CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-507

STATISTICAL REVIEW(S)

05/16/03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-507
Name of drug:	Naprapac (Naprosyn®/Prevacid® combination package)
Applicant:	Tap Pharmaceutical Products, Inc.
Indication:	Treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis in patients with a history of documented gastric ulcers
Documents reviewed:	\\CDESUB1\N21507\n_000\2002-09-06\clinstat \\CDESUB1\N21507\N_000\2003-01-14\crt\datasets
Project manager:	Melissa Furness
Clinical reviewer:	Narayan Nair, M.D.
Dates:	Received 09/06/02; user fee (10 months) 07/09/03
Statistical reviewer:	Dionne L. Price, Ph.D.
Statistics team leader:	Thomas Permutt, Ph.D.
Biometrics division director:	S. Edward Nevius, Ph.D.
Keywords:	NDA review, clinical studies

APPEARS THIS WAY
ON ORIGINAL

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

Tap Pharmaceuticals has proposed a co-packaged product containing naproxen and lansoprazole for the "treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, in patients with a history of documented gastric ulcer, who require risk reduction of gastric ulcers associated with the chronic use of an NSAID, such as Naprosyn® (naproxen)." A primary claim of the sponsor is that significantly higher proportions of patients remain free from gastric ulcer occurrence at 4, 8, and 12 weeks as compared to placebo. The evidence from the data presented indicates statistical support favoring the co-packaged product in the risk reduction of nonsteroidal anti-inflammatory drug (NSAID) associated gastric ulcers. No additional claims are made.

At a pre-New Drug Application (NDA) meeting dated 22 February 2002, the Division of Gastrointestinal and Coagulant Drug Products made several recommendations to the sponsor. The adequacy of the application to address the recommendations will be deferred to the medical review of Dr. Narayan Nair.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

Background

The present application was introduced to the Division of Gastrointestinal and Coagulation Drug Products at a meeting dated 22 February 2002. During the meeting, Tap Pharmaceutical Products, Inc. requested advice concerning their plan to file a new drug application for a convenience pack containing lansoprazole 15 mg and naproxen (varying doses). At that time, the division recommended that the sponsor address the specification and justification of the form of naproxen to be used in the product, the individualization of the naproxen dosage, the treatment of acute episodes of pain, the potential for lansoprazole to mask symptoms, and the need for or consequences of intermittent treatment.

NDA 21-507 was submitted on 06 September 2002. The goal of the submission was to investigate the safety and efficacy of the co-packaged product for the "treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and anklyosing spondylitis, in patients with a history of documented gastric ulcer, who require risk reduction of gastric ulcers associated with chronic use of an NSAID, such as Naprosyn® (naproxen)." Evidence was primarily derived from a subset of data originating from NDA 20-406/S-033 (for the approved drug, lansoprazole).

Study Design

Study M95-301 originating from NDA 20-406/S-033 was composed of individuals having an endoscopically documented history of gastric ulcer and negative *Helicobacter pylori* at screening. Patients meeting all eligibility requirements were randomized to placebo, lansoprazole 15 mg, lansoprazole 30 mg, or misoprostol 200 μg. The former groups received a single daily dose of treatment while the latter group was administered treatment four times daily. The latter group was blinded only to endoscopists. The study duration was 12 weeks, and patients continued taking NSAID therapy as directed by their physician. The current NDA considers the subset of 119 patients receiving naproxen only (250 mg, 375 mg, or 500 mg) or naproxen and concomitant low dose aspirin (≤ 325 mg daily).

Statistical Analyses

The primary measure of efficacy was the time to occurrence of gastric ulcer where the presence of gastric ulcer was confirmed by endoscopies performed at weeks 4, 8, and 12. The time of occurrence was calculated via Koch's midpoint rule utilizing 2 to 28 days, 29 to 56 days, and 57 to 84 days as respective time intervals of interest. Patients were classified as having experienced a recurrence during the interval, not having experienced a recurrence, or withdrawn as gastric ulcer-free for each time interval. Rates of gastric ulcer occurrence (or conversely, ulcer-free rates) were estimated via life-table methodology. The null hypothesis of equivalent occurrence rates for all treatments was tested via the Mantel-Cox test with time interval as a stratification factor. Additionally, pairwise treatment group differences were also assessed by the Mantel-Cox test.

Secondary measures of efficacy included occurrence and severity of day and night abdominal pain, day and night joint pain/swelling, and frequency of antacid use. The measures were assessed via patient diary records. Specifically, pain was characterized via a 4-point scale where 0 denoted no pain and 3 denoted severe daily pain. The Wilcoxon two-sample test was employed to compare day and night abdominal pain, day and night joint pain/swelling, and frequency of antacid use between treatment groups.

Sponsor's Results and Conclusions

A higher percentage of patients randomized to lansoprazole 15 mg remained free from gastric ulcer occurrence by week 12 as compared to patients randomized to lansoprazole 30 mg, misoprostol 200 μg, and placebo. Specifically, the percent of patients remaining gastric ulcer-free were 33%, 83%, 89%, and 83% in the placebo, misoprostol 200 μg, lansoprazole 15 mg, and lansoprazole 30 mg groups, respectively. No statistically significant differences were observed between lansoprazole 15 mg and placebo for any of the secondary variables.

1.3 PRINCIPAL FINDINGS

Following evaluation of the subset of data, I conclude that a significantly higher percentage of patients receiving the co-packaged product remained gastric ulcer-free as compared to placebo across the study duration. The conclusions are consistent with those of the all patient data of NDA 20-406/S-033. I am in general agreement with the methodologies and analyses employed by the sponsor with one exception. The sponsor's analyses are conducted with no adjustments for multiplicity. Indeed, several pairwise comparisons of interest are conducted. Without an adjustment, there may be an increased probability of falsely declaring some dose of treatment to be effective. In order to maintain an overall type I error rate of 0.05, I applied a sequentially rejective Bonferroni test. My analysis with an adjustment was post-hoc; however, the purpose was solely to validate conclusions.

The sponsor does not make any claims regarding subgroups (i.e. age, race, gender) or secondary variables. The results of my subgroup analyses lend support to the overall findings. Moreover, no statistically significant differences were observed between lansoprazole 15 mg and placebo for any of the secondary variables.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Naprapac is a proposed combination package containing lansoprazole and naproxen. Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) approved for treatment of rheumatoid arthritis, osteoarthritis, and anklyosing spondylitis. Lansoprazole is a proton pump inhibitor currently approved for several indications including short-term treatment of active benign gastric ulcer, healing of NSAID-associated gastric ulcer, and risk reduction of NSAID-associated gastric ulcer. The latter indication of lansoprazole was originally evaluated via adequate and well-controlled studies contained in NDA 20-406/S-033. The present submission investigates the safety and efficacy of the co-packaged product for the "treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and anklyosing spondylitis, in patients with a history of documented gastric ulcer, who require risk reduction of gastric ulcers associated with chronic use of an NSAID, such as Naprosyn (naproxen)." The submission utilizes a subset of the data from NDA 20-406/S-033 to support the proposed combination package.

On 22 February 2002, a pre-NDA meeting regarding NDA 21-507 occurred between the Division of Gastrointestinal and Coagulation Drug Products and Tap Pharmaceutical Products, Inc. The division recommended that the sponsor provide a justification for the form of Naprosyn® (naproxen) proposed and provide information regarding chronic use of a 7-day package. Additionally, the division informed the sponsor of the need to address the following: dosage titration during therapy, treatment of acute episodes of pain, potential for Prevacid® (lansoprazole) to mask symptoms/signs of gastric ulcers, and the need for or consequences of intermittent treatment.

2.2 DATA ANALYZED AND SOURCES

Study M95-301 (submitted in NDA 20-406/S-033) evaluated the safety and efficacy of lansoprazole in the risk reduction of NSAID-associated gastric ulcer "in subjects with no current gastric or duodenal ulcers or more than 25 gastric or duodenal erosions and the need for chronic NSAID therapy." The subset of interest from study M95-301 consists of patients who received the NSAID, naproxen. Additionally, NDA 20-406/S-033 included studies M95-299 and M95-352 supporting the use of lansoprazole in the healing of NSAID-associated gastric ulcers for patients continuing NSAID therapy. Healing studies are not of focus in this review as patients in those studies entered study M95-301 provided eligibility requirements were met. The reviewed documents included volumes 1-9 dated 06 September 2002. The data of interest were archived in the Food and Drug Administration internal document room under the network path location \\CDESUB1\N21507\N_000\2003-01-14. (A summary of the studies is provided in Table 1.)

Table 1: Table of Studies

Study number Number of centers	Study Design	Treatment arms	Primary measure of efficacy
M95-301 (naproxen subset)	Phase III, double-blind, multi-center, parallel group, placebo and active controlled	`Lansoprazole 15mg QD (37) `Lansoprazole 30 mg QD(24) `Misoprostol 200 µmg(28) `Placebo(30)	Percentage of naproxen patients remaining gastric ulcer-free
M95-299	Phase III, double blind, multi-center, parallel group, active controlled	`Lansoprazole 15 mg (118) `Lansoprazole 30 mg (117) `Ranitidine (117)	Percentage of patients with endoscopically documented healing of gastric ulcer at weeks 4 and 8
M95-352	Phase III, double blind, multi-center, parallel group, active controlled	`Lansoprazole 15 mg (114) `Lansoprazole 30 mg (112) `Ranitidine (116)	Percentage of patients with endoscopically documented healing of gastric ulcer at weeks 4 and 8

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

Study M95-301 was comprised of individuals having an endoscopically documented history of gastric ulcer and negative *Helicobacter pylori* at screening. Additionally, individuals with healed gastric ulcers in studies M95-299 and M95-352 were eligible for enrollment in M95-301. Patients meeting all eligibility requirements were randomized to placebo, lansoprazole 15 mg, lansoprazole 30 mg, or misoprostol 200 µg. The former groups received a single daily dose of treatment while the latter group was administered treatment four times daily. The latter group was blinded only to endoscopists. The study duration was 12 weeks, and patients continued taking NSAID therapy as directed by their physician. The current NDA considers the subset of 119 patients receiving naproxen only (250 mg, 375 mg, or 500 mg) or naproxen and concomitant low dose aspirin (≤ 325 mg daily).

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

A higher percentage of patients randomized to lansoprazole 15 mg remained gastric ulcer-free by week 12 as compared to patients randomized to lansoprazole 30 mg, misoprostol 200 µg, and placebo. Specifically, the percent of patients remaining gastric ulcer-free were 33%, 83%, 89%, and 83% in the placebo, misoprostol 200 µg, lansoprazole 15 mg, and lansoprazole 30 mg groups, respectively.

2.3.2 STATISTICAL METHODOLOGIES

The primary measure of efficacy as defined by the sponsor was the time to occurrence of gastric ulcer where the presence of gastric ulcer was confirmed by endoscopies performed at weeks 4, 8, and 12. The time of occurrence was calculated via Koch's midpoint rule utilizing 2 to 28 days, 29 to 56 days, and 57 to 84 days as respective time intervals of interest. Specifically, "the time to occurrence was linked to the interval that contained the midpoint between the time of observed ulcer occurrence (endoscopic) and the previous endoscopic evaluation." Moreover for each time interval, patients were

classified as having experienced a recurrence during the interval, not having experienced a recurrence, or withdrawn as gastric ulcer-free. Rates of gastric ulcer occurrence (or conversely, ulcer-free rates) were estimated via life-table methodology. The null hypothesis of equivalent occurrence rates for all treatments was tested via the Mantel-Cox test with time interval as a stratification factor. Additionally, pairwise treatment group differences were also assessed by the Mantel-Cox test.

Secondary measures of efficacy included occurrence and severity of day and night abdominal pain, day and night joint pain/swelling, and frequency of antacid use. The measures were assessed via patient diary records. Specifically, pain was characterized via a 4-point scale where 0 denoted no pain and 3 denoted severe daily pain. The Wilcoxon two-sample test was employed to compare day and night abdominal pain, day and night joint pain/swelling, and frequency of antacid use between treatment groups.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

Study M95-301 enrolled 537 patients across 63 sites within the United States and Canada. The sample size was adequate to provide at least 84% power to detect a difference in gastric ulcer occurrence between treatment and placebo, assuming a 12% occurrence of gastric ulcer in placebo and a 2% occurrence in the active treatment group. While on treatment, 191 patients received naproxen as their NSAID therapy (with or without concomitant low-does aspirin use). The sponsor stated, " naproxen was the second most commonly used NSAID after ibuprofen." The patients receiving naproxen comprised the subset of interest for the current application. Analyses based on the subset of naproxen patients had a lower power to detect a difference; however, I am under the assumption that the sponsor accepted the reduced power as implied by proceeding with the analyses. Analyses were performed on the intent-to-treat population consisting of all randomized patients receiving at least one dose of test medication.

Table 2 depicts the results of the sponsor's analysis performed on the primary efficacy variable, time to occurrence of gastric ulcer. The table was generated via life-table methodology as outlined in Section 2.3.2. Of note, the exact time of recurrence per patient was unknown; therefore, the sponsor formulated each patient's time to recurrence via the midpoint rule and subsequently performed analyses. Based on the results illustrated in the table, the sponsor concluded that a higher proportion of patients receiving lansoprazole 15 mg and lansoprazole 30 mg remained free from gastric ulcer at weeks 4, 8, and 12 as compared to placebo.

Table 2:Percentage of Naproxen-Only Subjects Remaining Gastric Ulcer-free at the End of the Time Intervalof Study M95-301 Calculated via Life-Table Methodology (as presented by sponsor)

	Time Interval (weeks)			95% Confidence Intervals	
Treatment group	**0-4**	**4-8**	**8-12**	**At 4-8 Weeks**	**At 8-12 Weeks**
Naproxen Subjects – Intent-to-treat Dataset					
Placebo	52%	52%	33%	(33.0, 70.7)	(14.0, 52.0)
Misoprostol 200 µg QID	88%	88%	83%	(75.3, 100.0)	(67.9, 98.3)
Lansoprazole 15 mg QD	91%	89%	89%	(78.0, 99.1)	(78.0, 99.1)
Lansoprazole 30 mg QD	83%	83%	83%	(67.1, 98.1)	(67.1, 98.1)

Overall, a significant difference in ulcer-free rates existed among treatments. Moreover, pairwise treatment group differences were assessed. Statistically significant differences in gastric ulcer occurrence were found to exist among each of the active treatments and placebo; however, no significant differences were found to exist among any of the pairwise comparisons between the active treatments. A detailed table depicting gastric ulcer occurrence is in the appendix.

The sponsor further stated that the sensitivity of the results was evaluated by considering two assumptions. The analyses were repeated optimistically assuming that patients who withdrew remained ulcer-free subsequent to withdrawal. Additionally, the analyses were conducted assuming that patients who withdrew experienced an occurrence subsequent to withdrawal. The results of the additional analyses were not included in the new drug application; however, I performed the analyses. I also considered a worse case scenario whereby withdrawals in the active group were considered as failures and withdrawals in the placebo group were considered as successes. The conclusions remain unchanged as a result of the additional analyses.

I examined the diary results as presented by the sponsor. I specifically focused on pairwise comparisons between lansoprazole 15 mg and placebo. No statistically significant differences were observed between lansoprazole 15 mg and placebo for any of the secondary variables. The resulting table from the sponsor's analysis of secondary variables is provided in the appendix.

2.3.4 STATISTICAL REVIEWER'S FINDINGS

The medical and statistical reviews of the original NDA expressed some concern regarding the width of the time intervals. An analysis that considered intervals of smaller width was conducted. Additionally, an investigative analysis of the last time interval was also conducted. Although an exploration as conducted in the original review may be informative; a test that accumulates evidence over the entire treatment period has desirability. Consideration of the entire time period usually provides a gain in the power to detect differences in the recurrence experience of the groups and additionally allows

for variation in the risk of recurrence over different time intervals. Thus, this review focused on the analyses as outlined by the sponsor.

During the course of my review, I identified a methodological issue warranting further discussion. The sponsor's analyses were conducted with no adjustments for multiplicity. Indeed, several pairwise comparisons of interest were conducted. Without an adjustment, there may have been an increased probability of falsely declaring some dose of treatment to be effective. In order to maintain an overall type I error rate of 0.05, I applied a sequentially rejective Bonferroni test. My analysis was post-hoc; however, the purpose was solely to validate conclusions.

During initial consultations with the medical officer, Dr. Nair, the influence of aspirin use and the data supporting the three proposed doses of naproxen emerged as points warranting further exploration. Patients were allowed to remain on previously initiated low doses of aspirin. Fifteen percent of the naproxen patients also received concomitant aspirin. Utilizing an analysis adjusting for aspirin, I found that concomitant aspirin use did not influence the overall conclusions. The proposed combination package will contain one 15 mg lansoprazole capsule and two naproxen tablets (250 mg, 375 mg, or 500 mg tablets). As a result of further investigation, I found that patients were allowed varying doses of naproxen during the study. The highest daily dose per patient was used as a viable measure of naproxen use by the sponsor. A statistical evaluation of the differences in the highest daily dose of naproxen among the treatments yielded no statistically significant differences in mean total daily dose of naproxen among the four treatment arms. The evaluation was completed via an analysis of variance model.

I am in general agreement with the sponsor's statistical results and conclusions. Based on the statistical evaluation of the evidence, I conclude that lansoprazole 15 mg is more effective than placebo in reducing the risk of NSAID-associated gastric ulcer in patients receiving naproxen.

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Analyses were performed with respect to gender and age. Again, the primary efficacy variable was the time to occurrence of gastric ulcer. Rates of gastric ulcer occurrence per subgroup were estimated via life-table methodology. The null hypotheses of equivalent occurrence rates for all treatments were tested via the Mantel-Cox test with gender and age as stratification factors, respectively. The variable age was categorized utilizing two subgroups, ages greater than 65 and ages less than or equal to 65. This categorization was used in the analysis of the original NDA.

A higher percentage of females and males randomized to lansoprazole 15 mg remained gastric ulcer-free by week 12 as compared to the placebo group. Specifically by the end of week 12, 89% of females and 88% of males receiving lansoprazole 15 mg were gastric ulcer-free as compared to 41% and 20%, respectively, in the placebo group. Similarly, a higher percentage of younger (less than 65) and older patients randomized to

lansoprazole 15 mg remained gastric ulcer-free by week 12 as compared to the placebo group. Of note, a subgroup analysis with respect to race was not performed. Eighty-eight percent of the patients were Caucasian.

The sponsor did not propose any efficacy claims for any subgroup of patients. Overall, the results were consistent and lend support to the findings presented in the preceding sections.

2.5 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

A primary claim of the sponsor is that the co-packaged product produces greater efficacy than placebo as measured by the proportion of patients remaining gastric ulcer-free. The evidence indicates that among the subset of patients receiving naproxen (with or without concomitant aspirin use) a higher percentage of patients receiving lansoprazole 15 mg remained gastric ulcer-free at weeks 4,8, and 12 as compared to placebo. The results are consistent with those produced by analysis of the all patient data in study M95-301 (NDA 20-406/S-033). No claims were made by the sponsor regarding secondary variables of interest.

2.6 CONCLUSIONS AND RECOMMENDATIONS

As a result of the analysis of the subset of interest, the sponsor suggest that the co-packaged product is effective 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 (naproxen)." Evidence supporting the indication has been provided via a subset of data containing patients receiving lansoprazole 15 mg and naproxen (250, 375, or 500 mg). A significantly higher percentage of patients receiving the co-packaged product remained gastric ulcer-free as compared to placebo. At a meeting dated 22 February 2002, the Division of Gastrointestinal and Coagulant Drug Products made several recommendations pertaining to NDA 21-507. The adequacy of the application to address the recommendations will be deferred to the medical review of Dr. Narayan Nair.

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2.7 LABELLING

A portion of the draft labeling reads as follows:

[redacted]

Of note, only lansoprazole 15 mg (taken once daily) is approved for the risk reduction of NSAID associated gastric ulcer; therefore, I suggest the exclusion of [redacted] in the above claim. Moreover, additional details may be of interest in the label. I propose the following:

[redacted]

2.8 APPENDIX

This appendix contains tables of the gastric ulcer occurrence and diary results, as presented by the sponsor.

Gastric Ulcer Occurrence Status for Naproxen-Only Subjects in Study M95-301 (as presented by the sponsor)

	Time intervals (weeks)		
Treatment Group	**0-4**	**4-8**	**8-12**
Naproxen-Only Subjects Intent-to-Treat Dataset			
Placebo (N=30)			
Occurrence	13	0	4
No occurrence	14	13	7
Withdrawal	3	1	2
Misoprostol 200 µg QID (N=28)[a]			
Occurrence	3	0	1
No occurrence	22	19	17
Withdrawal	3	3	1
Lansoprazole 15 mg QD (N=37)[a]			
Occurrence	3	1	0
No occurrence	32	31	28
Withdrawal	2	0	3
Lansoprazole 30 mg QD (N=24)[a]			
Occurrence	4	0	0
No occurrence	19	18	17
Withdrawal	1	1	1

a Statistically significant difference versus placebo group (ph0.05).

Diary Results for Naproxen-Only Subjects at the End of the 12-Week Double-Blind Treatment Period of Study M95-301 (as presented by sponsor)

	Treatment Group Mean			
Naproxen-Only Subjects Intent-to-Treat				
Variable	**Placebo (N=28)**	**Misoprostol 200 µg QID (N=27)**	**Lansoprazole 15 mg QD (N=37)**	**Lansoprazole 30 mg QD (N=24)**
Daytime Abdominal Pain				
% of Days with Pain	28.5	48.3#	23.5*	28.0*
Average Pain Severity Day	0.40	0.78	0.32	0.42
Nighttime Abdominal Pain				
% of Nights with Pain	24.3	39.3#	21.6*	22.7*
Average PainSeverity/Night	0.36	0.66	0.29	0.35
Gelusil Use				
Percent of Days Used	30.9	49.2#	21.1*	20.3*
Average Number/Day	0.99	1.76	0.57	0.58
Daytime Joint Pain/Swelling				
% of Days with Pain	58.2	51.3	47.3	55.4
Average Pain Severity/Day	0.95	0.91	0.84	0.82
Nighttime Joint Pain/Swelling				
% of Nights with Pain	56.6	51.4	45.2	53.5
Average Pain Severity/Night	0.89	0.92	0.79	0.76

* Statistically significant difference versus misoprostol treatment group (ph 0.05).
# Statistically significant differences versus placebo group (ph 0.05).

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/s/

Dionne Price
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Thomas Permutt
5/16/03 09:13:32 AM
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