

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-507

ADMINISTRATIVE DOCUMENTS

NAPROSYN[®] / PREVACID[®] Combination Package
NDA 21-507
TAP-02-000810-1.0

PATENT CERTIFICATION

The patent certification for Prevacid[®] (lansoprazole) Delayed-Release Capsules is included in the patent information section of this NDA.

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NAPROSYN[®] / PREVACID[®] Combination Package
NDA 21-507
TAP-02-000812-1.0

PATENT CERTIFICATION

The patent certification for Naprosyn[®] (naproxen) Tablets is provided by cross reference to Roche Laboratories Inc. approved NDA 17-581.

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EXCLUSIVITY SUMMARY for NDA # NDA 21-507 SUPPL # -----Trade Name Prevacid NaprapacGeneric Name (lansoprazole/naproxen sodium)Applicant Name Tap Pharmaceutical Products, Inc.
HFD- 180Approval Date 11/14/03**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.)? -----

- 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 /x/ NO /___/

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.

 N/A

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:

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?

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 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 /___/ NO /_x_/

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

NDA # _____

NDA #

NDA #

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 /_x_/ NO /___/

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

NDA # 20-406 (lansoprazole)

NDA # 17-581 (naprosyn)

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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /_x_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement

or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES // NO //

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES // NO //

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES // NO //

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_x_/

If yes, explain:

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # M95-301

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /_x_/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # 20406 Study # M95-301
NDA # _____ Study # _____
NDA # _____ Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_x_/
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____
Investigation #__, Study # _____
Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES / x / ! NO / / Explain: IND 30,159
!
!
!

Investigation #2 !
!
IND # YES / / ! NO / / Explain:
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1 !
!
YES / / Explain ! NO / / Explain
!

!

!

Investigation #2 !
!
YES / / Explain ! NO / / Explain
!

!

!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_x_/

If yes, explain: _____

Melissa Furness
Signature of Preparer

12/18/03
Date

Title: Regulatory Project Manager

Dr. Robert Justice
Signature of Office or Division Director

12/18/03
Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
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
12/18/03 05:00:35 PM

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PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: NDA 21-507 Supplement Type (e.g. SE5): Supplement Number: Stamp Date: 07/24/03 (current cycle) Action Date: 01/25/04HFD-180 Trade and generic names/dosage form: Prevacid NaprapacApplicant: Tap Pharmaceutical Products Therapeutic Class: Indication(s) previously approved: **Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**Number of indications for this application(s): 1Indication #1: risk reduction of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID

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

- 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: Age range: birth – 16 years

Min birth kg N/A mo. _____ yr. _____ Tanner Stage N/A
Max 16 kg N/A mo. _____ yr. _____ Tanner Stage N/A

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: A WR (written request) for Prevacid was issued previously – the sponsor is planning to complete studies to fulfill their WR by the time their patent expires

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

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete 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:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

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

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

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 complete 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:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

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

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Joyce Korvick
11/14/03 12:05:01 PM

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TAP PHARMACEUTICAL PRODUCTS INC.

375 North Field Drive
Lake Forest, IL 60045

NDA Amendment

November 13, 2003

Dr. Robert Justice, Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Parklawn Building Document Room 8B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20856

RE: NDA 21-507, Amendment No. 013
PREVACID[®] NapraPAC[™] (lansoprazole/naproxen) 15 mg/250mg,
15 mg/375 mg and 15 mg/500 mg

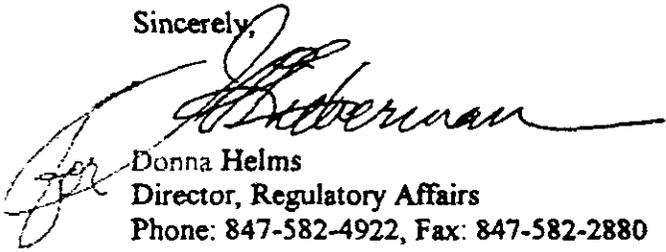
Dear Dr. Justice:

The applicant, TAP Pharmaceutical Products Inc., submits this amendment to the above-listed pending new drug application under the provisions of 21 CFR 314.60.

Per our discussion today and the request from the Labeling and Nomenclature Committee, enclosed is the revised draft labeling with the modification in the established name to include the word "kit". As agreed with the Division, TAP will implement this change and the change (submitted yesterday) in the Pediatric Use sections at the next printing. The next printing is anticipated to occur in the next month.

Any questions or comments on this submission may be communicated to me.

Sincerely,



Donna Helms
Director, Regulatory Affairs
Phone: 847-582-4922, Fax: 847-582-2880

66 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ _____ § 552(b)(5) Draft Labeling

ADDENDUM 11/14/03
1:34 PM

MEMORANDUM

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

DATE: 11/12/03

FROM: Joyce A Korvick, MD, MPH
DGCDP/ODE III

SUBJECT: Director (Deputy) Summary Approval Comments
NDA 21-507

APPLICANT: TAP Pharmaceutical Products Inc.

DRUG: Prevacid Napropac (lansoprazole delayed-release capsules and naproxen tablets kit) 15/250mg, 15/375 mg, and 15/500 mg capsules/tablets

DIVISION RECOMMENDATION:

The division recommends approval of this application for the following indication:

“Reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID for treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.”

Regulatory History:

The original NDA submission was made on October 31, 2002. The original action was an approvable one pending resolution of chemistry issues. A withhold recommendation letter was issued from the Office of Compliance due to GMP violations. _____ was found to have some manufacturing deficiencies. The approvable letter was sent on 7/9/03. TAP responded to the approvable letter by removing _____ and replacing them with _____ as an alternate release testing facility. On July 24, 2003 TAP submitted a complete response to this NDA.

Chemistry review has been completed. The chemists have concluded that the substitution _____ as an alternate release testing facility is acceptable. Chemistry further recommends that given the current data regarding stability, this combination package should be approved with a 2-year expiry date.

Labeling Recommendations:

The division completed review of the label on 6/26/03. The label was not sent with the approvable letter of 7/9/03. Upon final review of the complete response FDA made two additional recommendations to the label.

1. The nomenclature committee recommended the addition of the word "kit" to the establishment name. This would read Prevacid Napropac (lansoprazole delayed-release capsules and naproxen tablets kit) 15/250mg, 15/375 mg, and 15/500 mg capsules/tablets).
2. The DDMAC and Medical review both agreed that this kit was intended to be marketed to adults, because
 - a.) the study upon which this approval was based was conducted in the adult population,
 - b.) the indications are primarily seen in the adult population,
 - c.) the formulation (tablets and capsules) are intended to be taken without chewing and without opening the capsules,
 - d.) lansoprazole has not been studied in children for this indication (it is only approved for GERD), and
 - e.) the dose used for GERD ranges from 15 to 30 mg and this kit contains only the 15 mg dose.

Both of these changes were agreed to by TAP. However, TAP requested that they be required to make the changes on the next printing because they have already packaged the label with the drug product. The FDA agreed to this request.

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

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/s/

Joyce Korvick
11/14/03 01:37:06 PM
MEDICAL OFFICER
addendum to deputy director approval memo

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07/09/03

CONSULTATION RESPONSE**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)****DATE RECEIVED:** March 11, 2003**DUE DATE:** July 9, 2003**ODS CONSULT #:** 03-0141**TO:** Robert Justice, MD
Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180**THROUGH:** Melissa Furness
Project Manager
HFD-180**PRODUCT NAME:**_____ (Primary name)
Prevacid Naprapac (Alternate name)
(Lansoprazole Capsules) 15 mg and
(Naproxen Tablets) 250 mg, 375 mg, and 500 mg**SPONSOR:**

TAP Pharmaceutical Products, Inc.

NDA#: 21-507**SAFETY EVALUATOR:** Nora Roselle, PharmD**SUMMARY:** In response to a request 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 names _____ and "Prevacid Naprapac" to determine the potential for confusion with approved proprietary and established names as well as pending names.**RECOMMENDATIONS:**

1. DMETS does not recommend the use of the proprietary name _____. However, DMETS has no objections to the use of the proprietary name, "Prevacid Naprapac".
2. DMETS recommends implementation of the label and labeling recommendations outlined in section III of this review.
3. DDMAC finds the names, _____ and Prevacid Naprapac, acceptable from a promotional perspective.

 Carol Holquist, RPh
 Deputy Director
 Division of Medication Errors and Technical Support
 Office of Drug Safety
 Phone: (301) 827-3242 Fax: (301) 443-9664

 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-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 25, 2003

NDA#: 21-507

NAME OF DRUG: _____ (Primary name)
Prevacid Naprapac (Alternate name)
(Lansoprazole Capsules) 15 mg and
(Naproxen Tablets) 250 mg, 375 mg, and 500 mg

NDA HOLDER: TAP Pharmaceutical Products, Inc.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), for review of the proposed proprietary names _____; and Prevacid Naprapac. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

_____/Prevacid Naprapac is the proposed proprietary name for a combination package containing Naprosyn (naproxen) tablets and Prevacid (lansoprazole) delayed-release capsules. Naprosyn is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties and Prevacid is a proton pump inhibitor used for the risk reduction of gastric ulcers associated with NSAID use. The proposed combination product is indicated for the treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis in patients with a history of a documented gastric ulcer, who require risk reduction of gastric ulcers associated with the chronic use of an NSAID, such as Naprosyn. _____ Prevacid Naprapac will be supplied as a weekly blister card packaged as a 28 day course of therapy. Each blister card will contain seven Prevacid 15 mg capsules and fourteen Naprosyn tablets in either a 250 mg, 375 mg, or 500 mg strength. The usual adult dose of _____ /Prevacid Naprapac is one Prevacid capsule and one Naprosyn tablet taken in the morning with a glass of water before eating, followed by one Naprosyn tablet in the evening with a glass of water. Naproxen containing products are contraindicated in patients in whom aspirin or other non-steroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps. In addition, patients may be at risk of gastrointestinal ulceration, bleeding, and perforation with NSAID therapy.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names that sound-alike or look-alike to _____ and Prevacid Naprapac to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis⁴ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary names _____ and Prevacid Naprapac. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of 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.

1. Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with _____ and Prevacid Naprapac. These products are listed in Table 1 and Table 2, respectively (see pages 4 and 5), along with the dosage forms available and usual FDA-approved dosage.
2. DDMAC did not have concerns about the names _____ and Prevacid Naprapac with regard to promotional claims.

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¹ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.

³ The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

⁴ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Prevalite	Cholestyramine Resin, 4 g/5.5 g powder	4 g one to two times daily, to a maximum of 24 g/day	Look-alike
Naprosyn	Naproxen Tablet, 250 mg, 375 mg, 500 mg	Pain: Initial: 500 mg, then 250 mg every 6-8 hours Maximum: 1250 mg/day Arthritis: 500 mg - 1000 mg/day in two divided doses	Look-alike & Sound-alike
Naprelan	Naproxen Tablet, 375 mg, 500 mg	Pain: Initial: 500 mg, then 250 mg every 6-8 hours Maximum: 1250 mg/day Arthritis: 500 mg - 1000 mg/day in two divided doses	Look-alike
Naproxen	Naproxen Tablet, 250 mg, 375 mg, 500 mg	Pain: Initial: 500 mg, then 250 mg every 6-8 hours Maximum: 1250 mg/day Arthritis: 500 mg - 1000 mg/day in two divided doses	Look-alike

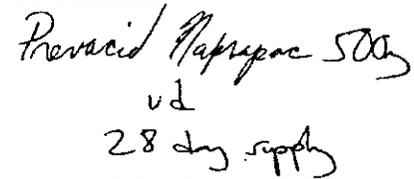
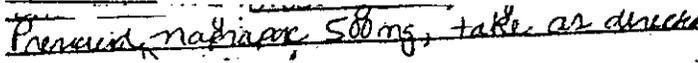
*Frequently used, not all-inclusive.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Six separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of _____ and Prevacid Naprapac with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 130 and 129 health care professionals (pharmacists, physicians, and nurses), respectively. These exercises were conducted in an attempt to simulate the prescription ordering process. Inpatient orders and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for either _____ or Prevacid Naprapac (see below and page 6). These prescriptions were optically scanned and were delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> <p>_____ 375mg as dir # 28 day supply</p>	<p>_____ 375 mg Use as directed. Twenty-eight day supply.</p>
<p>Inpatient RX:</p> <p>_____ 375mg as dir 28 day supply</p>	

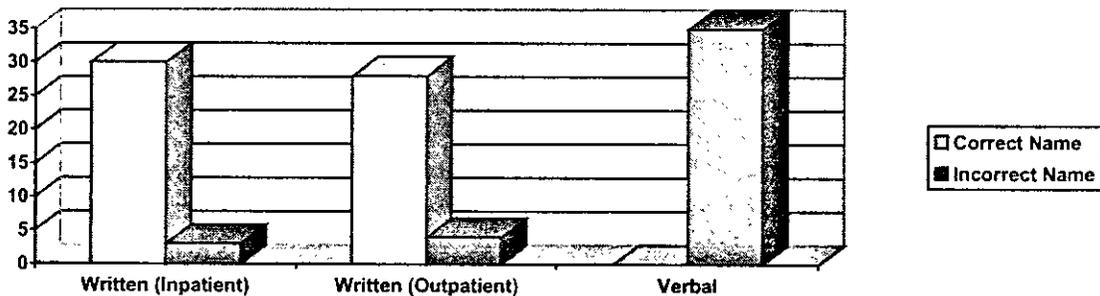
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	Prevacid Naprapac 500 mg Take as directed. Dispense a twenty-eight day supply.
Inpatient RX: 	

2. Results:

a. The results for _____ are summarized in Table 3.

Table 3

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	33 (77%)	30 (91%)	3 (9%)
Written Outpatient	43	32 (74%)	28 (88%)	4 (12%)
Verbal	44	35 (80%)	0 (0%)	35 (100%)
Total	130	100 (77%)	58 (58%)	42 (42%)



Among the written inpatient prescription study participants for _____, 3 of 33 (9%) of the participants interpreted the name incorrectly. The incorrect _____

addition, one respondent who correctly interpreted the name stated that there may be "possible confusion with _____". One of the incorrect responses, _____, contains the name Prevacid, a drug product currently marketed in the U.S.

Among the written outpatient prescription study participants for _____, 4 of 32 (12%) participants interpreted the name incorrectly. The incorrect responses were _____

The incorrect interpretation _____ contains the name Prevacid, a drug product currently marketed in the U.S. One respondent correctly interpreted _____, but commented that the name "could look like or sound like Prevacid, Prilosec, [and] _____"

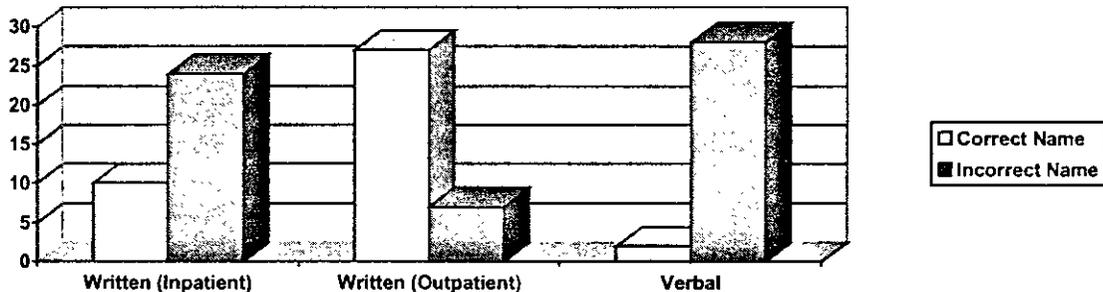
Among the verbal prescription study participants for _____, 35 of 35 (100%) of the participants interpreted the name incorrectly. Many of the incorrect responses contained phonetic variations of either _____ or _____, the incorrect responses were

None of the incorrect responses are names of currently marketed drug products; however, the response _____ is similar to the marketed drug name

b. The results for **Prevacid Naprapac** are summarized in Table 4.

Table 4

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	34 (79%)	10 (29%)	24 (71%)
Written Outpatient	43	34 (79%)	27 (79%)	7 (21%)
Verbal	43	30 (70%)	2 (7%)	28 (93%)
Total	129	98 (76%)	39 (40%)	59 (60%)



Among the written inpatient prescription study participants for Prevacid Naprapac, 24 of 34 (71%) of the participants interpreted the name incorrectly. The incorrect responses were *Prevacid Naprapore* (6), *Prevacid Naprapox* (2), *Prevacid Naprapone* (2), *Prevacid Napropore* (2), *Prevacid Naprapore* (1), *Prevacid Naprapre* (1), *Prevacid Napropac* (1), *Prevacid Naprapak* (1), *Previcid Naprapore* (1), *Prevnaeid Naprapac* (1), *Prenicrid Naprapore* (1), *Previced Napropore* (1), *Prevacid Napradose* (1), *Naprapore* (1), *Naproxen* (1), and *Prevacid* (1). The incorrect responses, Naproxen and Prevacid, are names of currently marketed drug products in the U.S. In addition, one respondent who correctly interpreted the name commented that "this might be some variation of a _____ that has some ingredients present at 500 mg strengths". _____ is a drug product currently marketed in the U.S.

Among the written outpatient prescription study participants for Prevacid Naprapac, 7 of 34 (21%) participants interpreted the name incorrectly. The incorrect responses were *Prevacid Napropac* (4), *Prevacid Naprapak* (1), *Prevacid Naprapen* (1), and *Prevacid* (1). The incorrect interpretation Prevacid is the name of a currently marketed drug product in the U.S. Out of the correct responses, 6 of 27 participants interpreted

clarithromycin), route of administration (oral), and dosing regimen (given twice daily; in the morning and evening). In addition, both drugs will be packaged as a type of blister card, with _____ available as either a weekly blister card or twenty-eight day course of therapy and Prevpac available in daily blister cards. Moreover, _____ and Prevpac will be stored in close proximity to each other on the pharmacy shelf increasing the risk of selection and dispensing errors. As confirmed by the study results, there is potential that Prevpac could be confused with _____ as one respondent from the written inpatient study incorrectly interpreted the name to be Prevpac. If a patient inadvertently receives the wrong medication, this may be reason for concern as each medication has different indications for use leading to an inappropriate drug therapy for the intended condition. In addition, if a patient with a history of allergies to either penicillin/amoxicillin or macrolide antibiotics is inadvertently administered Prevpac instead of the intended _____, one may suffer from a potentially serious allergic reaction and even anaphylaxis. DMETS acknowledges that there are differences in strength between the two drug products. For example, prescriptions for _____ will need to identify the strength of both of the active ingredients (naproxen 250 mg, 375 mg, or 500 mg, and lansoprazole 15 mg). Prescriptions for Prevpac, on the other hand, do not need to include a differentiating strength. However, we believe that the difference in strength may not prevent a medication error between _____ and Prevpac as the names are very similar. Due to the numerous product similarities, as well as overlapping look-alike and sound-alike characteristics, DMETS believes that there is increased risk for confusion and error between the two products.

Prevacid has a look-alike similarity to _____ especially if the _____ is inadvertently omitted. Prevacid is used in the short-term treatment of active duodenal ulcers and the maintenance of healed ulcers. Prevacid is available in 15 mg and 30 mg oral capsules. Each name contains overlapping prefixes ("Preva"). Below are the inpatient and outpatient handwriting samples provided to the study participants:

[] [] []
Prevacid

Besides look-alike similarities, _____ and Prevacid share an overlapping active ingredient (lansoprazole), dosage form (capsule), route of administration (oral), strength (15 mg), and dosing regimen for lansoprazole (once daily). Also, _____ and Prevacid will most likely be stored in close proximity to one another on some pharmacy shelves. One respondent correctly interpreted _____ but commented that the name "could look like or sound like Prevacid, [Prilosec, Prevpac]". In addition, two respondents, one from the written inpatient study and one from the written outpatient study, incorrectly interpreted the name to be *Prevacid Pac*. In this case, Prevacid, used in the treatment of ulcers, may incorrectly be administered instead of the intended _____ used in the treatment of various types of arthritis, leaving the patient's condition untreated. DMETS acknowledges that there are differences in strength between the two drug products. For example, prescriptions for _____ will need to identify the strength of both of the active ingredients (naproxen 250 mg, 375 mg, or 500 mg, and lansoprazole 15 mg). Prescriptions for Prevacid, on the other

hand, must identify a strength of 15 mg or 30 mg. However, we believe that the difference in strength may not prevent a medication error between _____ and Prevacid as the names are very similar. DMETS believes there is increased risk for confusion and error between _____ and Prevacid.

PreviDent has look-alike similarities to _____ if the _____ is inadvertently omitted. PreviDent is indicated for the prevention of dental caries. PreviDent is available as an oral topical gel (1.1%). PreviDent is applied to teeth after brushing, left on teeth for one minute and then spit out of mouth daily. Each name begins with the prefix "Prev" (see below).

[_____] *prevident*

However, the suffixes of each name ("-dent" vs. "_____") look different and help distinguish one name from the other. Both drugs have oral routes of administration and overlapping dosing schedules (once daily). However, _____ and PreviDent each have different dosage forms (capsule and tablet vs. topical gel), indications for use (arthritis vs. prevention of dental caries), and strengths (15 mg plus either 250 mg, 375 mg, or 500 mg vs. 1.1%). Due to these differences, DMETS believes there is minimal risk for confusion and error between _____ and PreviDent.

Prevalite has a look-alike similarity to _____, especially if the word _____ is inadvertently omitted from the name when prescribed. Prevalite used in the management of primary hypercholesterolemia. Prevalite is available as an oral powder for suspension (4 grams cholestyramine resin per 5.5 grams powder) in either individual use packets or bulk cans. Prevalite is dosed as 4 grams of powder given one to two times a day. Each powder packet is mixed with water or non-carbonated beverage. Each name contains identical looking prefixes ("Preva") increasing the risk for confusion between the two names when scripted.

[_____] *Prevalite*

Besides look-alike similarities, _____ and Prevalite share an overlapping daily dosing schedule (twice daily) and route of administration (oral). However, the two drugs do not share overlapping dosage forms (capsule and tablet vs. powder for suspension), strength (15 mg plus either 250 mg, 375 mg, or 500 mg vs. 4 g resin/5.5 g powder), and indication for use (arthritis vs. hypercholesterolemia). In addition, the use of _____ at the end of "_____ helps differentiate one name from the other especially taking into consideration that the strength of each product is so much different between the two products. In addition, Prevalite is a powder that must be mixed into an oral liquid before administration while _____ consists of a combination of capsules and tablets that may be taken without further preparation. Due to these differences, DMETS believes that there is minimal risk for confusion and error between Prevalite and _____

Pravigard Pac has a look- and sound-alike similarity to _____ Pravigard Pac was approved by the Agency on June 24, 2003. Pravigard Pac consists of co-packaged pravastatin sodium and buffered aspirin tablets. _____ is indicated in the reduction of the occurrence of cardiovascular events, including

death, myocardial infarction or stroke, in patients who have clinical evidence of cardiovascular and/or cerebrovascular disease. Both names have similar sounding prefixes ("Pravi-" vs. "Previ-") and end with the word ' — Both — and Pravigard Pac are multi-ingredient products that are available in multi-day packaging. — and Pravigard Pac have an overlapping dosage form (tablet) and route of administration (oral). While the two products do not share an overlapping strength, indication for use, or dosing schedule, there is risk for confusion as the two drugs will be launched into the market around the same time due to the similarity of the drug names.

[] Pravigard Pac

2. Prevacid Naprapac

In reviewing the proposed proprietary name "Prevacid Naprapac", the primary concerns raised were related to four look-alike and/or sound-alike names. The products considered to have potential for name confusion with Prevacid Naprapac were Prevacid, Naprosyn, Naprelan, and Naproxen.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Prevacid Naprapac could be confused with Prevacid and Naproxen. One respondent from the written outpatient study and one from the written inpatient study incorrectly interpreted the name to be Prevacid. Also, one respondent from the written inpatient study incorrectly interpreted the name to be Naproxen. In addition, two respondents from the verbal study incorrectly interpreted the name to be Prevacid Pak/Prevacid Pack, omitting the "Napra" portion from the name. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

Prevacid has a look- and sound-alike similarity to Prevacid Naprapac in that each name contains "Prevacid". Prevacid is used in the short-term treatment of active duodenal ulcers and the maintenance of healed ulcers. Prevacid is available in 15 mg and 30 mg oral capsules. Each name contains the identical root name "Prevacid", with the proposed name adding the "Naprapac" term to the end of the name. The following handwriting samples are those provided in the inpatient and outpatient studies:

Prevacid naprapac Prevacid Naprapac

Besides look- and sound-alike similarities, Prevacid and Prevacid Naprapac share an overlapping active ingredient (lansoprazole), dosage form (capsule), route of administration (oral), strength (15 mg), and dosing regimen for lansoprazole (once daily). DMETS believes that there is potential for practitioners to omit some parts of a multi-part name and prescriptions written for Prevacid Naprapac may be misinterpreted as Prevacid as shown in the study. Two respondents, one from the written inpatient study and one from the written outpatient study incorrectly interpreted the name to be the single ingredient drug, *Prevacid*. If a patient inadvertently receives only Prevacid instead of the

intended Prevacid Naprapac they will not receive the intended drug treatment. Prevacid Naprapac is indicated for the treatment of various types of arthritis with a history of a documented gastric ulcer, who require risk reduction of gastric ulcers associated with the chronic use of an NSAID while Prevacid is only indicated for the treatment of ulcers. However, DMETS acknowledges that there are differences in strength between the two drugs which will help differentiate one product from the other. For example, prescriptions for Prevacid Naprapac need to identify the strength of both of the active ingredients (naproxen 250 mg, 375 mg, or 500 mg, and lansoprazole 15 mg). Prescriptions for Prevacid, on the other hand, must identify a strength of 15 mg or 30 mg. DMETS believes that prescriptions written for Prevacid Naprapac with the strength of both active ingredients clearly expressed will help minimize confusion and error between the proposed proprietary name and Prevacid.

In addition, while not a safety concern, DMETS believes that a prescription for Prevacid Naprapac may be misinterpreted as two separate drugs "Prevacid" and "Naprosyn"; therefore, the intended combination pack, marketed by TAP Pharmaceuticals, would not be distributed to the patient. However, both ingredients would still likely be dispensed.

Naprosyn, Naprelan, and Naproxen were identified as a source of possible confusion with Prevacid Naprapac. Naproxen is the established name for Naprelan and Naprosyn. Naproxen is a non-steroidal anti-inflammatory drug (NSAID) used in the management of inflammatory disease, rheumatoid disorders, acute gout, mild to moderate pain, fever, migraine, and headaches. Naproxen is available in several tablet strengths: 250 mg, 375 mg, and 500 mg. Naproxen is also available in an over-the-counter formulation (Aleve). For the treatment of arthritis, Naproxen is dosed as 500 mg to 1000 mg per day in two divided doses. For the treatment of pain, the usual adult dose is 500 mg initially, then 250 mg every six to eight hours. Naproxen, Naprelan, and Naprosyn were identified to have look- and sound-alike similarities to the name Naprapac in Prevacid Naprapac. All four names share a similar looking and sounding prefix ("Napro" vs. "Napre" vs. "Napra").

<i>naprapac</i>	<i>naprelan</i>
<i>Naprapac</i>	<i>Naprosyn</i>
<i>Naprapac</i>	<i>Naproxen</i>

Besides look- and sound-alike similarities, Prevacid Naprapac and the various Naproxen products share an overlapping active ingredient (naproxen), dosage form (tablet), route of administration (oral), dosing schedule (twice daily), indication for use (arthritis), and strengths (250 mg, 375 mg, and 500 mg). DMETS believes that there is potential for practitioners to omit some parts of a multi-part name and prescriptions written for Prevacid Naprapac may be misinterpreted as Naprapac. One respondent from the written inpatient study incorrectly interpreted the name to be Naproxen (see below).

Prevacid naprapac

If a prescription for Prevacid Naprapac 500 mg is misinterpreted as the single ingredient Naprosyn 500 mg, a patient is at risk of not receiving the intended stomach protective qualities of Prevacid which may be beneficial with the use of NSAIDs. However, DMETS acknowledges that there are differences in strength between the two drugs which will help differentiate one product from the other. For example, prescriptions for Prevacid Naprapac need to identify the strength of both of the active ingredients (naproxen strength of 250 mg, 375 mg, or 500 mg, and lansoprazole 15 mg). Prescriptions for any of the naproxen products, on the other hand, only identify a single product strength of 250 mg, 375 mg, or 500 mg. DMETS believes that prescriptions written for Prevacid Naprapac with the strength of both active ingredients clearly expressed will help minimize confusion and error between the proposed proprietary name, Naprosyn, Naprelan, and Naproxen. In order to prevent medication errors with naproxen products, we encourage the sponsor to educate practitioners about the use of the full name "Prevacid Naprapac" rather than parts of the name such as "Naprapac".

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, _____ However, DMETS has no objections to the use of the proprietary name, Prevacid Naprapac.

_____ In reviewing the proposed proprietary name ' _____, the primary concerns raised were related to three look-alike and/or sound-alike names. The products considered to have potential for name confusion with _____ were Prevpac, Prevacid, and Pravigard Pac.

Prevpac was identified to have sound-alike and look-alike potential with the proposed proprietary name, _____. Each Prevpac daily blister card contains two lansoprazole (Prevacid) 30 mg capsules, four amoxicillin (Trimox) 500 mg capsules, and two clarithromycin (Biaxin) 500 mg tablets which represents one day of therapy. Prevpac is indicated for the treatment of patients with H. pylori infection with duodenal ulcer disease to eradicate H. pylori. _____ and Prevpac have sound-alike and look-alike similarities in that each name shares the prefix ' _____ and ends with the word " _____ The handwriting sample below is the sample provided in the inpatient study.

[_____]

Both drugs share an overlapping ingredient (lansoprazole), dosage forms (tablet and capsules), strength (500 mg naproxen vs. 500 mg amoxicillin and 500 mg clarithromycin), route of administration (oral), and dosing regimen (given twice daily; in the morning and evening). In addition, both drugs will be packaged as a type of blister card, with _____ available as either a weekly blister card or twenty-eight day course of therapy and Prevpac available in daily blister cards. Moreover, _____ and Prevpac will be stored in close proximity to each other on the pharmacy shelf increasing the risk of selection and dispensing errors. If a patient inadvertently receives the wrong medication, this may be reason for concern as each medication has different indications for use leading to an inappropriate drug therapy for the intended condition. In addition, if a patient with a history of allergies to either penicillin/amoxicillin or macrolide antibiotics is inadvertently administered Prevpac instead of the intended _____ one may suffer from a potentially serious allergic reaction and even anaphylaxis. DMETS acknowledges that there are differences in strength between the two drug products. For example, prescriptions for _____ will need to identify the strength of both of the active ingredients (naproxen 250 mg, 375 mg, or 500 mg, and lansoprazole 15 mg).

Prescriptions for Prevpac, on the other hand, do not need to include a differentiating strength. However, we believe that the difference in strength may not prevent a medication error between _____ and Prevpac as the names are very similar. Due to the numerous product similarities, as well as overlapping look-alike and sound-alike characteristics, DMETS believes that there is increased risk for confusion and error between the two products.

Prevacid has a look-alike similarity to _____ especially if the _____ is inadvertently omitted. Prevacid is used in the short-term treatment of active duodenal ulcers and the maintenance of healed ulcers. Prevacid is available in 15 mg and 30 mg oral capsules. Each name contains overlapping prefixes ("Preva"). Below are the inpatient and outpatient handwriting samples provided to the study participants:

[] []]
Prevacid

Besides look-alike similarities, _____ and Prevacid share an overlapping active ingredient (lansoprazole), dosage form (capsule), route of administration (oral), strength (15 mg), and dosing regimen for lansoprazole (once daily). Also _____ and Prevacid will most likely be stored in close proximity to one another on some pharmacy shelves. We believe that confusion between _____ and Prevacid is possible. For example, Prevacid, used in the treatment of ulcers, may incorrectly be administered instead of the intended _____, used in the treatment of various types of arthritis, leaving the patient's condition untreated. DMETS acknowledges that there are differences in strength between the two drug products. For example, prescriptions for _____ will need to identify the strength of both of the active ingredients (naproxen 250 mg, 375 mg, or 500 mg, and lansoprazole 15 mg). Prescriptions for Prevacid, on the other hand, must identify a strength of 15 mg or 30 mg. However, we believe that the difference in strength may not prevent a medication error between _____ and Prevacid as the names are very similar. DMETS believes there is increased risk for confusion and error between _____ and Prevacid.

_____ has a look- and sound-alike similarity to _____. Pravigard Pac was approved by the Agency on June 24, 2003. Pravigard Pac consists of co-packaged pravastatin sodium and buffered aspirin tablets. _____ is indicated in the reduction of the occurrence of cardiovascular events, including death, myocardial infarction or stroke, in patients who have clinical evidence of cardiovascular and/or cerebrovascular disease. Both names have similar sounding prefixes (' _____ vs. ' _____), and end with the word _____. Both _____ and Pravigard Pac are multi-ingredient products that are available in multi-day packaging. _____ and Pravigard Pac have an overlapping dosage form (tablet) and route of administration (oral). While the two products do not share an overlapping strength, indication for use, or dosing schedule, there is risk for confusion as the two drugs will be launched into the market around the same time due to the similarity of the drug names.

Additionally, DMETS reviewed the container (blister) labels, carton and insert labeling for the proposed product and has identified the following areas of possible improvement.

A. CONTAINER LABEL (Blister card)

1. The current expression of the proprietary name includes only the strength of the naproxen component and may be misleading as it implies that the product consists of a single active ingredient. In order to minimize the potential for medication errors with Prevacid or naproxen products, DMETS recommends that name and strength of each active ingredient be clearly expressed on the label of each tablet. Revise accordingly.
2. The established name listed as "naproxen XX mg tablets and lansoprazole XX mg capsules" implies the product is a combination formulation of the two ingredients in a single tablet. Consistent with other marketed co-packaged dosage form products, the established names should appear separately. Revise to read as follows:

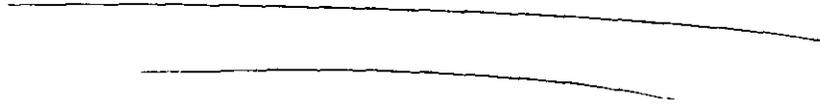
Each 7-Day Pack contains:
7 Prevacid (Lansoprazole) capsules (15 mg)
14 Naprosyn (Naproxen) tablets (250 mg, 375 mg, 500 mg)
3. We were not able to compare the three different strength cartons side-by-side. Please ensure the three different strength packs are clearly differentiated by using contrasting colors, boxing, or some other means.
4. We are unable to determine from the documents provided whether the established name is at least 1/2 the size of the proprietary name. Please revise accordingly.
5. We are unable to determine from the documents provided whether the proprietary and established names are the most prominent information on the label. Please revise accordingly.
6. Insert a warning statement that would help to reduce the risk of duplicate therapy with single ingredients. For example, include a statement that conveys that
┌7
7. DMETS recommends revising the blister card to avoid abbreviations such as "P" and "N" as this may cause confusion. Please revise to include the full name and strength of each medication with the appropriate "punch out" on the back of the blister card.
┌1
8. DMETS recommends the use of the words "Morning" and "Evening" instead of "AM" and "PM". The terms "Morning" and "Evening" should convey more information to the patient. For example, this wording would prevent the medication from being taken at 11:30 am with breakfast and 12:30 pm with lunch

B. CARTON LABELING

See comments A1-A6.

C. INSERT LABELING

1. See comments A1-A2.
2. The DESCRIPTION and HOW SUPPLIED section of the package insert is confusing with regard to the contents in each patient administration pack. Please revise as follows:



APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS:

- A. DMETS does not recommend the use of the proposed proprietary name, _____
However, DMETS has no objections to the use of the proposed proprietary name,
Prevacid Naprapac.
- B. In addition, DMETS recommends the labeling revisions in section III of this review 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.
- C. DDMAC finds the proposed names. _____ and Prevacid Naprapac, acceptable
from a promotional perspective.

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.

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

APPEARS THIS WAY
ON ORIGINAL

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this page is the manifestation of the electronic signature.

/s/

Nora L. Roselle
7/9/03 10:28:55 AM
CSO

Alina Mahmud
7/9/03 10:46:21 AM
PHARMACIST

Carol Holquist
7/9/03 10:51:26 AM
PHARMACIST

APPEARS THIS WAY
ON ORIGINAL

Jerry Phillips
7/9/03 10:55:06 AM
DIRECTOR

MEMORANDUM

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

DATE: 7/3/03

FROM: Joyce A Korvick, MD, MPH
DGCDP/ODE III

SUBJECT: Deputy Director (for the Division Director); and
Acting Team Leader Summary Approval Comments
NDA 21-507

APPLICANT: TAP Pharmaceutical Products Inc.

DRUG: naproxen 250 mg, 375 mg, 500 mg tablets and
lansoprazole delayed release 15 mg capsules.

REGULATORY RECOMMENDATIONS:

The review team recommends that this application should be approved for the following indication:

(Tradename TM) is indicated for reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of naproxen for treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

The acting Medical Team Leader concurs with this recommendation.

I. Background:

The applicant submitted the NDA on September 6, 2002. Both active products (naproxen and lansoprazole) are approved for the intended use. In this application the sponsor proposed co-packaging of Prevacid Delayed-Release 15 mg capsules and either Naproxyn 250 mg, 375 mg or 500 mg tablets. Regulations for combination drugs are found in 21 CFR 300.5, which discusses the medical rationale for the combination drug products. This regulation states that drugs may be combined "to enhance the safety and effectiveness of the principle active component". In this regulation, no mention of co-packaging is made. In draft Agency guidance on co-packaging it is stated that a medical rationale should be provided by demonstrating the clinical usefulness of simultaneous use of the co-packaged drugs. Review by the primary medical reviewer concluded that this application does fit the requirements in that the applicant has shown the use of Prevacid enhances the safe use of naproxen. In addition, there is a vast number of patients taking NSAIDS and between 13 and 17 patients per 1000 who take NSAIDS chronically will

have a serious gastrointestinal complications. Thus, large numbers of patients stand to benefit from this co-packaging.

In support of this application, TAP submitted an analysis of a subset of patient who were taking naproxen and lansoprazole in clinical study M95-301. In this study lansoprazole demonstrated a statistically significant risk reduction of NSAID-associated gastric ulcer disease compared to placebo. The original study was submitted previously in support of the indication in the current Prevacid label, which is "risk reduction of NSAID-induced gastric ulcers". Safety of the co-packaged product is established by a combination of postmarketing data, previous clinical trails and the analysis from this clinical study M95-301.

II. Discipline Review summary and commentary:

A. OPDRA/DDMAC/DMETS:

No significant issues were raised by these reviews. The Tradename is still being negotiated.

B. Chemistry:

The chemistry review was completed (5/21/03) and a list of labeling comments was communicated to the applicant. These included:

- 1.) the use of the words "delayed-release" in front of capsule;
- 2.) separation of active and inactive ingredients;
- 3.) verbiage on stability to light and pH should be incorporated before the listing of ingredients for Prevacid.

One outstanding issue at the time of this summary is the resolution of the current withhold recommendation from the Office of Compliance due to CMP violations. It is anticipated that the Office of Compliance will finalize their recommendations prior to the action goal date. These are serious issues that must be resolved prior to approval of this drug product.

C. Pharmacology/Toxicology:

There were no issues regarding pharmacology/Toxicology for these two approved drug products.

D. Biopharmaceutics:

No new pharmacokinetic (PK) studies or clinical trials were conducted to support this NDA. The sponsor provided "Overall Human Pharmacokinetics summary-Overview of the Drug-Drug Interaction (DDI) Potential Between Lansoprazole and Naproxen" which included a DDI study between omeprazole and naproxen from the literature to address the Agency's concern on the DDI potential between lansoprazole and naproxen. The

Biopharmaceutics reviewers concluded that clinically significant DDI between lansoprazole and naproxen was unlikely. The dissolution data obtained from naproxen IR 250 and 500-mg tablet lots is acceptable. The reviewers recommended approval of the co-packaged product.

E. Clinical Efficacy/Safety:

Efficacy results were obtained from the analysis of the subset of patients in study M95-301. A retrospective subset analysis of 119 patients whose NSAID was naproxen only or naproxen and aspirin only, was performed. The proportion of patients remaining free from gastric ulcer at 4, 8, and 12 weeks was significantly higher with 15 or 30 mg of PREVACID than placebo (see Table 1). Patients ranged in age from 37 to 84 years (median age 58 years), with 61% female patients and 39% male patients. Race was distributed as follows: 88% Caucasian, 8% Black, 4% other. Concomitant aspirin was used in 15% of the patients. The 30-mg dose of PREVACID demonstrated no additional benefit in risk reduction of the NSAID-associated gastric ulcer than the 15-mg dose.

Table 1 Gastric Ulcer Risk Reduction Rates in Patients whose NSAID was Naproxen Only or Naproxen and Aspirin Only

Week	% of Patients Remaining Gastric Ulcer-Free ¹			
	PREVACID 15 mg QD (N=37)	PREVACID 30 mg QD (N=24)	Misoprostol 200 µg QID (N=28)	Placebo (N=30)
4	91%	83%	88%	52%
8	89%	83%	88%	52%
12	89%	83%	83%	33%

% = Life Table Estimate

(p<0.001) PREVACID 15 mg QD versus placebo; PREVACID 30 mg QD versus placebo; and misoprostol 200 µg QID versus placebo.

For patients who received PREVACID the highest total daily dose of naproxen was as follows: 5 patients took < 750 mg/daily, 54 patients took 750-1000 mg/daily. Only 2 patients who received PREVACID took greater than 1000 mg of naproxen.

EFFICACY

Statistical: The statistical reviewer stated that there was no statistical difference between Prevacid 15 mg and Prevacid 30 mg daily in risk reduction of gastric ulcers. They agreed with the recommended 15 mg dose. Analyses of the varying dosages of naproxen and the use of aspirin in the study did not influence the outcomes.

Clinical: The medical reviewer made the point that the use of 1000 mg of naproxen or greater was only used in 2 study patients. Therefore the labeling should reflect the lack of data to support the efficacy of lansoprazole when the dose of naproxen is greater than 1000mg daily. The currently proposed doses in the co-packaged product are 250 mg, 375 mg or 500 mg of naproxen.

SAFETY:

Clinical: The medical reviewer concluded that the applicant demonstrated the safety of this combination package. Naproxen and lansoprazole are already approved as safe and effective. Naproxen is approved for over the counter use. Their combined use has already been approved in NDA 20-406/S-33. The combination of postmarketing data, previous clinical trials and the analysis from the study all combine to establish safety for this combination package.

F. Labeling Comments:

The label, as currently constructed, consists of the sections relevant to the proposed indication from the prescription drug package inserts for Naprosyn and Prevacid. The patent certification for Naprosyn is provided by cross-reference to Roche Laboratories Inc. approved NDA 17-581. In addition the results from the sub-analysis of Study M95-301 are included. Labeling agreement was reached between the applicant and the FDA on 6/24/03.

ADDENDUM

There the approval of this application was delegated to the Deputy Director of the Division of Gastrointestinal and Coagulation Drug Products. This memo will stand as the Team Leader Memo and the Division Director Summary.

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/s/

Joyce Korvick
7/9/03 03:41:48 PM
MEDICAL OFFICER

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4) CLINICAL STUDIES – “Patients took one or more NSAIDs during the study. Concomitant aspirin use (< 325 mg) was allowed.... Concomitant aspirin was used in 20% of the patients.”

- This information is not included in the Prevacid PI. Is it necessary to include this information in the combination product label?

5)

6) CLINICAL STUDIES – General Comment

- DDMAC recommends putting the naprosyn effectiveness data first in this section, as is done in the Arthrotec label, followed by the ulcer risk reduction data. Patients will take this product to reduce the pain and inflammation associated with OA, RA, and AS. If the risk reduction data is first, it seems like the indication should be changed to something like “... to reduce the risk of gastric ulcer in patients with OA/RA/AS with a history of documented gastric ulcer.”

7) INDICATION

- The Prevacid PI states “Controlled studies did not extend beyond 12 weeks.” This statement is not included in the proposed label for the combination product. DDMAC recommends adding this statement to be consistent with the Prevacid PI.
- Consider revising the indication to read _____

8) PRECAUTIONS – “Naprosyn cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency.”

- I did not see this sentence in the version of the Naprosyn PI that I have (from the Roche website).

9) Information for Patients

10) Geriatric Use

- The proposed label provides information about the Naprosyn in geriatric patients. This paragraph is not in the version of the Naprosyn PI that I have.

11) DOSAGE AND ADMINISTRATION

- The Prevacid PI states that Prevacid 15 mg should be used “once daily for up to **12 weeks**” for risk reduction of NSAID-associated gastric ulcer and “**Controlled studies did not extend beyond indicated duration.**” The proposed label does not include the information in bold above. DDMAC recommends adding this information to be consistent with the Prevacid PI.

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/s/

Marci C. Kiestler
5/5/03 09:24:21 AM
DDMAC REVIEWER

ALL INFORMATION CONTAINED
HEREIN IS UNCLASSIFIED
DATE 05-05-2003 BY 60322 UCBAW

Furness, Melissa

From: Fang, Christina L
Sent: Monday, May 19, 2003 1:24 PM
To: Goldkind, Lawrence; Witter, James P; DeBellas, Carmen
Cc: Furness, Melissa; Korvick, Joyce A; Nair, Narayan
Subject: RE: NDA 21-507 Consult

This is the response to the consult received by E-mail. Please let me know if you have further questions. Thanks.

Questions 1, 2, and 5:

1. We are currently revising the label for this co-packaging product from a GI perspective. Are there any further revisions or clarifications that that 550 can recommend regarding the naproxen portion of the label.
2. The naproxen portions of the label are based on a May 2001 version of the Naprosyn label are there any newer versions of the label or pending changes in the label that should be incorporated to the label for this co-packaged product?
5. The naproxen portion of this label has a section on Geriatric use. We cannot find a corresponding portion in the original naprosyn label. Is this section accurate?

Response to questions 1, 2, and 5:

The naproxen portion of the labeling, including the geriatric information, should be consistent with the most recent versions sent out to the Sponsor in the approvable letter dated January 29, 2003 (for geriatric labeling) and May 6, 2003 (for NSAID class labeling). Both the geriatric labeling and the NSAID class labeling were reviewed by the medical reviewer Dr. Tatiana Oussova and the drafts were finalized in the DFS on January 19, 2003 and February 20, 2003, respectively. The reviews can be located under the following NDA numbers: 20-067, 17-581, 18-164, and 18-965.

Question 3:

1. This co-packaged product is indicated for risk reduction of NSAID associated gastric ulcers in patients with a history of gastric ulcer who require continued treatment with NSAIDs. From a GI standpoint the label (with revisions) appears adequate. From the standpoint of the anti-inflammatory division do they feel this label adequately communicates the indication and intended population? Do they have any specific recommendations to improve the label in this regard?

Response to question 3:

The indication section of the proposed labeling is copied from the E-mail requesting for the consult below:

"INDICATIONS AND USAGE

TRADENAME™ (250, 375 or 500) is indicated for treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, in patients with a history of a documented gastric ulcer, who require risk reduction of gastric ulcers associated with the chronic use of an NSAID, such as NAPROSYN (naproxen). (See **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION**.)"

The indications for naproxen should be the formulation specific indications consistent with the most recently approved labeling as mentioned above. The important part here is to best characterize the target population for intended use of the drug. In my opinion, the key questions to ask here should be:

- (1) How to define the high-risk population for NSAID induced GI ulcer and complications? Is it represented mainly (or only) by patients with a history of a documented gastric ulcer? Or should it be defined by using a selective list of major risk factors (e.g., history of GI ulcer/bleeds, elderly, co-therapy, concurrent illness, etc.)?
- (2) What is the potential benefit of the combination therapy? Is it mainly (or only) for the "risk reduction of gastric ulcers"? Or is it for the risk reduction of GI ulcers and complications?
- (3) Is the "risk reduction of gastric ulcers" mainly (or only) "associated with the *chronic use* of an NSAID"? Or should drug exposure-related increase in GI risk be specified in terms of dose level (the amount of single dose and daily dose) and duration of exposure?

The only combination product I could find in the current PDR that is similar to this product is Arthrotec, which is a combination of diclofenac sodium and misoprostol. The indication section of the Arthrotec labeling is provided below for your reference:

"ARTHROTEC is indicated for treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications. See WARNINGS -- Gastrointestinal effects for a list of factors that may increase the risk NSAID-induced gastric and duodenal ulcers and their complications."

Review completed by Christina Fang, M.D., HFD-550, May 19, 2003

-----Original Message-----

From: Goldkind, Lawrence
Sent: Friday, May 16, 2003 2:48 PM
To: Fang, Christina L
Witter, James P; DeBellis, Carmen
Subject: FW: NDA 21-507 Consult

-----Original Message-----

From: DeBellas, Carmen
Sent: Friday, May 16, 2003 12:17 PM
To: Witter, James P
Cc: Goldkind, Lawrence
Subject: FW: NDA 21-507 Consult

-----Original Message-----

From: Furness, Melissa
Sent: Friday, May 16, 2003 11:27 AM
To: DeBellas, Carmen
Cc: Korvick, Joyce A; Nair, Narayan
Subject: NDA 21-507 Consult

Hi Carmen,

Our specific questions are as follows:

1. We are currently revising the label for this co-packaging product from a GI perspective. Are there any further revisions or clarifications that that 550 can recommend regarding the naproxen portion of the label.
2. The naproxen portions of the label are based on a May 2001 version of the Naprosyn label are there any newer versions of the label or pending changes in the label that should be incorporated to the label for this co-packaged product?
3. This co-packaged product is indicated for risk reduction of NSAID associated gastric ulcers in patients with a history of gastric ulcer who require continued treatment with NSAIDs. From a GI standpoint the label (with revisions) appears adequate. From the standpoint of the anti-inflammatory division do they feel this label adequately communicates the indication and intended population? Do they have any specific recommendations to improve the label in this regard?

5. The naproxen portion of this label has a section on Geriatric use. We cannot find a corresponding portion in the original Naprosyn label. Is this section accurate?

Thanks and have a nice weekend!

Melissa

Melissa Hancock Furness
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products
(p) 301-827-7450
(f) 301-443-9285
FurnessM@cder.fda.gov

APPLICING THIS WAY
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Jerry Philips, HFD-400 Parklawn 15B-23		FROM: Melissa Furness, HFD-180 Parklawn 6B-45		
DATE March 31, 2003	IND NO.	NDA NO. 21-507	TYPE OF DOCUMENT	DATE OF DOCUMENT September 6, 2002 and March 28, 2003
NAME OF DRUG Prevacid/Naprosyn Combination Packet	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE May 25, 2003	
NAME OF FIRM: Tap Pharmaceutical Products, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): See comments below.				
COMMENTS/SPECIAL INSTRUCTIONS: This is a type 4 New Drug Application. The PDUFA goal date is 07/09/03. Please note that this application was submitted electronically (09/06/03) and via hard copy (03/28/03), consequently, it may be found on the EDR (pathway - N 21507/labeling folder) or via the attached documents. Please let me know if you require hard copies as well and I can request these from the firm. Thanks much! Melissa Furness - x77450.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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Melissa Furness
3/31/03 06:15:00 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: 02/19/03

To: Dr. Nancy Knipher	From: Melissa Hancock Furness
Company: Tap Pharmaceuticals, Inc.	
Fax number: 847-236-2880	Fax number: 301-443-9285
Phone number: 847-236-2193	Phone number: 301-827-7450
Subject: NDA 21-507	
Total no. of pages including cover: 2	

Comments:

Attached please find requests for information regarding NDA 21-507.

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In our original facsimile communication to you dated 11/01/02 concerning N21-507, The Agency requested the following information:

- Please provide the efficacy data set(s) containing the Naproxen-only subjects in Study M95-301. The data set(s) should include all derived variables and their components as well as variables for age, gender, and race.

We acknowledge receipt of a response to this request; however, the data that you sent did not contain a primary efficacy variable. Therefore, The Agency initiated a teleconference with you that took place on 01/08/03. During this teleconference, we conveyed our desire for inclusion of the specific primary efficacy variable.

During further review of the data, we have realized that you have not included any secondary variables (in this case, variables from diary data) in either data set. The Agency would like this data in order to be able to perform a complete and thorough review. Specifically, we would like the data pertaining to the occurrence and severity of day and night abdominal pain, day and night joint pain and swelling, and frequency of antacid use. We would appreciate your continued cooperation in obtaining the data that we have requested.

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Melissa Furness
2/19/03 11:54:02 AM
CSO

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Frances LeSane, HFD-520 9201 Corporate Boulevard		FROM: Melissa Hancock Furness, HFD-180 Parklawn Building 6B-45		
DATE December 9, 2002	IND NO.	NDA NO. 21-507	TYPE OF DOCUMENT S-000	DATE OF DOCUMENT September 6, 2002
NAME OF DRUG Naprosyn/Prevacid		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE May 9, 2003
NAME OF FIRM: Tap Pharmaceutical Products, Inc				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> OTHER (SPECIFY BELOW): <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> See comments below				
COMMENTS/SPECIAL INSTRUCTIONS: Attached is a type 4 New Drug Application (co-packaged product). The PDUFA goal date is 07/09/02/03. Please note that this application was submitted electronically, consequently, it may be found on the EDR. Please let me know if you require hard copies as well and I can request these from the firm.				
SIGNATURE OF REQUESTER: Melissa Hancock Furness		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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Melissa Furness
12/9/02 03:43:51 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: 11/19/02

To: Doug Donovan	From: Melissa Hancock Furness
Company: Tap Pharmaceuticals, Inc.	
Fax number: 847-236-2880	Fax number: 301-443-9285
Phone number: 847-582-2557	Phone number: 301-827-7450
Subject: NDA 21-507	

Total no. of pages including cover: 3

Comments:

Attached please find the clarifications that you requested in your 11/08/02 facsimile regarding NDA 21-507.

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The clarifications are as follows (please note that our original question is in bold and the *clarifications* are in *italics*):

1. **Please provide the breakdown of Naprosyn dosing for subjects in studies m95-30, M95-299 and M95-352.**

Please provide the individual subject doses and a summary table.

2. **Please provide the duration of Naprosyn exposure for subjects in study m95-301, M95-299 and M95-352.**

Please provide the individual information consisting of a duration of naproxen in the studies and a summary table.

Please also note that it is acceptable for you to combine the data in all tables and datasets, and to exclude those subjects who stopped naproxen prior to the first dose of the study.

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Melissa Furness
11/19/02 03:38:54 PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: 11/01/02

To: Doug Donovan	From: Melissa Hancock Furness
Company: Tap Pharmaceuticals, Inc.	
Fax number: 847-236-2880	Fax number: 301-443-9285
Phone number: 847-582-2557	Phone number: 301-827-7450
Subject: NDA 21-507	

Total no. of pages including cover: 3

Comments:

Attached please find requests for information regarding NDA 21-507.

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The requests are as follows:

1. Please provide the breakdown of Naprosyn dosing for subjects in studies m95-30, M95-299 and M95-352.
2. Please provide the case report forms for any those with adverse events in the Naprosyn subset in studies m95-301, M95-299 and M95-352
3. Please provide the duration of Naprosyn exposure for subjects in study m95-301, M95-299 and M95-352
4. Please provided the age and other demographic information for the subjects in the Naprosyn subset in study m95-301, M95-299 and M95-352
5. Please provide the healing rates of subjects in the Naprosyn subset in studies M95-299 and M95-352
6. Please provide the proposed labeling in Word format
7. Please provide the efficacy data set(s) containing the Naproxen-only subjects in Study M95-301. The data set(s) should include all derived variables and their components as well as variables for age, gender, and race.
8. Please provide the efficacy data set(s) from studies M95-299 and M95-352. Again, the data set(s) should include all derived variables and their components as well as variables for age, gender, and race.

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/s/

Melissa Furness
11/1/02 12:43:32 PM
CSO

NOV 1 2002 12:43:32 PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-507

TAP Pharmaceutical Products, Inc.
Attention: Doug Donovan
Assistant Director, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Mr. Donovan:

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) Delayed-Release Capsules and
Naprosyn (naproxen) Tablets

Review Priority Classification: Standard (S)

Date of Application: September 6, 2002

Date of Receipt: September 9, 2002

Our Reference Number: NDA 21-507

Unless we notify you within 60 days of the 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 November 8, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 9, 2003.

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. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. 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, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Consumer Safety Officer
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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Melissa Furness
10/9/02 02:13:34 PM

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Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-507

Name of Drug: Prevacid Naprosyn combination packet

Sponsor: Tap Pharmaceuticals

Date Review Completed: 09/26/02

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): electronic

Submission Date: 09/06/02

Receipt Date: 09/09/02

Filing Date: 11/08/02

User-fee Goal Date(s): 07/09/03

Proposed Indication:

The above listed NDA 21-507 provides for combination packages containing two established and approved individual drug components, Prevacid Delayed-Release 15 mg capsules and either Naprosyn 250mg, 375mg or 500mg tablets. These packages have been developed in support of TAP's approved indication for "risk reduction of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID" (PREVACID Delayed-Release Capsule NDA 20-406/S-033).

Other Background Information:

TAP's approved NDA for Prevacid (lansoprazole) Delayed-Release Capsules is NDA 20-406. Roche Laboratories Inc.'s approved NDA for Naprosyn (naproxen) Tablets (Letter of Authorization provided within NDA 21-507) is NDA 17-581.

Review

PART I: OVERALL FORMATTING^{a,d,e}

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers)
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		(If electronic: list folder & page numbers)
1. Cover Letter	x	Cover letter folder
2. Form FDA 356h (original signature)	x	356H folder
a. Establishment information	x	356H folder
b. Reference to DMF(s) & Other Applications	x	356H folder
3. User Fee FDA Form 3397	x	Other folder; patinfo.pdf and patcert.pdf
4. Patent information & certification		
5. Debarment certification (Note: Must have a definitive statement)	x	Other folder; debar.pdf
6. Field Copy Certification	x	Other folder; fieldcer.pdf
7. Financial Disclosure		N/A
8. Comprehensive Index	x	TOC file
9. Pagination		N/A due to electronic submission
10. Summary Volume	x	Summary folder
11. Review Volumes	x	NN, MK, DP, AC (checked 09/26/03)
12. Labeling (PI, container, & carton labels)	x	Labeling folder
a. unannotated PI	x	Labeling folder; labeltoc.pdf; proposed labeling link; unannotated folder
b. annotated PI	x	Labeling folder; labeltoc.pdf; proposed labeling link; annotated folder
c. immediate container	x	Labeling folder; container folder; container.pdf
d. carton	x	Labeling folder; container folder; container.pdf
e. patient package insert (PPI)		x N/F
f. foreign labeling (English translation)		x N/F

13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)		x	N/A
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)		x	N/A

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY^{b,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits		x	N/F
2. Foreign Marketing History		x	N/F
3. Summary of Each Technical Section	x		Summary Folder; TOC folder
a. Chemistry, Manufacturing, & Controls (CMC)	x		Summary Folder; TOC folder; Overall CMC folder
b. Nonclinical Pharmacology/Toxicology		x	N/A
c. Human Pharmacokinetic & Bioavailability	x		Summary Folder; TOC folder; Overall Human Pharmacokinetic folder
d. Microbiology		x	N/A
e. Clinical Data & Results of Statistical Analysis	x		Summary Folder; TOC folder; Overall Clinical Summary folder
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	x		Summary Folder; TOC folder; Overall Clinical Summary folder; Benefits and Risks of Lansoprazole and Naprosyn Combination Packaging
5. Summary of Safety		x	N/F
6. Summary of Efficacy		x	N/F

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS^{c,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators		x	N/F
2. Controlled Clinical Studies		x	N/F
a. Table of all studies		x	N/F
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)		x	N/F
c. Optional overall summary & evaluation of data from controlled clinical studies		x	N/F
3. Integrated Summary of Efficacy (ISE)		x	N/F
4. Integrated Summary of Safety (ISS)		x	N/F
5. Drug Abuse & Overdosage Information		x	N/A
6. Integrated Summary of Benefits & Risks of the Drug	x		Summary folder; Overall Clinical Summary folder
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		x	N/F

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS^{d,e}

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population			

2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		See a-e
a. Proposed unannotated labeling in MS WORD	x	N/F (asked sponsor to submit)
b. Stability data in SAS data set format (only if paper submission)	x	N/F (asked sponsor to submit)
c. Efficacy data in SAS data set format (only if paper submission)	x	N/A
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)	x	N/A (electronic)
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)	x	N/A
3. Exclusivity Statement (optional)	x	N/A (no clinical studies)

Y=Yes (Present), N=No (Absent)

^a"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

^b"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

^c"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

^d"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

^e"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Melissa Hancock Furness
Regulatory Project Manager
09/26/02

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