranged per the format required by 21 CFR 25.31(a)(1993) and FDA's Guidance for Industry "Environmental Assessment of Human Drugs and Biologics Applications " (1998). For your convenience we have attached the two EA statements (Attachment 1 and 2).

The following includes all the requested calculations and references of all the manufactured, packaged and distributed dosages of Prevacid® (lansoprazole), i.e, 15 and 30 mg. This EA covers all the retail and samples for all formulations (i.e., capsules, oral suspensions and tablets) (See Table 1). It also includes the support for TAP's claim of categorical exclusion. The drug product, Prevacid has been specifically formulated as capsules, oral suspensions or tablets for oral administration.

Claim of Categorical Exclusion

FDA's Guidance for Industry on "Environmental Assessment of Human Drugs and Biologics Applications" published in July 1998, states that certain classes of actions are subject to categorical exclusion and therefore, ordinarily, do not require the preparation of an Environmental Assessment because, as a class, these actions, individually or cumulatively, do not significantly affect the quality of the human environment (21 CFR 25.5(c)).

A categorical exclusion for Prevacid is sought on the basis that the estimated concentration of lansoprazole at the point of entry into the aquatic environment [Expected Introduction Concentration (EIC)] will be [redacted]. The [redacted] year production estimate for lansoprazole indicates that lansoprazole would not exceed [redacted]. Accordingly, the calculated EIC in the [redacted] year (worst case scenario of the upcoming [redacted] years) of production is expected to be [redacted], which is the [redacted] cut-off limit proposed by the FDA, CDER (1995). See Table 1 for all calculations. Furthermore, the included EAs from previous submissions support the lack of any significant impact of lansoprazole on the environment.

Table 1 **Forecasted Annual Requirements of the Lansoprazole Drug substance and the Expected Introduction Concentrations**

Year	Dosage	Total Number of Produced Capsules (Prevacid)	Total Number of Produced LFDT (Prevacid)	Total Production in (Kg/year)	Expected Introduction Concentration (EIC)-
2003	30 mg	[		]	
	15 mg				
	TOTAL				
2004	30 mg	[		]	
	15 mg				
	TOTAL				
2005	30 mg	[		]	
	15 mg				
	TOTAL				
2006	30 mg	[		]	
	15 mg				
	TOTAL				
2007	30 mg	[		]	
	15 mg				
	TOTAL				

1 Figures are based on TAP Marketing estimates for retail and samples; and includes total capsules and oral suspensions and PREVPAC® (under capsules) and tablets (under LFDT).
2 Expected introduction concentration (EIC) of lansoprazole at the point of entry into the aquatic environment
3 The decline in production is based on the expected impact of the introduction of new products

The EIC of an active moiety into the aquatic environment based on FDA guidance is estimated as follows:

Conclusions

The experimental data provided in the attached two EA statements support the lack of any impact of lansoprazole on the environment. The worst-case scenario in the upcoming ——————————is within the limit of — Accordingly, we are submitting the current EA package under (21 CFR 25.31(b)), and believe that the current EIC estimation qualifies for categorical exclusion. To the applicant's knowledge, no extraordinary circumstances exist (21 CFR 25.15 (d)).

FDA Comment:

The following are Comments/Recommendations that we have after completion of our review of the Chemistry, Manufacturing and Controls section of your submission:

- **Provide the vendor's Certificate of Analysis for the excipients and the testing protocols used to qualify the excipients before their use in manufacturing.**

TAP Response:

Takeda receives excipients along with a certificate of analysis issued by the vendor. Each lot of compendial excipient is then tested by Takeda per USP/NF specifications and released prior to its use in manufacturing. The non-compendial excipients, namely, Lactose Monohydrate-Microcrystalline Cellulose Spheres and Strawberry Durarome flavor are tested and released by their respective specifications and test methods which were included in the original NDA.

Tables 2 and 3 provide the lot number information for excipients used for manufacturing of bioequivalence (BE) Lot 01274 (15 mg) and Lot 01224 (30 mg) PREVACID SoluTab. Two lots of enteric-coated microgranules (Lot 006 and Lot 010) were combined with two lots of inactive granules (Lot 01124 and Lot 01134) to make one batch of mixed granules (Lot 01174). This lot of mixed granules was then split to manufacture Lot 01274 of 15 mg tablets and Lot 01224 of 30 mg tablets.

Table 2. Vendor and Lot Information for Excipients used for Enteric Coated Microgranules in Bioequivalence Lots of Lansoprazole Tablets

Excipient	Vendor	Vendor Lot No.	Takeda Lot No.	Vendor COA Specification	Takeda COA Specification
Magnesium Carbonate		D00324	155	USP, JP,EP	USP
Low-Substituted Hydroxypropyl Cellulose		703093	012	JP	NF
Hydroxypropyl Cellulose		JE-1231	001	JP	NF
Hydroxypropyl Methylcellulose		708431	004	JP	USP
Titanium Dioxide		I90160206	122	USP, JP,EP	USP
Talc		0502	222	USP, JP,EP	USP
Mannitol		K26596188	230	JP	USP
		K26847288	231	JP	USP
Glyceryl Monostrearate		Y032302	001	JP	USP
Polysorbate 80		S95500	010	JP	NF
Ferric Oxide (Yellow)		9803098	003	E172	USP
Ferric Oxide (Red)		75-3704	002	E172	USP
Methacrylic Acid Copolymer		1291114324	067	NF, EP, JPE	NF
Polyacrylate		1290412026	001	EP, JPE	Ph. Eur.
Polyethylene Glycol 8000		S003107	322	NF, EP, JP	NF
Citric Acid		S902253	001	JP	USP
Triethyl Citrate		N93094	001	JP	NF

Table 3 Vendor and Lot Information for the Excipients used for Inactive Granules and Mixed Granules in Bioequivalence Lots of Lansoprazole Tablets

Excipient	Vendor	Vendor Lot No.	TIL Lot No.	Vendor COA Specification	Takeda COA Specification
Mannitol		K27184588	000141	JP	USP
Low-Substituted Hydroxypropyl Cellulose		003094	000142	JP	NF
Citric Acid		S909043	000145	JP	USP
Microcrystalline Cellulose		K043	000143	JP	NF
Crospovidone		03000026897	000144	NF, EP, JPE	NF
Aspartame		MT90908	000146	JPE	NF
Strawberry					
Magnesium Stearate		X08458	000038	NF, EP, JP	NF

Vendor certificates of analysis for all the excipients used in the BE lots are provided in Attachment 3 (——————Some of these documents are in Japanese. For the BE lots, ——————tested excipients used in the inactive and mixed granules for——————For commercial manufacture.——————will test and release the excipients used in the inactive granules and mixed granules.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: August 21, 2002

To: Nancianne Knipher, Ph.D.	**From:** Melissa Furness
Company: TAP Pharmaceutical Products, Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (847) 236-2880	**Fax number:** (301) 443-9285
Phone number: (847) 236-2193	**Phone number:** (301) 827-7450

Subject: Marked-Up Draft Labeling from NDA 21-428

Total no. of pages including cover: 36

Comments:

I've attached our mark-up of the draft labeling submitted with NDA 21-428. We look forward to discussing it with you on Friday 08/23/02. Thanks.

Document to be mailed: ☐ YES ☑ NO

36 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-428

DISCIPLINE REVIEW LETTER

TAP Pharmaceutical Products Inc.
Attention: Nancianne Knipher, Ph.D.
Project Manager, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Ms. Knipher:

Please refer to your October 30, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid® (lansoprazole delayed-release orally disintegrating tablet) Solutab.

We also refer to your submissions dated April 26, June 20, and July 11, 2002.

Our reviews of the Chemistry,Manufacturing and Controls, and Biopharmaceutics sections of your submission are complete, and we have identified the following deficiencies:

- The environmental assessment is considered deficient for this application. The following items need to be addressed:
  1. Provide the specific citation for the categorical exclusion, for example, 21 CFR 25.31 a, b, or c
  2. Calculate the total number of kilograms of lansoprazole based upon the total lansoprazole use for all of your applications
  3. Calculate the level of lansoprazole use by using a timeframe that is based upon the highest quantity of lansoprazole use in any of the next five years.

  Note: Additional information on the environmental assessment calculation may be obtained from the Environmental Assessment Guidance in section III.A.2 (http://www.fda.gov\cder\guidance\index.htm).

Note: these above deficiencies will need to be addressed prior to approval of this application.

The following are Comments/Recommendations that we have after the completion of our review of the Chemistry, Manufacturing and Controls section of your submission:

- Provide the vendors' Certificates of Analysis for the excipients and the testing protocols used to qualify the excipients before their use in manufacturing.

- Explain how the labeled amount (assay) calculation is performed on enteric coated lansoprazole microgranules. Justify the assay results of [redacted]

We would like to see you commit in writing to the following phase IV commitment:

- Provide a timeframe for the tablet imprinting development and implementation. Provide this information in a prior approval supplement with at least 3 months stability data.

If you have any questions, please call Melissa Furness, Regulatory Project Manager, at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Victor Raczkowski, M.D., M.Sc.
Acting Director
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
8/14/02 10:20:24 AM
for Victor Raczkowski

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 5, 2002

FROM: Hugo E. Gallo-Torres, M.D., P.N.S., Ph.D.
Medical Team Leader
Division of Gastrointestinal Coagulation Drug Products, HFD-180

SUBJECT: Recommendations for Regulatory Action:
NDA 21-428, Prevacid® Solutab (Lansoprazole delayed-release orally Disintegrating tablets, 15 and 30 mg)

Tap Pharmaceutical Products Inc.

TO: Division File, NDA 21-428

I. BACKGROUND INTRODUCTION:

The sponsor has submitted NDA 21-428 in support of Prevacid® Solutab, an orally administered tablet to be placed on the tongue and expected to disintegrate in the mouth in 30 to 60 seconds, without chewing. The dissolved contents are then swallowed with or without water. This mode of administration of lansoprazole is intended for all patients but may be more useful in patients who **have difficulties swallowing capsules.**

Prevacid® (lansoprazole) is a proton pump inhibitor (PPI) approved for the treatment of a variety of indication where pronounced antisecretory effects are needed. These indications include short-term treatment of active duodenal ulcer, *H. pylori* eradication in combination with amoxicillin plus clarithromycin, gastric ulcer, and short- and long-term treatment of gastroesophageal reflux disease (GERD) and hypersecretory conditions.

Because lansoprazole like all PPIs, is unstable in acidic environment the drug product dosage form requirement is to deliver the PPI as an enteric-coated granule resistant to acidic environment. Lansoprazole is already approved as Delayed-Release **capsules** and Delayed-Release **suspension**. The current NDA submission is for a tablet formulation with enteric-coated granules that are different from the enteric-coated granules used in the already approved dosage forms (capsules and suspension).

In support of the current application, the sponsor submitted[1]: a) results of PK study reports [2 pivotal bioequivalence (BE) studies (**M98-948** and **M98-949**) and 2 supportive

[1] • **Original submission:** 10/30/01
• **Food Effect Study and *in vitro* stability data:** 02/20/02, 03/05/02, 04/11/02, 04/12/02, 04/26/02 and 06/21/02.

studies] plus 5 supportive PK study summaries; b) data on chemistry, manufacturing and controls, with an environmental assessment; and c) no clinical safety and efficacy data with the delayed-release orally disintegrating table (ODTs). [NOTE: It is concluded that no new S & E data are needed]. Therefore, demonstration of BE between the delayed-release ODTs vs the delayed-release capsules is critical to the approval of the newly proposed dosage form.

II. Summary of Reviews

A. CMC

Details of the multi-step process for the manufacture of the final drug product, that meets the manufacturing and patient requirements, are given in Dr. J. Sieczkowski Chemistry Review of 07/24/02. Lansoprazole coated (LC) microspheres, the starting point, are composed of [redacted]

Among the inactive ingredients [redacted] and [redacted] are used to increase [redacted] upon disintegration of the tablet orally. The final step in tablet manufacturing is [redacted]

[redacted] Additional details on the drug product and the drug substances are given in Dr. Sieczkowski's Chemistry Review of 07/24/02.

- The Chemistry Review Recommendations are:

1. The application is **approvable** with respect to CMC;

2. To assess the sponsor's responses to deficiencies in environmental assessment; and

3. [redacted]

[NOTE: The CMC deficiencies listed on pages 66-67 of Dr. Sieczkowski's reviews are important to enhance the understanding of the NDA application but are not sufficiently important to recommend non-approval of the application]. It is further recommended to

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- **Response to FDA Information Requests:** 07/11/02

request Post-Marketing commitment from the applicant for Methods Validation, Tablet Imprinting, and Dosage Form Name.

B. Clinical Pharmacology and Biopharmaceutics

The summary that follows was extracted from Dr. Tien-Chen's review of August 8,2002 and his presentation on the Biopharm Day of July 31, 2002 [Div. of PE-II, Office of Clinical Pharmacology and Biopharmaceutics = OCPB].

Results of pivotal studies **M98-948 and -949** show that both the 15 and 30 mg Prevacid® Solutab tablets are bioequivalent[3] to the currently marketed Prevacid® capsules[4]. The oral disintegrating times (on the tongue) are (mean ± SD) 48.4 ± 19.4 seconds for the 15 mg tablet and 53.4 ± 21.5 seconds for the 30 mg tablet. Supportive study **M99-070**, which tested the to-be-marketed delayed-release orally disintegrating formulation administered with or without water, also showed bioequivalence.

The approved Prevacid® capsules and suspension must be taken on an empty stomach (before eating) due to known food effects. Because of this as well as marked differences in formulation between Prevacid® Solutab tablets and Prevacid® capsules, the sponsor was asked to do a food effect study with the tablets formulation. Study **MO2-421**, a single dose, 2 X 2 crossover study which used Prevacid® Solutab 30 mg tablets (the same biobatch) in 36 healthy volunteers showed pronounced food effects on Prevacid® Solutab. These pronounced food effects were manifested by a 73% ↓ in C_{max} and 52% ↓ in $AUC_{0-\infty}$. Therefore, as the capsules and suspension, the Prevacid® Solutab tables should be taken on an empty stomach.

The sponsor proposed two alternative methods of administration: [redacted] However, the submitted [up to 2 h] stability data **do not support these proposed alternative methods of administration.** In addition, the CPB reviewer noted that there were no data evaluating the [redacted]

- OCPB finds NDA 21-428 for Prevacid® Solutab 15 and 30mg tablets acceptable. The Biopharm reviewer proposes:

[3] This conclusion is further supported by the fact that an audit of the two BE study sites conducted by the DSIs concluded that M98-948 and -949 are acceptable for Agency's review.

[4] A previously validated assay method for the determination of plasma lansoprazole concentration, also used in the current NDH, is acceptable.

1.

2. Specific changes (deletions) in the labeling.

III. Conclusions/Recommendations

1. NDA 21-428 **should be approved.**

This recommendation is based on results of pivotal studies **M98-948** and **-949** demonstrating that the proposed Prevacid® Solutab tablets (lansoprazole delayed-release orally disintegrating tablets) are **bioequivalent** to the approved Prevacid® capsules. Bioequivalence was also shown in supportive study **M99-070**, which tested the to-be-marketed delayed-release orally disintegrating formulation administered **with** or **without water**. Study **MO2-421** showed the expected/predictable food effects (a marked decrease in bioavailability as measured by a 73% ↓in C_{max} and 52% ↓ in $AUC_{0-\infty}$. Therefore, in a fashion similar to the capsule and suspension formulations of Prevacid®, the Solutab tablets should be taken on an empty stomach.

2.

It is recommended that until the sponsor proposes an adequate alternative medium, the mode of administration of Prevacid® Solutabs should not be altered.

The use of the PPI through NG tube with the capsule should continue, as described in the currently approved labeling.

.....
Hugo E. Gallo-Torres, M.D., P.N.S., Ph.D.

cc:
NDA 21-428
HFD-180
HFD-180/HEGallo-Torres
HFD-180VRaczkowski
HFD-180/JKorvick
HFD-180/FHoun
HFD-180/MFurness
HFD-180/LZhou
HFD-180/JSieczkowski
HFD-870/Tien-Mien Chen
HFD-870/SDoddapaneni
HFD-870/SAl-Fayoumi
HFD-180/NNair
HFD-180/GDellaZanna
HFD-870/HMalinowski
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/s/

Hugo Gallo Torres
8/21/02 03:45:47 PM
MEDICAL OFFICER

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ON ORIGINAL

APPEARS THIS WAY

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: March 13, 2002	**DUE DATE:** May 28, 2002	**ODS CONSULT #:** 02-0041

TO: Victor Raczkowski, M.D.
Acting Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

THROUGH: Cheryl Perry
Project Manager
HFD-180

PRODUCT NAME: **Prevacid SoluTab** (Lansoprazole Oral Disintegrating Tablets) 15 mg and 30 mg **NDA#: 21-428**	**NDA SPONSOR:** Tap Pharmaceuticals Inc

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Prevacid SoluTab" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objections to the use of the proprietary name, Prevacid SoluTab. This name, along with its associated labels and labeling, must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document. However, DMETS recommends implementing the labeling revisions outlined in Section III of this review, in order to minimize potential errors with the use of this product.

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 28, 2002

NDA#: 21-428

NAME OF DRUG: Prevacid SoluTab (Lansoprazole Oral Disintegrating Tablets) 15 mg and 30mg

NDA HOLDER: Tap Pharmaceuticals Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), for assessment of the tradename "Prevacid SoluTab," regarding potential name confusion with other proprietary drug names. The container labels, carton labeling and package insert labeling for Prevacid SoluTab were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Prevacid SoluTab is a gastric acid (proton) pump inhibitor that is a member of the class of antisecretory compounds known as substituted benzimidazoles. These antisecretory compounds suppress gastric acid secretion but do not exhibit anticholinergic or histamine H_2 receptor antagonist properties. Prevacid SoluTab is supplied as a disintegrating tablet for oral administration. The tablet should not be crushed or chewed during administration. The tablet is placed on the patient's tongue and allowed to disperse until the particles can be easily swallowed. Prevacid SoluTab disintegrates rapidly and additional liquid administration is usually not necessary. Prevacid SoluTab contains phenylalanine. Prevacid SoluTab is used for the treatment of the following indications:

- Short-term treatment of active duodenal ulcer
- Maintenance of healed duodenal ulcers
- Short-term treatment of active benign gastric ulcer
- Healing of NSAID-associated gastric ulcer
- Gastroesophageal reflux disease
- Maintenance of healing of erosive esophagitis
- Pathological Hypersecretory Conditions including Zollinger-Ellison Syndrome
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence

The usual dosage range is 15 to 30 mg daily for approximately four to eight weeks for most of the indications of use. *H. pylori* eradication is usually treated with a dose of 30 mg every 12 hours in combination with amoxicillin and/or clarithromycin. Treatment of Zollinger-Ellison Syndrome may require daily doses up to 120 mg.

II. RISK ASSESSMENT:

A search was conducted of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to Prevacid SoluTab to a degree where potential confusion between drug names could occur under the usual clinical practice settings. Searches of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. Members of DMETS' Expert Panel were queried via e-mail to provide their opinion on the acceptability of the proposed name Prevacid.

The standard DMETS prescription analysis studies were not conducted because the proprietary name Prevacid was approved on May 10, 1995.

Additionally, the FDA Adverse Event Reporting System (AERS) was searched to determine if any current confusion exists with the use of the name Prevacid.

A. REFERENCE SEARCH AND EXPERT PANEL OPINION

The search of the reference texts and databases did not identify any sound-alike or look-alike names of concern. Members of the DMETS Expert Panel were queried via e-mail to gather professional opinions on the safety of the proprietary name, Prevacid SoluTab, and any potential concerns regarding drug marketing and promotion. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

In their e-mail responses, several of the Expert Panel members identified Solu-Cortef, Solu-Medrol, and ——— as proprietary names that contained the prefix 'Solu' and were thought to have the potential for confusion with SoluTab, the modifier part of the proprietary name Prevacid SoluTab. The Expert Panel also noted that Remeron SolTab and Celestone Soluspan have modifiers that may be confused with Prevacid SoluTab. These products are listed in Table 1 (page 4) along with the dosage forms available and usual dosage.

DDMAC expressed no concerns with regard to the name.

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[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Solu-Cortef was identified as a potential look-alike product that may have potential for confusion with *SoluTab*, the modifier of *Prevacid SoluTab*. Three of the most common indications of use for *Solu-Cortef* are the treatment of adrenal cortex insufficiency, inflammatory disorders, and allergic disorders. Both products begin with the same prefix "Solu." Additionally, each product ends in letters that may be similar when scripted 'tef' vs. 'tab. The usual dosage range of *Solu-Cortef* is 100 mg to 500 mg per dose. Potentially, there could be confusion between specific doses of Solu-*Cortef* and *Prevacid SoluTab*, if the 15 mg and 30 mg strengths of *Prevacid SoluTab* are written with a trailing zero. In spite of these similarities, there are other distinguishing factors between *Solu-Cortef* and *Prevacid SoluTab* that may decrease the potential risk of medication errors. *Solu-Cortef* is an injectable product that is administered via the intravenous or intramuscular route whereas *Prevacid SoluTab* is a tablet that is administered orally. Moreover, it is unlikely that prescribers will prescribe 'SoluTab' the modifier without the proprietary name—Prevacid. The differences in the route of administration and the improbability that the modifier will be ordered without the proprietary name would decrease the potential risk of medication errors between *Solu-Cortef* and *Prevacid SoluTab*.

Solu-Medrol and *SoluTab* may look-alike when scripted according to the Expert Panel. Some of the indications of use for Solu-Medrol include inflammatory disorders, allergic reactions, ophthalmic disorders, and endocrine disorders. Both products begin with the prefix 'Solu.' The usual dosage range for Solu-Medrol is 10 mg to 250 mg per dose. Solu-Medrol and SoluTab may share overlapping strengths and dosage regimens (i.e., daily). The dosage formulation and the routes of administration are different (intravenously/intramuscular vs. oral). Additionally, as noted above the improbability that the modifier will be ordered without the proprietary name would decrease the potential risk of medication errors.

———— is the other product identified as a potential look-alike that may have potential for confusion with the Prevacid modifier (SoluTab). ———— established name is Dexamethasone Sodium Phosphate. ———— is used in the treatment of dermatologic disorders, endocrine disorders, allergic reactions and many other disorders. The usual dosage range of ———— is 0.5 mg to 40 mg. The daily dosage regimen and strengths of ———— and *Prevacid SoluTab* may overlap. However, the difference in the route of administration and the fact that clinicians will probably not prescribe the modifier without the proprietary name may decrease the potential risk of medication errors.

Remeron SolTab and *Prevacid SoluTab* may look-alike according to the Expert Panel. The modifiers SolTab and SoluTab look-alike when scripted. *Remeron SolTab* is indicated for the treatment of depression. *Remeron SolTab* is dispensed as a 15 mg, 30 mg, and 45 mg orally disintegrating tablet. The dosage formulation and strengths overlap for both *Remeron SolTab* and *Prevacid SoluTab*. Both products are usually administered once daily, though *Prevacid SoluTab* can be administered every twelve hours when treating H. Pylori. These similarities may contribute to the potential occurrence of medication errors relating to name confusion. However, several factors may decrease the risk of medication errors between these two products. Although the first letters—'R' vs. 'P'—of both products can be misinterpreted, overall Remeron and Prevacid do not look-alike when scripted. Additionally, an AERS search did not reveal any reports of medication errors related to confusion between Remeron and Prevacid tablets. The tablet formulation of both products has been approved for approximately six years. Therefore DMETS has no current reason to believe the addition of a modifier will change this scenario. Furthermore, the

pharmacological class and indications for use of these products are different and they probably will not be stored near each other on pharmacy shelves. Based on these differences the risk of product confusion is minimal.

The Expert Panel identified the modifier of Celestone Soluspan as a potential look-alike. *Celestone Soluspan* is indicated for various disorders. Endocrine, inflammatory, and rheumatic disorders are only a few of the indications of use. *Celestone Soluspan* is a combination of betamethasone sodium phosphate and betamethasone acetate. The recommended usual dose is 0.25 mL to 2 mL every three to seven days depending upon the indication of use. Potentially there could be confusion if the leading zero is omitted and the decimal is not noted (e.g. .15 mL). However, other factors should help to minimize the potential for medication errors between *Celestone Soluspan* and *Prevacid SoluTab*. Additionally, *Celestone Soluspan* is an injectable product that is administered intralesionally, intra-articularly, or intradermally and *Prevacid SoluTab* is an oral tablet. Finally, although the modifiers look-alike the proprietary names do not look-alike (i.e., Celestone vs. Prevacid).

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Prevacid SoluTab, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has reviewed the current container labels, carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. DMETS cannot assess if the 15 mg and 30 mg strengths are clearly differentiated using the label and labeling provided (i.e., black and white presentation). We recommend that a contrasting color, boxing, or other method be used to distinguish the two strengths.

2. Include the dosage form "Oral Disintegrating Tablets" in the established name (i.e., Lansoprazole Oral Disintegrating Tablets).

B. BLISTER FOIL LABEL (15 mg and 30 mg – Stock and Sample)

1. Include the dosage form "Oral Disintegrating Tablet" in the established name (i.e., Lansoprazole Oral Disintegrating Tablet) since each blister contains only one tablet.

2. Revise the "PKU:Phenylalanine XX mg/Tablet" to read "Phenylketonurics: Contains Phenylalanine XX mg Per Tablet"

C. UNIT DOSE CARTON LABELING (15 mg and 30 mg)

1. Revise the statement "Contains: 1 Patient Sample of 5 Tablets" to read "Contains: 5 Tablets". Patients may be confused by the statement "1 Patient Sample..." and think that all five tablets are one dose.

2. Relocate the statement "contains: 3 packs of 10 tablets" to appear in conjunction with the net quantity statement.

D. SAMPLE CARTON (15 mg x 5 tablets and 30 mg x 5 tablets)

1. See comment C1.

2. Relocate the statement "contains 1 patient sample of 5 tablets" to appear in conjunction with the net quantity statement.

V. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Prevacid SoluTab.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

B. DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Attachment One

ISR #	FDA Receipt Date	Summary of Case Narrative
3243756-6	4/22/1999	Reporter noted that a potential medication error could occur because of an illegible prescription for Prevacid or Pravachol
3303960-5	7/14/1999	A 71-year old man was admitted to the hospital for respiratory failure and/or COPD (questionable) after taking Prevacid 240 mg daily for 3 days. The patient also had a prescription for PrevPac which had not been filled. The patient experienced cardiac arrest and was resuscitated. A cardiac catheterization revealed an acute myocardial infarction and some occlusion. The reporter noted that the patient had subsequently died but no additional information was available. The reporter did not evaluate the relationship between Prevacid and the adverse event.
3719181-8	5/09/2001	An illegible copy of a Prevacid prescription was submitted. The reporter noted that a potential error could occur because of the illegibility.
3887756-1	3/22/2002	A 37-year old female submitted a prescription for Pulmicort Inhaler to a [redacted] pharmacy. The prescription was filled with Prevacid 30 mg tablets instead of Pulmicort Inhaler.

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/s/

Denise Toyer
5/28/02 04:11:53 PM
PHARMACIST

Jerry, Carol told me to bypass her once I added Oral Disintegrating to the document

Jerry Phillips
5/30/02 09:40:44 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

Perry, Cheryl

From: Perry, Cheryl
ent: Wednesday, April 24, 2002 1:30 PM
o: Zhou, Liang; Sieczkowski, Joseph
Subject: FYI FW: N21-428 (lansoprazole tablet) consult

FYI

-----Original Message-----
From: Mille, Yana R
Sent: Wednesday, April 24, 2002 1:27 PM
To: Perry, Cheryl
Subject: RE: N21-428 (lansoprazole tablet) consult

Cheryl,

I am not certain exactly what the release should say but I believe it is important for the firm to know that we want to make sure the name given to the product by CDER is one that USP is likely to use as well --- IF a monograph were ever developed for the product. To accomplish that, we will need to tell the USP that a firm has come up with an orally disintegrating tablet that contains enteric coated ———————————————— It is sometimes helpful to name a specific product (although we generally try not to mention specific products). I believe the release from the firm should give us permission to talk about this unique product with USP in order to select an appropriate dosage form name. As such, we envision having to discuss what it is physically ——— enteric coating), what happens to the product when it is placed on the tongue, and what the active ingredient is. [The latter is optional if the firm is insistent that we do not release this info.] Our discussions with USP will actually begin in mid-May as we work on establishing the agenda for the June meeting. It would be nice if we could get a release from the company by May 10th.

Thanks,
Yana

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

MEMORANDUM OF TELECONFERENCE

DATE/TIME: **April 12, 2002** 2:00 – 2:30 PM

APPLICATION: **NDA 21-428**
PREVACID® (lansoprazole) tablets

BETWEEN:

Nancianne Knipfer, Ph.D., Project Manager, Regulatory Affairs
Donna Helms, Associate Director, Regulatory Affairs
Dean Sundberg, Vice President, Regulatory Affairs
Shuyen Huang, Ph.D., Project Leader, Pharmaceutical Development
Dilip Vishwasrao, Ph.D., Senior Formulation Investigator, Pharmaceutical Development
Edward Tews, Ph.D., Manager Pharmaceutical Analysis
Harald Steltzer, Assistant Director, Project Management

Phone: 847-267-4922
Representing: TAP Pharmaceutical Products, Inc.

AND

OPS/Division of New Drug Chemistry II (DNDCII)
Liang Zhou, PhD, Chemistry Team Leader
Joseph Sieczkowski, PhD, Chemistry Reviewer
Division of Gastrointestinal and Coagulation Drug Products (DGCDP), HFD-180
Cheryl Perry, RN, BSN, Regulatory Health Project Manager

Meeting Chair: Liang Zhou, PhD
Chemistry Team Leader

Meeting Recorder: Cheryl Perry
Regulatory Health Project Manager, DGCDP

Background:
TAP asked for this teleconference to discuss their request for a waiver of imprinting or embossing the tablet with a unique identifier, per 21 CFR 206.

DISCUSSION POINTS

TAP's Comments:
Our tablets are adequately identified by blister labeling because the blister card is perforated, and each dose shows the drug product name/strength as compared to being packaged as loose pills in a bottle. Our February 2002 amendment to this NDA demonstrated our attempts to try unique identifiers. Our information comes from Takeda Japan and centers technically on the [redacted] specification. The drug product will be labeled with instructions to patients not to take the pill out of the blister package until they are ready to swallow the pill. The lansoprazole tablets are uncoated powder. When imprinting uncoated tablets, the amount of ink is inconsistent and of poor quality. We have really tried to look at other products, but they are lyophilized. We do not have pictures of tablets that we have attempted to imprint.

Agency Comments:
The regulations require tablet imprinting unless the sponsor demonstrates that they cannot do it because of physical limitations. Our Office of Drug Safety and our Division Director will make the final determination whether it will be acceptable for your tablet not to be imprinted with a unique identifier. A statement that you have attempted to imprint, but were unsuccessful, is not good enough evidence. We advise your company to develop this unique imprint because of the possibility of medication error, especially since this drug product may be used in the elderly population. Before sponsors submit a NDA, they should address this issue. It is important that we are fair to all companies. You might have to change the shape of the pill. We have consulted the imprint issue and the dosage name to our Office of Drug Safety. Their review is pending. It may be a potential Phase IV commitment.

{See appended page for electronic signature}
Minutes Preparer: Cheryl Perry

{See appended page for electronic signature}
Chair Concurrence: Liang Zhou, PhD

cc: Archival NDA
HFD-180/Div. Files
HFD-180/L. Zhou
HFD-180/J. Sieczkowski
HFD-180/C.Perry

Drafted by: C. Perry/April 22, 2002
Initialed by: L. Zhou/
Final: C. Perry/
Filename: n21428.T-con CMC.12-Apr-02.doc

MEMO OF TELECONFERENCE

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/s/

Cheryl Perry
4/24/02 11:04:49 AM
CSO
NDA 21-428 Telecon

Liang Zhou
4/24/02 11:22:17 AM
CHEMIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Associate Director, Medication Error Prevention
Office of Post Marketing Drug Risk Assessment, HFD-400
(Rm. 15B-03, PKLN Bldg.)

FROM *(Division/Office)*:
Division of Gastrointestinal and Coagulation Drug Products (DGCDP), HFD-180
(Rm 6B-45, PKLN Bldg)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
March 11, 2002	60,103	**21-428**	Original NDA, Amendment 003	February 27, 2002

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Lansoprazole Tablet	Standard	Proton Pump Inhibitor (PPI)	June 20, 2002

NAME OF FIRM: TAP Pharmaceutical Products, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

The proposed dosage form is **orally disintegrating tablet**.
The following **tradenames** are proposed in order of preference:

First Choice: **Prevacid SoluTab™**
Second Choice: ———

TAP states in their amendment dated February 27, 2002 that they checked to ensure that neither tradename is already registered.

PDUFA DATE: August 30, 2002
ATTACHMENT: Draft Package Insert (below)
****For Container and Carton Labels – Please refer to the Acrobat files archived in the EDR under NDA 21-428.**

CC:
Archival NDA 21-428
HFD-180/Division File
HFD-180/C.Perry
HFD-180/J. Sieczkowski
HFD-180/L. Zhou

SIGNATURE OF REQUESTER: *(see attached electronic signature page)* Cheryl Perry, Regulatory Health Project Manager, HFD-180, x7-7475	METHOD OF DELIVERY (Check one) ☑ DFS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

30 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Cheryl Perry
3/11/02 07:39:54 PM
NDA 21-428 lansoprazole tablet, tradename review consult

5 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Division of Gastrointestinal and Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 21-428

Name of Drug: PREVACID® SoluTab™ (lansoprazole) Delayed –Release Orally Disintegrating Tablets, 15mg and 30 mg

Sponsor: Tap Pharmaceutical Products, Inc.

Material Reviewed:

Submission Date(s): October 30, 2001

Receipt Date(s): August 29, 2002

Background and Summary

NDA 21-428 for PREVACID® SoluTab™ (lansoprazole) Delayed-Release Orally Disintegrating is a new NDA, submitted 10/30/01 . There are two other dosage forms of PREVACID® that are currently approved, NDA 20-406 for Prevacid® (lansoprazole) Delayed-Release Capsules and NDA 21-281 for Prevacid® (lansoprazole) for Delayed-Release Oral Suspension. These three dosage forms share the same labeling. The drug product for NDA 21-428 for PREVACID® SoluTab™ (lansoprazole) Delayed-Release Orally Disintegrating Tablets has the same active pharmaceutical ingredient (API) and indications as NDA 20-406 for Prevacid® (lansoprazole) Delayed-Release Capsules.

NDA 20-406 for Prevacid®(lansoprazole) Delayed-Release Capsules was approved on May 10, 1995 for the following indications: reflux esophagitis, duodenal ulcer, and pathological hypersecretory conditions. Supplement S-047 was submitted January 30, 2002. Draft labeling for this SNDA included updates to the *Clinical Pharmacology, Clinical Studies, Indications and Usage, Precautions, Adverse Reactions, and Dosage and Administration* sections of the Prevacid package insert. This supplement was approved on July 31, 2002. Note: this SNDA incorporated pediatric labeling into the Prevacid® label.

Draft labeling included in this submission (TAP DN018-V7 08/29/02) was compared to the currently approved labeling (TAP DN061-V1 05/24/02) and to the labeling approved July 31, 2002 with NDA 20-406 S-047. The differences were noted below.

Review

Package Insert

Description, Clinical Pharmacology, Contraindications, Indications and Usage, Precautions, and Dosage and Administration sections

Various changes were made to these sections consistent with the proposed new dosage form. The changes are indicated in the attachment by highlighted and struck-out text. The acceptability of these changes was the subject of the appropriate discipline reviews or was discussed at the labeling teleconferences with the firm. All changes were agreed upon at the teleconferences between the agency and the firm, Tap Pharmaceutical Products, Inc., on 08/23/02 and 08/28/02. The final agreed upon labeling has been attached as an enclosure to this document.

Conclusions

In the draft labeling submitted with this NDA 21-428 submission, changes to the Description, Clinical Pharmacology, Contraindications, Indications and Usage, Precautions, and Dosage and Administration sections were proposed. The acceptability of these changes was the subject of the appropriate discipline reviews or was discussed at labeling teleconferences with Tap Pharmaceutical Products, Inc. The proposed labeling has been placed on the Division's shared drive and the reviewers have been notified of its location.

_____

Melissa Hancock Furness
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

_____

Dr. Joyce Korvick
Deputy Director

Attachment:
Marked-up draft package insert

Drafted: MHF 08/20/02
Revised/Initialed: MHF 08/21/02
Finalized:
Filename: Prevacid_PM_LabelingReview_N21428

CSO LABELING REVIEW

JAY

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-428

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products, Inc.
Attention: Ms. Leslie Abelson
675 North Field Drive
Lake Forest, IL 60045

Biopharm
JAN - 8 2002

Dear Ms. Abelson:

Please refer to your October 30, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Tablets, 15 mg and 30 mg.

We are reviewing the Biophamaceutical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the location in the NDA of the statistical printouts (similar to pages 543 and 544, Volume 11) for bioequivalence (BE) assessments for Study Nos. M98-948 and M98-949. If the data are not already provided in the NDA, please submit them.

2. There is a significant food effect on the approved capsule formulation. The fast-disintegrating tablet formulation is different from the capsule formulation, therefore, the effect of food on the fast-disintegrating tablet formulation could be different. Provide data to address the effect of food on the fast-disintegrating tablet formulation.

3. The fast-disintegrating tablets dissolved completely in [redacted] Thus, the dissolution methodology used may not be discriminatory. Provide dissolution data [redacted] if available, to support your statement [redacted] Page 88, Volume 10).

If you have any questions, call Cheryl Perry, Regulatory Health Project Manager, at 301-827-7475.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, RN, MSN
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
1/8/02 09:22:48 AM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-428

INFORMATION REQUEST LETTER

Tap Pharmaceutical Products, Inc.
Attention: Ms. Leslie Abelson
675 North Field Drive
Lake Forest, IL 60045

CMC
DEC 20 2001

Dear Ms. Abelson:

Please refer to your October 30, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lansoprazole Tablets, 15 mg and 30 mg.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide scientific data that is the basis for your request for an exemption from imprinting under 21 CFR 206 "Imprinting of Solid Oral Dosage Form Drug Products for Human Use". Specifically identify the exemption in 21 CFR 206.7 that applies to your request.

2. Submit a proposed tradename and the dosage form name. These two items must be submitted to complete the review of the labeling, and may affect any proposals concerning the imprinting of the dosage form.

3. Provide a reasonable date when you will complete your commitment to the Agency for providing additional drug product stability data.

If you have any questions, please call Cheryl Perry, Regulatory Health Project Manager, at 301-827-7475.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team Leader for the Division of Gastrointestinal & Coagulation Drug Products, HFD-180
DNDC 2, Office of New Drug Chemistry
Center for Drug Evaluation and Research

NDA 21-428

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/s/

Liang Zhou
12/20/01 11:22:18 AM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-428

DEC 18 2001

Tap Pharmaceutical Products, Inc.
Attention: Ms. Leslie Abelson
Assistant Director, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Abelson:

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

Name of Drug Product:	Prevacid® (lansoprazole) Tablets, 15 mg and 30 mg
Review Priority Classification:	Standard (S)
Date of Application:	October 30, 2001
Date of Receipt:	October 31, 2001
Our Reference Number:	NDA 21-428

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 December 30, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary and secondary user fee goal dates will be August 31, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not

granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA 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, call me at (301) 827-7475.

Sincerely,

{See appended electronic signature page}

Cheryl Perry, RN, BSN
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
12/18/01 03:56:48 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-428

INFORMATION REQUEST LETTER

Tap Pharmaceutical Products, Inc.
Attention: Ms. Leslie Abelson
675 North Field Drive
Lake Forest, IL 60045

DEC - 5 2001

Received response from firm on Dec 17, 2001

Dear Ms. Abelson:

Please refer to your October 30, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lansoprazole Tablet, 15 mg and 30 mg.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Regarding the proposed lansoprazole tablet manufacturing facilities:

1. Provide the CFN number, full address, and the exact function(s) performed at each facility.

2. Provide the CFN number, full address, and the exact function(s) performed at TAP Pharmaceutical Development Laboratories' (DPL).

3. Provide assurance that all sites have been identified in the NDA; sites from which TAP has acquired information and submitted in the NDA chemistry section to support the application proposal.

If you have any questions, please call Cheryl Perry, Regulatory Health Project Manager, at 301-827-7475.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team Leader for the Division of Gastrointestinal & Coagulation Drug Products, HFD-180
DNDC 2, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
12/5/01 03:06:08 PM

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