

- For both the first 4 and all episodes, NIZ-treated subjects had significantly more episodes adequately relieved at 120 and 180 min.

[The results for all episodes were confirmed using a GEE logistic model (Table 21)].

**TABLE 24**  
Study NZ-95-04

Mean Proportion of Each Subject's episodes for Which Adequate Relief Was Attained by Time Point  
Intent-to-treat Subjects

I. Based on the First 4 Episodes					
Minutes After Dosing with Study Medication	PL [n=231]	NIZ 75 Mg [n=226]	Therapeutic Gain (NIZ-PL)	Treatment p-value <sup>a</sup>	Treatment-Site Interaction p-value
15	0.16	0.17	0.01	N.S.	N.S.
30	0.33	0.34	0.01	N.S.	N.S.
45	0.48	0.50	0.02	N.S.	N.S.
60	0.63	0.68	0.05	N.S.	N.S.
120	0.69	0.76	0.07	0.020	N.S.
180	0.67	0.75	0.08	0.009	N.S.
II. Based on All Episodes					
15	0.16	0.17	0.01	N.S.	N.S.
30	0.32	0.32	NONE	N.S.	N.S.
45	0.49	0.50	0.01	N.S.	N.S.
60	0.63	0.67	0.04	N.S.	N.S.
120	0.69	0.75	0.06	0.047	N.S.
180	0.67	0.74	0.07	0.026	N.S.
a) Cochran-Mantel-Haenszel row mean score test controlling for site					

- e) Proportions of Episodes Within Each Subject for Which Rescue Medication Was Taken (Table 25)

NIZ-treated subjects took rescue medication for a significantly lower proportion of both their first four episodes and all episodes than did PL-treated subjects [therapeutic gain=6% for both the first 4 and all episodes].

[The results for all episodes were confirmed using a GEE logistic model (Table 21)].

**TABLE 25**  
Study NZ-95-04

Proportion of Each Subject's Episodes for Which Rescue Medication Was Taken  
Intent-to-Treat Subjects

Episode Interval		PL [n=231]	NIZ 75 mg [n=226]	Therapeutic Gain (NIZ-PL)	Treatment p-value <sup>a)</sup>	Treatment-Site Interaction p-value
First 4 Episodes	n	231	226			
	Mean	0.27	0.21	-0.06		
	Std	0.32	0.30		0.022	N.S.
	Median	0.25	0.00	-0.25		
Range						
All Episodes	n	231	226			
	Mean	0.27	0.21	-0.06		
	Std	0.28	0.29		0.020	N.S.
	Median	0.20	0.07	-0.13		
Range						

a) Cochran-Mantel-Haenszel row mean score test controlling for site

f) Proportion of Episodes Within Each Subject  
for Which Complete Relief Was Reported at the  
3-h Timepoint (Table 26)

NIZ-treated subjects reported complete relief in a significantly higher proportion of both their first 4 episodes and all episodes than did placebo-treated subjects [therapeutic gain=9% for first 4 episodes, and 8% for all episodes]. [Thus, NIZ provided not only significantly more adequate relief, but also significantly more complete relief than PL.

[The results for all episodes were confirmed with the GEE analysis (Table 21)].

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**TABLE 26**  
Study NZ-95-04

Proportion of Each Subject's Episodes for Which Complete Relief Was Reported at the 3-h Time Point

Intent-to-Treat Subjects

Episode Interval		PL [n=231]	NIZ 75 mg [n=226]	Therapeutic Gain (NIZ-PL)	Treatment p-value**	Treatment-Site Interaction p-value
First 4 Episodes	n	230	225			
	Mean	0.64	0.73	0.09	0.004	N.S.
	Std	0.35	0.34			
	Median	0.75	1.00	0.25		
Range						
All Episodes	n	231	225			
	Mean	0.64	0.72	0.08	0.006	N.S.
	Std	0.32	0.32			
	Median	0.70	0.83	0.13		
Range						

a) Cochran-Mantel-Haenszel row mean score test controlling for site

g) Sustained Adequate Relief Score for the First Episode (Table 27)

As shown in this Table, the treatment groups could not be differentiated when using this secondary parameter of evaluation. NIZ-treated subjects had a mean SARS of 2.44 compared to PL-treated subjects with a mean of 2.31; this therapeutic (0.13) difference was not significant (p=0.383).<sup>11</sup>

**TABLE 27**  
Study NZ-95-04

SARS for the First Episode (%)

Intent-to-Treat Subjects

Sustained Relief Attained	PL [n=231]	NIZ 75 mg [n=226]	Therapeutic Gain (NIZ-PL)	Treatment p-value**	Treatment-Site Interaction p-value
At 15 or 30 min. (4)	78 (34%)	71 (31%)	-3%	N.S.	N.S.
At 45 or 60 Min. (3)	61 (26%)	75 (33%)	7%		
At 120 Min. (2)	16 (7%)	18 (8%)	1%		
At 180 Min. (1)	7 (3%)	7 (3%)	NONE		
Not Within 3 h or Rescue Medication Taken (0)	69 (30%)	55 (26%)			
Mean of Sustained Adequate Relief Scores	2.3	2.4			

a) Cochran-Mantel-Haenszel row mean score test controlling for site

<sup>11</sup> As stated in the protocol, the primary analysis of this endpoint was to be based on the combined data from the two pivotal studies due to sample size considerations.

h) Percentage of Subjects Achieving Sustained Adequate Relief at All Recorded Episodes (Table 28)

A significantly higher percentage of NIZ-treated subjects had sustained adequate relief at all of their episodes than did PL-treated subjects (therapeutic gain=15%).

**TABLE 28**  
Study NZ-95-04

Number (%) of Subjects Achieving SAR for All Episodes (%)

Intent-to-Treat Subjects

	PL [n=231]	NIZ 75 mg [n=226]	Therapeutic Gain (NIZ-PL)	Treatment p-value**	Treatment-Site Interaction p-value
Subjects Achieving SAR for All Episodes					
NO	175 (75%)	136 (60%)	15%	0.001	N.S.
YES	58 (25%)	90 (40%)	15%		
a) Cochran-Mantel-Haenszel general association test controlling for site					

i) Percentage of Subjects Achieving Complete Relief at All Recorded Episodes (Table 29)

A significantly higher percentage of NIZ-treated subjects had complete relief at all of their episodes than did PL-treated subjects. This represented a therapeutic gain of 15%.

**TABLE 29**  
Study NZ-95-04

Number (%) of Subjects Achieving Complete Relief for All Recorded Episodes (%)

Intent-to-Treat Subjects

	PL [n=231]	NIZ 75 mg [n=226]	Therapeutic Gain (NIZ-PL)	Treatment p-value**	Treatment-Site Interaction p-value
Subjects Achieving Complete Relief for All Episodes					
NO	176 (76%)	138 (61%)	-15%	0.001	N.S.
YES	55 (24%)	87 (39%)	15%		
a) Cochran-Mantel-Haenszel general association test controlling for site					

4) Within-Investigator Results<sup>12</sup>

As in study NZ-95-01, the variables analyzed were:

- 1) SARS Averaged over a Subject's First Four Episodes,
  - 2) Proportion of Episodes within Each Subject for Which Sustained Adequate Relief was Attained Based on the First Four Episodes
  - 3) Proportion of Subjects Achieving Sustained Adequate Relief for All Episodes, and
  - 4) Proportion of Episodes within Each Subject for Which Complete Relief was Reported Based on the First Four Episodes.
- Results showed NIZ's superiority to PL was generally consistent across the sites, without any individual site clearly accounting by itself for this superiority.

5) Intent-to-Treat: Subgroup Analyses

- Efficacy analyses using data from subgroups based on HB frequency, HB episode severity, and success of antacid use (based on the single-blind phase of the study) are summarized in Table 30.
- The subgroup analyses according to HB frequency and antacid use were based on the subject's first 4 episodes; the subgroup analysis according to the severity of HB episodes was based on all episodes.
- The reviewer agrees with the sponsor that NIZ was superior to PL within most of the subgroups. Some of the differences were at least borderline significant despite the reduced sample size within the subgroups. The sponsor also notes that NIZ's effectiveness versus PL was clearly apparent with more severe episodes of HB with mean SARS of 2.03 versus 1.57, respectively (therapeutic gain=0.46, p=0.070).

6) Evaluable Analyses<sup>13</sup>

These results were similar to those discussed for the ITT population. The pattern of significant results was nearly identical to those in the intent-to-treat analysis.

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<sup>12</sup> For selected variables, summaries of the results within investigator were found in sponsor's Tables B.13 through B.16, while their Figures B.1 through B.4 contained the site-specific treatment differences and 95% confidence intervals for these differences. The full set of within-investigator results were in sponsor's Appendix VII.

<sup>13</sup> The results for the evaluable population were presented in sponsor's Tables B.20 through B.29.

d. Safety Results

- Study NZ-95-04 showed that NIZ was safe and well tolerated.
- No serious, unexpected AES or deaths due to test medication occurred in this trial.
- There was no significant difference between the treatment groups in the number of AEs.
- The most common adverse AEs in the NIZ group were headache, diarrhea and back pain.
- This AE profile is similar to that reported for NIZ in the submission for prevention of HB (NDA 20-555, Vol 1.70, p 08-20306).

10. Sponsor's Conclusions

"The clear benefit of nizatidine 75mg in the treatment of episodic heartburn was demonstrated in this study. Its efficacy has been shown and was robust in its consistency across all parameters analyzed. Nizatidine 75mg was safe and well-tolerated when taken up to twice a day for the treatment of episodic heartburn."

11. Reviewer's Additional Comments/Conclusions

Study NZ-95-04 is the other clinical efficacy trial set to evaluate the effect (and safety) of single oral doses of NIZ, in relieving episodic heartburn, when taken as needed up to twice daily compared to PL. The study protocol was the same as that used in study NZ-95-01. Both studies used similar study populations (the same inclusion-exclusion criteria) and the same primary and secondary efficacy endpoints.

All in all, results of study NZ-95-04 indicate that NIZ 75 mg is superior to PL in the relief of HB. As indicated by the FDA statistician's reviewer (A.J. Sankoh, Ph.D., April 8, 1997), analysis of the primary efficacy endpoint, sustained adequate relief score (SARS), with respect to the first 4 episodes, all episodes and first 4 episodes separated by at least 12 hours, by both the Cochran-Mantel-Haenszel (CMH) and the generalized estimating equations (GEE) methods consistently support NIZ 75 mg superiority over PL. However, the effectiveness results for this study were not as convincing as those for study protocol #NZ-95-01, in spite of the fact that there was more consistency of results across centers than was observed in study #NZ-95-01.

The FDA's statistician-reviewer also noted that gender analysis results from the two studies showed mixed effectiveness results. For study NZ-95-01, the drug was relatively more effective among females than males. This observed gender effectiveness difference in this study may be due to the fact that there were more females than males (302 females vs 235 males). For study NZ-95-04, however, the drug was dramatically more effective among males than females even though there were more females than males in this study (236

females vs 220 males). It is, therefore, not clear why the drug appears to have no advantage over PL among females in study NZ-95-04 when it appeared to do so in study NZ-95-01, and vice versa. Race analysis results from both studies were consistent with the observed overall effectiveness results in that the results among whites (at least 80% of patients in both studies) were consistent with the observed overall results. The samples sizes for non-whites were too small to detect and/or confirm any meaningful treatment benefit.

It should also be noted that the sponsor's efficacy analysis results on the evaluable patient population were consistent with those based on the ITT patient population (presented and discussed in detail in the present review). The Evaluable patient population analyses were therefore not presented in the present review.

Finally, as in study NZ-95-01, the results of study NZ-95-04 showed that NIZ, at doses of 75 mg, up to two doses per day, is well tolerated.

In summary, the MO agrees with the sponsor's main conclusions about study NIZ-95-04. The efficacy data in the latter trial support the effectiveness of NIZ 75 mg in the treatment/relief of episodic heartburn. In addition, this trial showed that doses of NIZ, 75 mg, up to twice a day, were well tolerated.

#### IX. RECOMMENDATIONS FOR REGULATORY ACTION

The following is recommended.

1. Approval of NIZ 75 mg tablets for the relief of heartburn, acid indigestion and sour stomach. In the target population, these symptoms are expected as a result of consuming certain foods and/or beverages. For relief of these symptoms, the patient is to take 1 tablet with water, when the symptoms occur, with a maximum of two tablets per day.

This recommendation is based on the MO's review of results from two pivotal studies, NZ-95-01 and NZ-95-04. These were adequate and well-controlled, with an adequate primary efficacy endpoint (Sustained Adequate Relief Score = SARS). Although the efficacy results from one trial were more robust than those from the other, both studies demonstrated superiority of the NIZ 75 mg dose over PL in the relief (more frequently and/or sooner) of heartburn.

2. As per similar OTC preparations, the labeling should make clear

a) that NIZ 75 mg tablet is not intended for chronic use ("do not take the maximum daily dosage for more than 2 weeks continuously unless directed by a doctor"),

and

b) that patients with persistent or unresponsive heartburn symptoms should consult a physician.

*November 25, 1997*

*JSI*

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:

NDA 20-555

HFD-180

HFD-180/LTalarico

HFD-180/HGallo-Torres

HFD-181/CSO

HFD-180/JChoudary

HFD-180/EDuffy

f/t 11/25/97 jgw

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*Concurrence JSI/11/25-97*

*Received  
On 11/25/97*

**MEDICAL OFFICER LABELING REVIEW**  
**Division of Over-The-Counter Drug Products**

**NDA #: 20-555/S-003**

**NAME: Axid® AR (nizatidine) Tablets, 75 mg for OTC Use**

**SPONSOR: Whitehall-Robins Healthcare**

5 Giralda Farms

Madison, NJ 07940-0891

**TYPE OF SUBMISSION: Commercial Pharmaceutical**

**DATE OF SUBMISSION: December 16, 1996 CDER: December 17, 1996**

**DATE OF REVIEW: December 2, 1997**

**REVIEWER: Rosemarie Neuner, MD, MPH**

**CSO: Ms. Sakineh Walthers**

Axid® AR (nizatidine) 75 mg Tablets, manufactured by Whitehall-Robins Healthcare, was approved for marketing as an over-the-counter drug product by the Agency on May 9, 1996 for the prevention of heartburn, acid indigestion and sour stomach when this product is taken 30-60 minutes prior to eating. The manufacturer has submitted this efficacy application in support of an indication for the treatment of meal-induced heartburn. This review is based on xeroxed copies of draft labels and labeling (i.e., carton label, package insert, container and pouch label) for Axid AR® Tablets that have been submitted by the manufacturer.

**Proposed Draft Labeling**

**1. Carton Label: (12 Tablets)**

(Refer to the following attached figure, Figure 1.)

The carton label submitted for review by the manufacturer is nearly identical in format and content to the currently approved labeling for Zantac 75® Tablets, with the following exceptions:

**Front Panel Riser:**

1a. The word "NEW!" has been removed from the upper right-hand corner of the riser since the product has been available on the over-the-counter (OTC) market for more than 6 months. (See Fig. 1.)

1b. The draft labeling indications line located on the riser now reads: "*Relieves and Prevents: Heartburn, Acid Indigestion & Sour Stomach*" instead of "*Prevents: Heartburn, Acid Indigestion & Sour Stomach.*" (See Fig 1.)

**Reviewer's Comments:**

*The sponsor's modifications as noted in 1a. and 1b. are acceptable, but the riser noted in comment 1b. needs to be modified as follows: "Relieves and Prevents:*

Heartburn [redacted] Acid Indigestion & Sour Stomach."

**Principle Display Panels:**

1c. Statement of Identity (21 CFR 201.61) - "Such statement of identity shall be in terms of the established name of the drug, if any there be, followed by an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug. . . ." Therefore, this product's statement of identity (SOI) needs to be revised as follows:

AXID AR  
Nizatidine Tablets 75 mg  
Acid Reducer

**Back Panels:**

The following sections (1d.-1i.) should be revised by the sponsor as per the Over-The-Counter Human Drugs; Proposed Labeling Requirements: Proposed Rule (21 CFR 201, 330, and 358) published in the Federal Register on February 27, 1997.)

1d. The "Active Ingredient" section needs to be revised with a [redacted] section added as shown:

**Active Ingredient (In Each Tablet)**  
Nizatidine 75 mg [redacted]

1e. The "Uses" section needs to be revised with the new indication added as shown:

**Uses:** [redacted]

1f. As per Proposed 21 CFR 201.66, a "Warnings" section follows the [redacted]

[Large redacted area]

[Redacted]

1g. As per 21 CFR 201.63 and 330.1 a pregnancy and overdose section should follow as shown:

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

**Keep this and all drugs out of the reach of children.** In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.

1h. A "Directions" section follows next as shown with additional instructions on how to take the product for the new indication:

**Directions:**

[Redacted]

*(Note: In the "Directions" section the sponsor needs to state that the product be taken with a full glass of water.)*

1i. The "Other Information" section should follow next as shown:

**Other Information:** 20°-25°C(68°-77°F). Protect from light.

**Read** [Redacted]

Keep the carton and information sheet. They contain important information.

1j. The "Inactive Ingredients" section comes next with the ingredients listed alphabetically as shown:

**Inactive Ingredients:** Colloidal Silicon Dioxide, Corn Starch, Hydroxypropyl Methylcellulose, Magnesium Sterate, Microcrystalline Cellulose, Polyethylene Glycol, Pregelatinized Starch, Propylene Glycol, Synthetic Iron Oxides, Titanium Dioxide.

1k. Information for consumer help and manufacturing follows next as shown:

**Comments:** [REDACTED]

Call [REDACTED] 1-800-555-AXID

[REDACTED] by Whitehall-Robins Healthcare, Madison, NJ 07940 Made in the U.S.A.

**End-flaps:**

1l. The end-flaps are identical to the most currently approved carton label, but the SOI on the right end-flap needs to be reformatted as stated in comment 1d. (See comment 1d. above.)

**Reviewer's Comments:**

*The sponsor needs to reformat the carton label as discussed above (see comments 1c. - 1l). Attached is a prototype carton label that the sponsor may want to use as reference. (See attached figure, Fig. 6.)*

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ON ORIGINAL

## **2. Package Insert:**

The sponsor has submitted for review a proposed two-sided package insert (see Figures 2 and 3, attached). Side-1 of the proposed package insert needs to be reformatted like the carton label as discussed above. (Refer to comments 1d.-1l.) The attached figure, Fig. 7, is a prototype of Side-1 of the package insert that the sponsor may want to use as reference.

Side-2 of the proposed package insert is nearly identical in format and content to the currently approved package insert for Axid<sup>®</sup> AR Tablets, with the following exceptions:

2a. The wording of the first, left-sided, bullet point has been changed from "***Axid<sup>®</sup> AR is a non-prescription medicine that contains nizatidine, an ingredient that doctors have prescribed for years.***"

2b. The wording of the second, left-sided, bullet point has been changed from "***Axid<sup>®</sup> AR reduces the production of acid in the stomach so you can prevent symptoms,***" to read "***Axid<sup>®</sup> AR works by reducing the production of stomach acid that can cause heartburn.***" This proposed change is acceptable to this reviewer.

2c. The sponsor has added a third, left-sided, bullet point as follows: "***In clinical studies, Axid<sup>®</sup> AR was significantly better than placebo in completely relieving and preventing heartburn symptoms.***" Since this bullet point is not substantiated by the 3 bar graphs which demonstrate the results from the prevention and treatment clinical trials submitted in support of these indications, it needs to be revised as follows: "***In clinical studies, Axid<sup>®</sup> AR was significantly better than placebo in preventing and relieving heartburn symptoms.***"

2d. At the bottom right-hand corner of Side-2, the sponsor has added a new bar graph demonstrating the combined results from the 2 heartburn relief trials (Studies NZ-95-01 and NZ-95-04) submitted in support of this new indication. Only the results from Study NZ-95-04 should be shown in graph format to consumers since the effectiveness data from Study NZ-95-01 was less convincing.

2e. The sponsor needs to remove the "x% better" headers located at the top of each bar graph in all 3 graphs since this information is promotional and confusing to consumers.

2f. The paragraphs in the right handed column under the header "Heartburn: a problem that can interfere with your lifestyle," have been changed from:

*"The stomach normally produces acid following eating and drinking. Sometimes acid backing up into the esophagus can cause a burning pain and discomfort. This pain and discomfort, commonly known as heartburn,*

[Redacted]

[Redacted]

[Redacted]

*When taken as directed, Axid® AR relieves and/or prevents heartburn."*

[Redacted]

APPROVED THIS WAY  
ON ORIGINAL

**3. Container Label: (12 tablet bottle)**

The sponsor has submitted for review the proposed container label for a 12-tablet bottle (see Fig. 4). This label also needs to be revised by the sponsor as per the Over-The-Counter Human Drugs; Proposed Labeling Requirements: Proposed Rule (21 CFR 201, 330, and 358) published in the Federal Register on February 27, 1997.) The sponsor may refer to the attached figure, Figure 8, which demonstrates a prototype container label for this product. The sponsor is also referred to comment 1c. (see above) as to how the SOI needs to be formatted on the principle display panel.

ADRIANO BILGIMNY  
CANTON, OHIO

ADRIANO BILGIMNY  
CANTON, OHIO

#### **4. Pouch Label:**

The sponsor has submitted for review the proposed front and back labels for a single-dose pouch (see Fig. 5, attached). This label also needs to be revised by the sponsor as per the Over-The-Counter Human Drugs; Proposed Labeling Requirements: Proposed Rule (21 CFR 201, 330, and 358) published in the Federal Register on February 27, 1997. The sponsor may refer to the attached figure, Figure 8, which demonstrates a prototype front pouch label for this product. The sponsor is also referred to comment 1c. (see above) as to how the SOI needs to be formatted on the front of the pouch.

**General Comments:**

Attached are prototypes of the carton label, package insert, container and pouch labels that the sponsor may want to use as reference. (See attached figures, Fig. 6-8.) The sponsor should refer to the Over-The-Counter Human Drugs; Proposed Labeling Requirements: Proposed Rule (21 CFR 201, 330, and 358) published in the Federal Register on February 27, 1997 with regards to label formatting (i.e., font size, bolding, etc.) when setting up mock-ups of this product's carton and container labels.

**/S/**

Rosemarie Neuner, MD, MPH  
Medical Officer, HFD-560

**/S/**

Helen Cothran, IDS  
Team Leader

**/S/**

Linda M. Katz, MD, MPH  
Deputy Director, HFD-560

cc: orig NDA  
HFD-560/Div. File  
HFD-180  
HFD-560/MO/Neuner  
HFD-560/IDS/Robinson  
HFD-560/TeamLeader/Cothran  
HFD-560/PM/Walters  
HFD-560/Dep Dir/Katz  
HFD-560/Div Dir/Bowen

**/S/** 12/09/97

13 *pages of revised draft  
labeling have been  
redacted from this portion  
of the document.*

*J. Hendt*

FEB 23 1998

NDA 20-555  
SE2-004

AXID AP™ (Nizatidine) OTC

75 mg Tablets

Sponsor: Whitehall-Robins

Prevention of heartburn, acid indigestion, and  
sour stomach related to foods and beverages when  
taken 0 to 60 minutes before eating or drinking

Reviewer:  
Hugo E. Gallo-Torres, M.D., Ph.D.

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA: 20-555/SE2-004

Sponsor: Whitehall-Robins  
Madison, NJ

Date Submitted: March 31, 1997

Name of Product: AXID AP<sup>®</sup> (nizatidine)

Formulation: Tablets (75 mg)

Route of Administration: Oral

Pharmacological Category: H<sub>2</sub>-receptor antagonist (anti-ulcer)

Indication Sought: Prevention of heartburn, acid indigestion and sour stomach when taken right before a meal or up to one hour before consuming food and beverages.

Reviewer: Hugo E. Gallo-Torres, M.D., Ph.D.

<u>Material Reviewed</u>	<u>Item</u>	<u>Contained in Volume Numbers</u>
Index	1	1.1, 1.2, 1.3, 1.13
Summary	2	1.1, 1.2, 1.3, 1.13
Labeling	4	1.1, 1.2, 1.3, 1.13
Human Pharmacokinetics/Bioavailability <sup>a</sup>	6	1.2
Clinical Data	8	1.3-1.12 (10 volumes)
Safety Update <sup>b</sup>	9	Included in Items 8 & 10
Statistical Data	10	1.13-1.23
Data Listing (Case Report Tabulations)	11	Included in Items 8 & 10
Case Report Forms	12	1.24

a) This is merely a brief summary of data that was submitted in the original NDA  
 b) A SU Report is included as the Integrated Summary of Safety in the Clinical and Statistical Data Sections (Items 8 and 10, respectively).

**I. BACKGROUND INFORMATION**

The drug which is the subject of this application is AXID® (nizatidine - NIZ), a competitive, reversible inhibitor of histamine at the histamine H<sub>2</sub>-receptors, particularly those in the gastric parietal cells.

NIZ is currently marketed for oral administration in the United States as AXID® capsules, by Eli Lilly and Company (NDA 19-508). The currently approved indications for oral prescription NIZ include 1) short-term (up to 8 weeks) Tx of active DU (300 mg once daily at bedtime; an alternative dosage regimen is 150 mg once daily at bedtime); 2) maintenance (up to 1 year) of healed DU (150 mg once daily at bedtime); 3) short-term (up to 12 weeks) treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn due to GERD (150 mg twice daily). In addition, AXID® (nizatidine) OTC 75 mg tablets has been approved for the prevention of heartburn (HB), acid indigestion, sour stomach and upset stomach associated with these symptoms. The medication is to be taken one-half to one hour before eating.

In the current submission, Whitehall-Robins seeks approval for marketing of NIZ 75 mg tablet (OTC), taken 0 to 60 minutes before eating or drinking.

**II. ADEQUACY OF THE TRIALS SUBMITTED IN SUPPORT OF THE SOUGHT INDICATION**

In support of the current application, the sponsor has submitted results of two pivotal clinical trials: studies NZ-95-02 and NZ-95-03. Both studies are adequate and well-controlled.

Studies NZ-95-02 and NZ-95-03 are multicenter, single-dose, placebo-controlled, 3-arm, randomized balanced parallel group trials. A single-blind placebo pretreatment qualifying provocative test meal period is followed by a 3-arm double-blind pretreatment provocative meal period is followed. The arms of the trials consist of: placebo, NIZ 15 min. prior to the meal (-15 min) and NIZ 0 min prior to the meal (0-min).

**III. SUMMARY ON CLINICAL PHARMACOLOGY**

The material that follows was excerpted from MOR of NDA 20-555 for NIZ 75 mg for the prevention of HB, acid indigestion, sour stomach and upset stomach associated with these symptoms, with the OTC medication taken one-half to one hour before eating (MOR of June 22, 1995).

In this section, reference is made to the antisecretory activity of NIZ at the oral dose of 75 mg, the proposed dose for OTC marketing.

According to the information in the labeling this dose is less effective than 150 mg NIZ in the inhibition of gastric acid output (GAO) induced by betazole, pentagastrin, meal or caffeine. Depending upon the stimulus, the duration of effect for diurnal inhibition of GAO was 3 to 6 h. No data are cited for nocturnal GAO for the 75 mg NIZ dose. Except for nocturnal GAO (73% inhibition for up to 10h), there are no data evaluating the antisecretory effect of 100 mg NIZ but this dose produced a 73% inhibition of nocturnal GAO, lasting up to 10 h

after dosing. According to these labeling data, single doses of NIZ of 20 to 50 mg inhibited meal-stimulated GAO by 41% but this percent inhibition was lower than that with 75 mg NIZ (64% of meal stimulated diurnal GAO), an effect that lasted up to 4 h.

The results from several additional studies have provided additional information on the effects of 75 mg NIZ in comparison with 25 mg and 225 mg. These new studies have not tested the effects of 50 mg NIZ. As shown below, there are no strong reasons to propose the use of 25 mg NIZ (instead of 75 mg of the drug) but there is little information about the antisecretory effect of the 50 mg dose of the drug.

In the trials summarized in MOR of June 22, 1995 the parameters of evaluation included the duration of time that each dose elevated gastric pH  $>3$  and 4, the time of onset of PD activity and the PK onset and duration of adequate NIZ concentrations  $>EC_{50}$  level (182 ng/ml) required to inhibit meal-stimulated gastric acid production.

One parameter of interest was activity during the first 4h post-dosing. The results of Study WM-550 showed a dose-response trend in serum NIZ concentrations and derived PK parameters for the NIZ 225 mg, 75 mg and 25 mg doses evaluated. The AUEC for the NIZ 25 mg dose was statistically significantly lower than for the 75 mg and the 225 mg doses. The three dose levels tested showed a dose-response effect on gastric pH levels over time and the derived PD parameters. Both the 75 mg and the 225 mg dose of NIZ produced a sustained gastric pH  $\geq 4$  for a clinically relevant time duration ( $>3h$ ). The 25 mg dose of NIZ did not produce an adequate pH elevation or sustained it for the clinically relevant 3-h time period.

Study WM-575 demonstrated a dose-response effect for NIZ doses of 75, 225 or 25 mg taken one hour prior to a meal. This conclusion was based upon the serum NIZ concentrations measured over time and the derived PK parameters. Also shown was a dose-response effect on post-meal gastric pH levels over time and in the derived PD parameters. In comparison to PL, both NIZ doses, 75 and 225 mg, produced significantly longer durations of pH  $\geq 3$  and  $\geq 4$ . But the durations produced by the NIZ 25 mg dose were not statistically different from those of PL. Although all three NIZ doses resulted in a statistically significantly higher maximum pH than and PL, the onset times for the NIZ 25 mg dose were comparable to PL and those for the higher doses were numerically but not statistically shorter than for PL.

Study WM-578 showed a consistent dose-response effect for all three doses of NIZ on the measured parameters of gastric pH. Meal-related HB was reduced by both the 225 mg and the 75 mg NIZ in comparison to PL but the 25 mg was less effective and not differentiated from PL.

The results of Study WM-529 showed no statistically significant between-Tx differences for serum and urine PK parameters, and this is taken as evidence that coadministered antacid has no significant effect on NIZ (75 mg) absorption, bioavailability, or excretion. This lack of effect was shown in both the fasted and the fed states. Although food delayed the onset of NIZ absorption, the presence of food in the g.i. tract did not affect NIZ bioavailability or excretion.

Study B5Q-LC-NBBP explored possible interactions between NIZ and alcohol. In patients given 0.15 or 0.45 g/Kg ethanol, Pre-Tx with a single (high) 300 mg dose of NIZ in fed individuals produced statistically significant increases in blood alcohol concentrations. The increases were small in magnitude and in these NIZ-Tx patients, blood alcohol concentrations did not go from below to above the legal limit (100 mg/dl) for driving under the influence. The reviewer agrees with the sponsor's conclusion that these changes in blood alcohol concentrations were neither clinically nor socially (legally) meaningful.

Finally, comparison of four PK parameters namely AUC,  $AUC_{0-12h}$ ,  $C_{max}$  and extent of absorption in Study WM-673 demonstrated that the NIZ 75 mg tablet and capsule formulation a) were bioequivalent; and b) had similar elimination and urinary excretion profiles.

In summary, this information shows that NIZ is well suited for OTC use as judged by the absence of meaningful food, antacid, or drug-drug interactions as well as the consistent kinetic performance when given to patients with hepatic impairment or mild renal insufficiency. The PK performance of the drug appears to be reliable and predictable under the wide range of dosing

situations evaluated. These have included studies with or without concomitant antacid, with or without food and with or without the presence of liver insufficiency or mild renal impairment. The MO agrees with the sponsor that these findings, together with the 75 mg OTC dose, which is one-fourth of the maximum prescription dose, episodic dosing regimen and excellent clinical safety profile provide a wide margin of safety which support the continued use of this approved OTC product. These factors also support the expanded indication in the current supplemental application.

IV. STUDY NZ-95-02

*"A Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Dose of Nizatidine 75mg in the Prevention of Test-Meal Induced Heartburn"*

1. Objective/Hypothesis Tested

The study was set to evaluate the effectiveness and safety of a single dose of NIZ 75 mg (marketed product) when administered 15 min. prior or 0 min. (immediately) prior to a meal compared to PL in the prevention/reduction of HB in subjects experiencing acute HB following a provocative meal.

The study tested the hypothesis that a single dose of NIZ 75 mg administered either 15 min. or 0 min. (immediately) prior to consuming a **provocative meal** would be superior to PL administered at the same time in the complete prevention of HB.

2. Study Design

From all the information provided by the sponsor in the Clinical Report, Appendices, Tabulations, Figures and related materials, this 3-arm, single-dose, multicenter study was randomized, double-blind and PL-controlled.

3. Study Population

Subjects were men or women, 16y of age or older, that although generally in good health had a history of HB associated with meals occurring at least 3 times/week, a 1-y history of experiencing moderate or greater HB within 60 min. of eating a meal consisting of foods similar to those in the test meal, that was generally treated with OTC medications, including antacids and nonprescription H<sub>2</sub>-receptor antagonists.

Inclusion/Exclusion Criteria

These were adequate for the proposed evaluations.

Included in the trial were subjects that a) were 16y of age or older with a history of HB defined as a substernal burning discomfort radiating cephalad that was associated with meals; the HB was experienced a minimum of 3 times/week, b) had at least a 1-y history of experiencing HB, usually of

moderate or greater intensity, occurring within 60 min. of consuming a meal consisting of foods similar to those in the provocative meal, c) were using OTC medications for the treatment of HB, d) were medically cleared by the Investigator to participate in the trial, e) had a willingness to participate in the study in accordance with the requirements of the protocol (i.e., no non-study food, drink, smoking, or any other medication during each 3.75-h study period, and no alcoholic or caffeinated beverages, antacids, or other OTC stomach remedies within 5 hours prior to dosing), and f) from whom written informed consent had been obtained. Subjects younger than 18y of age had parental or guardian consent.

Not included in the trial were subjects that a) had a history of esophageal or gastric surgery other than surgery for infantile pyloric stenosis, b) had a recent history (within the past year) of UGI disease, other than hiatal hernia, such as PUD, pyloric stenosis, G.I. malignancy, esophageal stricture, esophageal ring, esophageal bleeding, symptoms of dysphagia, unexplained weight loss, or melena, c) had a recent history (within the past 2 years) or clinical evidence of acute hepatitis, non-surgically treated cholelithiasis or cholecystitis, pancreatitis, IBD, IBS, or lactose intolerance. Also excluded from the trial were d) subjects with any concurrent serious systemic disorders, such as angina pectoris, uncontrolled hypertension, cardiopulmonary, renal or hepatic insufficiency, PA, or DM, e) those with a history of (within the past 2 years) or currently abusing alcohol or drug substances, f) those who had current treatment with a prescription regimen of systemic corticosteroids, NSAIDs, calcium blockers, benzodiazepines, sedative hypnotics, tricyclic antidepressants, bethanechol, tetracycline, or were taking a daily regimen of aspirin, g) those who were using any prescription G.I. medication (e.g., PPIs, prokinetic agents, cytoprotective agents, anticholinergics, or sucralfate) within the past 30 days, h) those with a history of allergic response to any of the food ingredients of the provocative meal, i) those with a history of hypersensitivity, significant adverse reaction, or contraindication to any H<sub>2</sub>-receptor antagonist or antacid, and j) those who were using any investigational drug within the past 30 days. k) Women who were pregnant (positive urine pregnancy test) or lactating or of child-bearing potential who were not using a medically-approved form of birth control were not included in the trial. [Abstinence alone, rhythm method alone, withdrawal alone, or partner's vasectomy alone were not considered medically approved methods of contraception.] Other reasons for exclusion from the trial were: l) failure to understand or adequately complete the rating scales, m) being a member of or related to a member of the study site staff directly involved with the study or the Sponsor, and n) previous enrollment in the study.

#### 4. Materials/Randomization/Blinding/Labeling/Storage and Accountability of Concomitant Medications

All of these were adequate. The sponsor supplied the medications listed below.

## NZ-95-02 Test Medication

Study Drug	Per Tablet	Per Dose	Lot No.
NIZ	NIZ 75 mg	1 tab	WH-0463-013W
PL	Inert Ingredients	1 tab	WH-0463-15E

A description of the test medication formulations was presented in sponsor's Appendix V.

- All test medications (NIZ and PL) were tablets identical in appearance.
- Each assessment period was 3.75h: dosing at 15 min. and immediately prior to the provocative meal, a 30-min. period to consume the provocative meal, and a 3-h post-meal follow-up period.

### 5. Clinical Procedures/Observations

#### a. Pre-screening

Prospective subjects were pre-screened by telephone interview to determine their suitability to enter the trial. The subjects were now screened at a visit and offer to participate in the trial was extended. Those meeting inclusion/exclusion criteria were asked to sign an IC.

#### Test Meals

Each subject received the same chili for both the single-blind qualifying and double-blind treatment meals. The provocative meal<sup>1</sup> consisted of chili, nacho cheese chips and Coca-Cola®.

- At each of the two provocative test meals, subjects signed-in and were questioned to confirm that they had complied with all appropriate pre-study instructions.
- At the S-B qualifying meal, subjects were assigned a S-B screening identification number and then were administered a PL tablet at 15 min. before and 0 min. (immediately) before the meal.
- After the 0-min. dose and immediately before eating, subjects indicated the presence or absence of HB on the Heartburn Presence Scale (HBPS) by answering "YES" or "NO" to the question "Do you have heartburn - a burning discomfort - at this time?"
- Subjects also indicated the severity of their HB on a 100 mm visual analog HB Severity Scale (HBSS) with the endpoints 0 on the left labeled "NONE" and 100 mm on the right labeled 'Very Severe' in the diaries.
- Subjects then ate the provocative meal.

<sup>1</sup> The original protocol designed a meal of chili with added cayenne pepper. The protocol was amended on August 1996 to delete the added cayenne pepper in order to reduce the spiciness of the test meal to decrease the screening failure rate. It was believed that the high screening failure rate was due to subjects not consuming enough chili to promote HB.

- Subjects had a period of 30 min. in which to consume the meal.
- The amount of food consumed was recorded on each subject's case report form.
- Subjects recorded whether or not they had HB on the HBPS in diaries at 30, 60, 90, 150 and 210 min. after the start of the test meal. At these same times subjects also indicated the severity of their heartburn on the HBSS.
- Subjects reporting a HB severity rating of  $\geq 50$  mm at least once during the post-meal assessment period of the S-B qualifying meal were eligible for randomization at the double-blind treatment meal.
- Subjects were permitted to take rescue antacid after 90 min. if they needed medication to obtain relief from their HB.
- Eligible subjects were scheduled for randomization at the D-B treatment meal within 6-10 d of the S-B qualifying meal. Before each subject left the study site, the study coordinator reviewed any adverse experiences and diary with each subject.
- At the D-B treatment meal, subjects were randomly assigned to one of the three treatment groups. Subjects were required to eat the same amount of food as eaten at the S-B qualifying meal.
- All meal procedures and HB assessments were completed in the same way as during the S-B qualifying meal.
- For both the S-B qualifying meal and D-B Tx meal, any subject who reported a complaint of at least severe HB at 90 min. or more after the start of the meal could receive rescue antacid upon request. The schedule of study assessments and procedures was shown in sponsor's Table 2.

Eligibility to the D-B Treatment Period

To be eligible for randomization into the D-B treatment meal, subjects were required to meet all of the above mentioned inclusion/exclusion criteria and also:

- a. Report at least moderate HB as evidenced by a score of  $\geq 50$  mm on the 100-mm visual analog HBSS for at least one timepoint during the 3-h post-meal follow-up of the single-blind qualifying meal.
- b. Not to use any nonprescription histamine H<sub>2</sub>-receptor antagonist within 7 days of the meal, to discontinue use of any nonprescription stomach remedy and other nonprescription medications for at least 5h immediately prior to the meal and to consume no food during the 5h prior to the meal.

6. Efficacy Assessments

a. Efficacy Measurement: HBPS

At time 0, 30, 60, 90, 150 and 210 min. from the start of the meal, each

subject was instructed to answer the question:

"Do you have heartburn - a burning discomfort - at this time?"

(Circle one response)

YES

NO

Each category on this scale was assigned a whole number value of 0 = 'No' or 1 = 'Yes'.

b. Efficacy Measurement: HBSS

At time 0, 30, 60, 90, 150 and 210 min., each subject was instructed:

"Place a mark on the line that best describes the burning discomfort of your heartburn now:"

NONE

VERY  
SEVERE

Scores on this 100-mm linear scale were measured to the nearest millimeter from the left. During the S-B qualifying meal, a score  $\geq 50$  mm for at least one post-meal assessment was required for a subject to be eligible for the D-B treatment meal.

7. Safety Evaluations

These were all adequate.

8. Quality Assurance in Data Collection

According to the information provided in the Clinical Report, the study was adequately monitored by the CRO, the information in the CRFs was properly gathered and corrected when necessary, appropriately transcribed and re-checked in the Tables submitted by the sponsor.

9. Statistical Methodology

- The sample size of ca. 175 subjects per treatment group was planned to achieve 80% power to detect a difference between NIZ 75 mg and PL when administered 30 min. prior to a meal, assuming that the response rate for being completely free of HB over the entire 3 h of post-meal assessments would be approximately 5% for PL and 15% for NIZ. A 10% improvement over PL was considered to be a clinically meaningful difference.
- Data from two sets of subjects were analyzed for efficacy. The primary analysis was an ITT analysis using all available data from all randomized subjects who took study medication and provided efficacy data. The secondary analysis, Evaluable Subjects, included randomized subjects without major protocol violations.
- The statistical procedures to analyze efficacy and safety were all

adequate.

10. Results

a. Enrollment/Subject Disposition (Table 1)

- 1082 subjects were enrolled into the S-B qualifying meal at 13 sites<sup>2</sup>.
- Table 1 lists the reasons why 438 subjects failed to qualify for randomization.
- 35 subjects qualified but discontinued prior to randomization for reasons detailed in Table 1.

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<sup>2</sup> Small sites were defined *a priori* as those with fewer than five intent-to-treat subjects per any one treatment group. Five sites met this criterion and were combined for all analyses (site #299).

**TABLE 1**  
Study NZ-95-02

Subject Disposition With Number and Reasons for Discontinuance After Each Trial Visit

Enrolled in S-B Qualifying Meal	Failed to Qualify for Randomization	Qualified but W/D prior to Randomization	Entered D-B Treatment Trial	D/C During D-B Treatment Meal	Non-Evaluable	Evaluable																																																						
1082	438	35	609	27	12 <sup>b</sup>	597																																																						
	<table border="0"> <tr> <td><b>REASON</b></td> <td><b>#</b></td> </tr> <tr> <td>Ineligible</td> <td>424</td> </tr> <tr> <td>Protocol violation</td> <td>6</td> </tr> <tr> <td>Withdrew voluntarily</td> <td>4</td> </tr> <tr> <td>AE</td> <td>3</td> </tr> <tr> <td>Administrative/Other<sup>a</sup></td> <td>1</td> </tr> <tr> <td><b>TOTAL</b></td> <td><b>438</b></td> </tr> </table>	<b>REASON</b>	<b>#</b>	Ineligible	424	Protocol violation	6	Withdrew voluntarily	4	AE	3	Administrative/Other <sup>a</sup>	1	<b>TOTAL</b>	<b>438</b>	<table border="0"> <tr> <td><b>reason</b></td> <td><b>#</b></td> </tr> <tr> <td>HB presence before meal</td> <td>15</td> </tr> <tr> <td>Administrative/Other</td> <td>9</td> </tr> <tr> <td>Lost to follow-up</td> <td>7</td> </tr> <tr> <td>Voluntary W/D</td> <td>2</td> </tr> <tr> <td>Protocol violators</td> <td>2</td> </tr> <tr> <td><b>TOTAL</b></td> <td><b>35</b></td> </tr> </table>	<b>reason</b>	<b>#</b>	HB presence before meal	15	Administrative/Other	9	Lost to follow-up	7	Voluntary W/D	2	Protocol violators	2	<b>TOTAL</b>	<b>35</b>	<table border="0"> <tr> <td><b>PL</b></td> <td><b>NIZ</b></td> <td></td> </tr> <tr> <td></td> <td>15 min</td> <td>0 min</td> </tr> <tr> <td>204</td> <td>202</td> <td>203</td> </tr> </table>	<b>PL</b>	<b>NIZ</b>			15 min	0 min	204	202	203	<table border="0"> <tr> <td><b>Reason</b></td> <td><b>#</b></td> </tr> <tr> <td>Ineligible</td> <td>22</td> </tr> <tr> <td>Protocol Violation</td> <td>5</td> </tr> <tr> <td><b>TOTAL</b></td> <td><b>27</b></td> </tr> </table>	<b>Reason</b>	<b>#</b>	Ineligible	22	Protocol Violation	5	<b>TOTAL</b>	<b>27</b>		<table border="0"> <tr> <td><b>PL</b></td> <td><b>NIZ</b></td> <td></td> </tr> <tr> <td></td> <td>15 min</td> <td>0 min</td> </tr> <tr> <td>199</td> <td>199</td> <td>199</td> </tr> </table>	<b>PL</b>	<b>NIZ</b>			15 min	0 min	199	199	199
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<p>a) Includes subject #1145 who received D-B medication during the S-B qualifying meal and was D/C from trial</p> <p>b) <u>Reasons for Unevaluability</u></p> <table border="0"> <tr> <td>Use of Prescription Medication within 30 days</td> <td>8</td> </tr> <tr> <td>Medical History Violation</td> <td>4</td> </tr> <tr> <td><b>TOTAL</b></td> <td><b>12</b></td> </tr> </table>							Use of Prescription Medication within 30 days	8	Medical History Violation	4	<b>TOTAL</b>	<b>12</b>																																																
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- 609 (PL=204; NIZ -15 min=202; NIZ 0-min=203) were randomized into the D-B treatment phase.
- All of these 609 subjects took D-B trial medication, provided safety and efficacy data and were included in both the safety and ITT efficacy population.
- Of these 609 subjects, 12 subjects were determined to be unevaluable (PL=5; -15 min NIZ=3 and 0 min NIZ=4) (Table 1). The remaining 597 subjects (PL=199, -15 min NIZ=199 and 0 min NIZ=199) qualified for the evaluable subjects population.

b. Demographic and Clinical Characteristics (Table 2)

- Except for alcohol use, the treatment groups were comparable to each other for all demographic characteristics. The -15 min NIZ group consisted of fewer regular users of alcohol than the PL and the 0 min NIZ group (Table 2).
- The demographic characteristics for those subjects that completed only the S-B qualifying meal were similar to those of the randomized patients.
- The treatment groups were comparable to each other for all P.E. characteristics and all vital signs.

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**TABLE 2**  
Study NZ-95-02

Summary of Subject Demographic Characteristics

Demographic Characteristics		Overall [n=609]	PL [n=204]	NIZ 75 mg		p-value
				-15 min NIZ [n=202]	0 min NIZ [n=203]	
Gender	M	43%	48%	43%	38%	N.S.
	W	57%	53%	57%	62%	
Race	Caucasian	65%	63%	65%	66%	N.S.
	Black	22%	22%	22%	21%	
	Asian	1%	1%	1%	1%	
	Hispanic	12%	13%	12%	10%	
	Other	1%	2%	1%	2%	
Age (y)	Mean	39.1	39.2	39.7	38.3	N.S.
	Range					
Weight (lb)	Mean	188.8	188.1	190.0	188.2	N.S.
	Range					
Height (in)	Mean	67.0	67.2	67.0	66.9	N.S.
	Range					
Tobacco Use	NO	73%	75%	76%	69%	N.S.
	YES	27%	26%	24%	31%	
Alcohol Use	NO	96%	94%	99%	96%	0.043
	YES	4%	6%	2%	6%	
Caffeine Use	NO	29%	31%	33%	24%	N.S.
	YES	71%	69%	67%	76%	

c. Efficacy Results

1) Single-Blind Qualifying Meal

- All (100%) subjects had HB at entry.
- There were no statistically significant differences among the three treatment groups for Average Severity of HB [(0-100 mm VAS = 43.0 to 44.2 mm)] or Maximum Severity of HB [(0-100 mm VAS = 69.9 to 71.4 mm)].
- There were no statistically significant differences among the 3 treatment groups - analyzed according to subjects' subsequent D-B treatment - in the percentage of subjects without HB at individual time points (0, 30, 60, 90 150 and 210 min) either comparing HBPS or HBSS (0-100 mm VAS).

2) Double-Blind Treatment Meal Results (Table 3)

Depicted in this Table are results of the primary (complete prevention of HB = % of subjects without post-meal HB) and two secondary efficacy parameters [average severity of HB (mm) and maximum severity of HB (also mm)].

TABLE 3  
Study NZ-95-02

Results of Primary and Secondary Efficacy analyses of ITT Population

Parameters of Evaluation	PL (n=204)	-15 min NIZ (n=202)	Therapeutic Gain-15 min NIZ > PL	p-value	0-min NIZ (n=203)	Therapeutic Gain 0 min NIZ > PL	p-value
% of subjects without post-meal HB	11	22	11 %	0.002	22	11 %	0.004
Average severity of HB (mm)	26	20	6 mm	0.002	19	7 mm	0.001
Maximum severity of HB (mm)	44	36	8 mm	0.010	34	10 mm	<0.001

The results in Table 3 can be summarized as follows.

- A significantly higher percentage of subjects taking NIZ 75 mg either 15 min. before a meal or immediately before a meal had complete prevention of HB compared to PL-treated subjects.
  - The therapeutic gains over PL for the two NIZ treatment groups were 11% for both NIZ groups.
  - Both NIZ treatment groups had a significantly higher percentage of subjects free of HB compared to the PL group starting at the 60-min. time point and continuing throughout the remainder of the 3-h assessment period [data not shown].
- NIZ 75 mg taken at either 15 min. before a meal or immediately before a meal significantly reduced post-meal HB severity compared to PL [therapeutic gains of 6 and 7 mm, respectively, (Table 3)].
- Both NIZ 75 mg taken 15 min. before a meal and taken immediately (0 min.) before a meal significantly reduced subjects' maximum post-meal HB severity compared to PL-treated subjects [therapeutic gain of 8 and 10 mm, respectively (Table 3)].

### 3) Efficacy Response by Site

- Both the sponsor and the FDA statistician summarized the differences in the percentages of subjects without HB for study NZ-95-02 by investigator.
- There was a consistent advantage trend of favoring NIZ 75 mg taken either 15 min. before a meal or immediately before a meal relative to PL for all centers except centers 0299 (both treatments) and 0208 (0 min. NIZ 75 mg). In figures 4 to 12 of [redacted] review, he displayed HB absence versus HB presence for each center. It is to be noted that, there was no significant treatment by site interaction effect as evidenced by the test of homogeneity [p-value =0.383].

### d. Results of Safety Analyses

In this trial, single doses of NIZ 75 given either 15 min. before or immediately prior to the meal, were well tolerated. There were no significant differences among the treatment groups for the incidence of AEs.

- Headache was the most commonly reported AE reported by PL-treated subjects and subjects taking NIZ 75 mg immediately prior to the meal [headache was reported by 4 (2%) PL-treated subjects and 4 (2%) subjects taking NIZ 75 mg immediately prior to the meal].
- There were no AEs reported in more than one subject taking NIZ 75 mg 15 min. before a meal.
- There were no SAEs reported and no subjects were discontinued due to AEs during the D-B treatment meal.

11. Sponsor's Conclusions

"Compared to placebo, nizatidine 75mg taken 15 minutes prior or immediately prior to a heartburn-producing meal is safe and well-tolerated, provides complete prevention of heartburn in a significant proportion of subjects, and significantly reduces average and maximum heartburn severity. These results, considered with the results of previous trials, show that nizatidine can be taken safely and effectively any time up to an hour before a meal."

12. Reviewer's Additional Comments

Study NZ-95-02 is one of two pivotal symptom prevention trials (the other is NZ-95-03) submitted by the sponsor of this NDA Supplement to demonstrate the efficacy of pre-meal dosing with NIZ 75 mg - administered 15 min. or immediately before consuming a provocative meal - in the prevention/reduction of post-prandial HB.

This multicenter, single-dose trial was well-designed and apparently well-executed. The study consisted of two phases (or two provocative meals): an initial S-B PL qualifying provocative meal (S-B qualifying meal) followed within approximately 6 to 10 days by a PL-controlled, 3-arm, parallel group, randomized, double-blind, treatment provocative meal (double-blind treatment meal) comparing NIZ 75 mg to PL when administered 15 min. or 0 min. (immediately) prior to a meal. The provocative meal consisted of chili, nacho cheese chips and Coca Cola®. Each study period lasted 3.75 h: dosing at 15 min. and 0 min. (immediately) prior to the provocative meal, a 30-min. period to consume the meal, and a 3-hour post-meal follow-up period.

For the S-B qualifying meal, subjects received S-B PL at 15 min. and 0 min. (immediately) before the meal. At 0 min., subjects indicated the presence or absence of HB and its severity, received their S-B PL dosing, and then ate the provocative meal. Subjects had a period of 30 min. to consume a minimum of one serving of the meal. At the end of the meal (i.e., at 30 min.), and at 60, 90, 150 and 210 min. after the start of the meal, subjects evaluated the presence and severity of heartburn. Subjects reporting heartburn with a severity rating of  $\geq 50$  mm at least once during the 3-h post-meal follow-up period of the S-B qualifying meal were eligible to participate in the D-B treatment meal. Study procedures for the D-B treatment meal were identical to those of the S-B qualifying meal. At both meals, following the 90 min.

evaluation, subjects complaining of severe HB could receive a rescue antacid upon request.

In study NZ-95-02, the study population was adequate. It consisted of generally healthy subjects who had a Hx of at least moderate HB distress in relation to the types of food (spicy and hot) that were to be served at the study meals. These subjects suffered with meal-related HB and, in general, treated this symptom with OTC H<sub>2</sub>-receptor antagonists and/or non-prescription antacids. The most important efficacy assessments in this and the other trial were the Heartburn Presence Scale (HBPS), based on a YES/NO question and the Heartburn Severity Scale (HBSS), based on a 0 to 100 mm VAS.

The efficacy endpoints were all adequate. For HB Prevention, the primary efficacy endpoint was the proportion of subjects (%) with total HB absence assessed by both the HPSS and the HBSS. The two efficacy endpoints measuring HB reduction, both measured in the 0 to 100 mm VAS, were the Average HB Severity and maximum severity of HB. The most important assumptions by the sponsor were a) that the proportion of PL-treated subjects likely not to develop HB was not expected to be greater than 5% and b) that the test med. would be considered superior if the proportion of subjects on NIZ that reported no HB was at least 15%. In other words, using the primary efficacy parameter (NO HB), a therapeutic gain of 10% of NIZ over PL was expected.

The MO carried out a detailed evaluation of the patients' baseline characteristics. This assessment demonstrated that the three Tx groups were essentially comparable in demographic, HB Hx, medical Hx and additional background characteristics. The only difference found was that the -15 min. NIZ group consisted of fewer regular users of alcohol than the PL and the 0-min. NIZ groups, but this difference is not expected to influence outcome. Since there were no clinically significant pre-drug differences among the Tx groups it is appropriate to assess comparative efficacy and safety analyses. Also, it is important to mention that the randomized study population was similar to the broad screening populations and the population receiving single-blind medication.

Under the experimental conditions used in Study NZ-95-02, single oral doses of NIZ 75 mg were found to be both effective and safe. NIZ 75 mg taken either 15 min. or immediately prior to a meal demonstrated a significant advantage [therapeutic gain 11% ( $p \leq 0.002$ )] over PL in the complete prevention of HB, where 22% of the subjects in each NIZ treatment group were completely free of heartburn for the entire 3-h post-meal assessment period versus 11% of the subjects in the PL group. From 60 min. through the end of the study, significantly ( $p \leq 0.045$ ) more subjects in the two NIZ treatment groups reported NO HB compared to placebo at each time point. In addition, NIZ 75 mg significantly ( $p \leq 0.002$ ) reduced average HB severity (20.4 mm and 19.5 mm, for -15 min. NIZ and 0 min NIZ, respectively) compared to PL (25.6 mm). Also, NIZ 75 mg significantly ( $p \leq 0.010$ ) reduced maximum HB severity (36.3 mm and 33.8 mm, for -15 min NIZ and 0 min NIZ, respectively) compared to placebo (44.0 mm). Moreover, from 90 min. through the end of the study, the reported HB severity at each time point for the two nizatidine treatment groups was significantly ( $p \leq 0.016$ ) less than reported for PL.

Single oral doses of NIZ 75 mg were well tolerated.

In summary, the MO agrees with the sponsor's conclusions. Single oral doses of NIZ 75 mg taken either 15 min. before or immediately prior to a heartburn-

producing meal are safe and well-tolerated and provide complete prevention of HB in a significant proportion of subjects. this NIZ single dose also significantly reduced average and maximum HB severity.

V. STUDY NZ-95-03

*"A Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Dose of Nizatidine 75mg in the Prevention of Test-Meal Induced Heartburn"*

1. Objective/Hypothesis Tested

In a fashion similar to that for study NZ-95-02, the objective of study NZ-95-03 was to evaluate the effectiveness and safety of a single dose of NIZ 75 mg (marketed product) when administered 15 min. prior or 0 min. (immediately) prior to a meal compared to PL in the prevention/reduction of HB in subjects experiencing acute HB following a provocative meal.

The study tested the hypothesis that a single dose of NIZ 75 mg administered either 15 min. or 0 min. (immediately) prior to consuming a **provocative meal** would be superior to PL administered at the same time in the complete prevention of HB.

2. Study Design

From all the information provided by the sponsor in the Clinical Report, Appendices, Tabulations, Figures and related materials, this 3-arm, single-dose, multicenter study was randomized, double-blind and PL-controlled.

3. Study Population

Subjects were men or women, 16y of age or older that - although generally in good health - had a history of HB associated with meals occurring at least 3 times/week, a 1-y history of experiencing moderate or greater HB within 60 min. of eating a meal consisting of foods similar to those in the test meal, that was generally treated with OTC medications, including antacids and non-prescription H<sub>2</sub>-receptor antagonists.

Inclusion/Exclusion Criteria

As per study NZ-95-02, the inclusion/exclusion criteria were adequate for the proposed evaluations.

4. Materials/Randomization/Blinding/Labeling/Storage and Accountability/Concomitant Medications

All of these were adequate. The sponsor supplied the medications listed below.

**NZ-95-03 Test Medication**

Study Drug	Per Tablet	Per Dose	Lot No.
NIZ	NIZ 75 mg	1 tab	WH-0463-013W
PL	Inert Ingredients	1 tab	WH-0463-15E

A description of the study medication formulations was presented in sponsor's Appendix V.

- All test medications (NIZ and PL) were tablets identical in appearance.
- Each assessment period was 3.75h: dosing at 15 min. and immediately prior to the provocative meal, a 30-min. period to consume the provocative meal and a 3-h post-meal follow-up period.

5. Clinical Procedures/Observations

These were the same as in Study NZ-95-02.

The composition of the test meals was the same as in Study NZ-95-02. Each subject received the same chili for both the single-blind qualifying and double-blind treatment meals. The provocative meal consisted of chili, nacho cheese chips and Coca-Cola®.

- The study consisted of two provocative meals: an initial S-B PL qualifying provocative meal (single-blind qualifying meal) followed within ca. 6 to 10d by a PL-controlled, 3-arm, parallel group, randomized D-B treatment provocative meal (double-blind treatment meal) comparing NIZ 75 mg to PL when administered 15 min. of 0 min. (immediately) prior to a meal.
- For the S-B qualifying meal, subjects received single-blind PL at 15 min. and 0 min. (immediately) before the meal.
- At 0 min., subjects indicated the presence or absence of HB and its severity, received their S-B placebo dosing, and then ate the provocative meal.
- Subjects had a period of 30 min. to consume a minimum of one serving of the meal. At the end of the meal (i.e., at 30 min.), and at 60, 90, 150 and 210 min. after the start of the meal subjects evaluated the presence and severity of HB.
- Subjects reporting HB with a severity rating of  $\geq 50$  mm at least once during the 3-h post-meal follow-up period of the S-B qualifying meal were eligible to participate in the D-B treatment meal.

- Study procedures for the double-blind treatment meal were identical to those for the single-blind qualifying meal.
- At both meals following the 90 min. evaluation, subjects complaining of severe HB could receive a rescue antacid [ ] upon request.

In summary, to be eligible for randomization into the D-B treatment meal, subjects were required to meet all of the inclusion/exclusion criteria and also:

- a. Report at least moderate HB as evidenced by a score of  $\geq 50$  mm on the 100-mm visual analog HBSS for at least one timepoint during the 3-h post-meal follow-up of the single-blind qualifying meal.
- b. Not to use any nonprescription histamine  $H_2$ -receptor antagonist within 7 days of the meal, to discontinue use of any nonprescription stomach remedy and other nonprescription medications for at least 5h immediately prior to the meal and to consume no food during the 5h prior to the meal.

#### 6. Efficacy Assessments

The efficacy measurements were the same as in Study NZ-95-02 and consisted of  
HBPS (heartburn presence scale)  
HBSS (heartburn severity scale)

#### 7. Safety Evaluations

These were all adequate, as in Study NZ-95-02.

#### 8. Quality Assurance in Data Collection

This was adequate, as in Study NZ-95-02.

#### 9. Statistical Methodology

As in study NZ-95-02, the statistical procedures to analyze efficacy and safety were all adequate.

#### 10. Results

##### a. Enrollment/Subject Disposition (Table 4)

- 1014 subjects were enrolled into the S-B qualifying meal.
- The reasons why 407 subjects failed to qualify for randomization are listed in Table 4.
- 52 qualified but discontinued prior to randomization, for reasons detailed on Table 4.

**TABLE 4**  
Study NZ-95-03

Subject Disposition, With Number and Reasons for Discontinuance After Each Trial Visit

Enrollment in S-B Qualifying Meal	Failed to Qualify for Randomization	Qualified but W/D prior to Randomization	Entered D-B Treatment Meal	Did Not Complete the Study	Non-Evaluable	Evaluable
1014	407	52	555	4 <sup>a</sup>	9 <sup>b</sup>	546
	<b>Reason</b> <b>#</b> Ineligible            390 Protocol violation    10 W/D Voluntarily      3 Uncooperative        3 AE                      1  <b>TOTAL</b> <u>407</u>	<b>Reason</b> <b>#</b> HB presence         24 before meal Voluntary W/D        14 Lost of Follow-up    6 Uncooperative        4 AE                      2 Ineligible              1 Protocol Violators    1  <b>TOTAL</b> <u>52</u>	<b>PL</b> <b>NIE</b>  187 <u>15 min.</u> <u>0 min</u> 184            184	<b>Reasons for Unevaluability</b> #1106 Protocol Violation #1111 Protocol Violation #1134 Protocol Violation #1161 Not Given #2128 Protocol Violation? #2132 Not Given #8104 Not Given #8109 Not Given #9136 Not Given	<b>PL</b> <b>NIE</b>  183 <u>15-min.</u> <u>0 min</u> 181            182	

a) Reasons for not completing the study:  
 #1107 Randomized in error (Protocol Violation)  
 #2120 Had HB at time "0" at Meal 1 (Protocol Violation)  
 #5101 Administrative/Other  
 #9184 Had HB at 0 min of Meal #2 (Ineligible)

**NOTE:** In spite of not completing the trial, these 4 subjects were considered evaluable (they were included in the ITT analysis).

b) All of these 9 patients completed the study.

- A total of 555 [PL=187, NIZ-15 min=184; NIZ 0 min=184] were randomized into the D-B treatment phase.
- 4 subjects were classified on the CRFs as D/C due to HB presence prior to the D-B treatment meal, although the protocol did not specify that this was a reason for discontinuation.
  - All 4 subjects completed the full post-meal assessment period of the D-B meal.
  - Reasons for D/C during the D-B treatment meal for individual subjects are given in Table 4.
- Of the 555 randomized subjects who took D-B test medication, 9 subjects (4 PL, 3 -15 min NIZ and 2 0 min NIZ) were determined to be unevaluable. There is a discrepancy in the reason for unevaluability for these 9 subjects. According to the sponsor, 6 were due to use of prescription H<sub>2</sub>-receptor antagonists within 30 days of entering the study and 3 were due to use of nonprescription H<sub>2</sub>-receptor antagonists within 7 days of entering the study. However, according to the MO's Table 4, in 4 of these 9, protocol violations were listed but in 5, no reasons for unevaluability were given. Specific subjects and their reasons for unevaluability were detailed in the data listings included in sponsor's Appendix VIII. Although this discrepancy is mentioned here for completeness, in reality it does not have an impact on efficacy assessments because the important analyses were based on total number of patients randomized (ITT population = 555 subjects).<sup>3</sup>

b. Demographic and Clinical Characteristics (Table 5)

- Except for gender, the three treatment groups were comparable for all demographic characteristics. As shown in Table 5, the PL group had a greater percentage of women than did the NIZ groups.

This imbalance is not expected to impact on efficacy results. Nonetheless, the Summary efficacy endpoints were subgrouped according to gender in order to determine if the significant difference between the number of women and men had any effect in efficacy results.

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<sup>3</sup> Many protocol deviations, not leading to subject unevaluability were listed for 17 subjects in sponsor's Table 10 of the Clinical Report.

**TABLE 5**  
Study NZ-95-03

Summary of Subject Demographic Characteristics

Demographic Characteristic		Overall [n=555]	PL [n=187]	NIZ 75 mg		p-value
				-15 min NIZ [n=184]	0-min NIZ [n=184]	
Gender	M	42%	35%	44%	48%	0.037
	W	58%	65%	56%	52%	
Race	Caucasian	74%	72%	74%	76%	N.S.
	Black	14%	15%	14%	12%	
	Asian	1%	2%	2%	1%	
	Hispanic	11%	11%	10%	12%	
	Other	0%	1%	1%	0%	
Age (y)	Mean	36.7	36.5	38.4	35.0	N.S.
	Range					
Weight (lb)	Mean	176.2	176.5	177.0	175.0	N.S.
	Range					
Height (in)	Mean	66.8	66.4	66.8	67.2	N.S.
	Range					
Tobacco Use	NO	73%	77%	72%	70%	N.S.
	YES	27%	23%	28%	30%	
Alcohol Use	NO	95%	95%	96%	94%	N.S.
	YES	5%	5%	4%	7%	
Caffeine Use	NO	30%	32%	28%	29%	N.S.
	YES	71%	68%	72%	71%	

- The demographic characteristics for those subjects that completed only the S-B qualifying meal were similar to those of the randomized subjects.
- The treatment groups were comparable to each other for all P.E. characteristics and all vital signs.

c. Efficacy Results

1) Single-Blind Qualifying Meal

- All (100%) subjects had HB at entry.
- There were no statistically significant differences among the three treatment groups for Average Severity of HB [(0-100 mm VAS); (40.3 to 42.9 mm)] or Maximum Severity of HB [(0-100 mm VAS); (67.6 to 68.6 mm)].
- There were no statistically significant differences among the 3 treatment groups - analyzed according to subjects' subsequent D-B

treatment - in the percentage of subjects without HB at individual time points (0, 30, 60, 90, 150 and 210 min.) either comparing HBPS or HBSS (0-11 mm VAS).<sup>4</sup>

## 2) Double-Blind Treatment Meal Results (Table 6)

Depicted in this Table are results of the primary (complete prevention of HB = % of subjects without post-meal HB) and two secondary efficacy parameters [average severity of HB (mm) and maximum severity of HB (also mm)].

The results in Table 6 can be summarized as follows.

- A higher percentage of subjects taking NIZ 75 mg at either 15 min. or immediately before a meal had complete prevention of HB (19% and 27%, respectively) compared to PL-treated subjects (14%).
  - The therapeutic gain for subjects completely free of HB in the -15 min. NIZ group was numerically (+5%)<sup>5</sup> but not statistically significantly better than PL.
  - The therapeutic gain for subjects completely free of HB in the 0 min. NIZ treatment group, was significantly ( $p=0.001$ ) greater (+13%) than PL.
  - Both NIZ treatment groups had a significantly higher percentage of subjects free of HB compared to the PL group starting at the 90-min. time point and continuing throughout the remainder of the 3-h assessment period [data not shown].
- NIZ 75 mg taken 15 min. or immediately before a meal significantly reduced post-meal HB severity compared to PL.<sup>6</sup> [Therapeutic gains =5 mm for both comparisons to PL, (Table 6)].
- Both NIZ 75 mg taken 15 min. and taken immediately (0 min.) before a meal significantly reduced subjects' maximum post-meal HB severity compared to PL-treated subjects. [Therapeutic gain of 9 and 10 mm, respectively (Table 6)].

<sup>4</sup> The exception was a statistically significant difference between -15 min NIZ (50.1 mm) vs PL (55.4 mm),  $p < 0.05$  at 150 min. This imbalance is not expected to influence efficacy analyses.

<sup>5</sup> The sponsor stated that, although the predetermined statistical convention selected to protect for multiple comparisons (sponsor's Section VII.D.3) required the -15 min NIZ vs PL comparison to be significant before the 0 min. NIZ vs PL comparison was eligible for significance, the result for the 0 min NIZ treatment group is robust. Even with the application of a Bonferroni adjustment (i.e., multiplying the p-value by the number of relevant parameters) for the three summary endpoints to protect against false-positive results the statistical significance remains strong ( $p=0.003$ ) confirming that this result was not due to chance alone.

These results remained the same when subgrouped according to which chili (original or modified recipe) a subject consumed. A breakdown of these results by chili recipe (original or modified) was found in sponsor's Tables B.5.a & 6.

<sup>6</sup> Despite the large reduction in sample size, these HB severity results remained at least borderline significant when subgrouping according to which chili recipe (original or modified) a subject consumed (sponsor's Tables B.5.a & b).

**TABLE 6**  
Study NZ-95-03

Results of Primary and Secondary Efficacy Analyses of ITT Population

Parameters of Evaluation	PL (n=187)	-15 min NIZ (n=184)	Therapeutic Gain-15 min NIZ > PL	p-value	0 min NIZ (n=184)	Therapeutic Gain 0 min NIZ > PL	p-value
% of subjects without post-meal HB	14	19	5 %	N.S.	27	13 %	0.001
Average severity of HB (mm)	24	19	5 mm	0.006	19	5 mm	0.003
Maximum severity of HB (mm)	42	33	9 mm	0.004	32	10 mm	<0.001

### 3) Efficacy Response by Site

- Both the sponsor and the FDA statistician summarized the differences in the percentages of subjects without HB for study NZ-95-03 by investigator.
- The results reported in [redacted] Table 1.6 of his review showed a consistent numerical advantage favoring NIZ 75 mg taken either 15 min. before a meal or immediately before a meal relative to PL for all centers except center 0309. He noted that overall there was no significant differences (p-value = 0.166) between PL and -15 min. Axid 75 mg. Furthermore there was no significant treatment by center interaction effect of at the 0.05 level as evidenced by the test of homogeneity (p-value = 0.110) for the all center-pooled results.

There is, however, a numerical trend favoring PL over the treatments (0 min and -15 min, p-value 0.781) and a statistically significant difference (p-value 0.052) for PL versus -15 min. treatment comparisons for center 0309.

In [redacted] figures 12 to 19, he compared HB absence vs presence for study NZ-95-03 by center. It is to be noted that upon exclusion of center 0309 from the analysis data, the statistical findings in favor of -15 min. NIZ approached significance (p-value = 0.012), thus indicating the impact of center 0309 on the overall result.

### d. Results of Safety Analyses

In this trial, single doses of NIZ 75 mg given either 15 min. before or immediately prior to a provocative meal, were well tolerated. There were no significant differences among the treatment groups for the incidence of any AE.

- As in study NZ-95-02, headache was the most commonly reported AE among the two NIZ 75 mg treatment groups. Headache was reported by 3 (2%) subjects taking NIZ 75 mg 15 min. before a meal and 5 (3%) subjects taking NIZ 75 mg immediately prior to a meal, and 1 (1%) subject taking PL.

- There were no SAEs reported.
- No subjects discontinued due to AEs during the D-B treatment meal.

#### 11. Sponsor's Conclusions

"Compared to placebo, nizatidine 75mg taken 15 minutes or immediately prior to a heartburn-producing meal is safe and well-tolerated, provides complete prevention of heartburn in a significant proportion of subjects, and significantly reduces average and maximum heartburn severity. These results, considered with the results of previous trials, show that nizatidine can be taken safely and effectively at the time of a meal or up to an hour before a meal for the prevention/reduction of heartburn."

#### 12. Reviewer's Additional Comments

Study NZ-95-03 is the second of two pivotal symptom prevention trials (the other was NZ-95-02) submitted by the sponsor of this NDA supplement to demonstrate the efficacy of pre-meal dosing with NIZ (either 15 min. before or immediately before the provocative meal) vs PL in the prevention/reduction of post-prandial HB.

As NZ-95-02, this trial was well-designed (double-blind, randomized, parallel, single dose), well-controlled (PL) and apparently well executed. As NZ-95-02, this D-B treatment meal phase was preceded 6 to 10 days earlier by a single-blind qualifying meal.

For the S-B qualifying meal, subjects received S-B PL at 15 min. and 0 min. (immediately) before the meal. At 0 min., subjects indicated the presence or absence of HB and its severity, received their S-B PL dosing, and then ate the provocative meal. As in the previous trial, the latter consisted of chili, nacho cheese chips and Coca-Cola®. Subjects had a period of 30 min. to consume a minimum of one serving of the meal. At the end of the meal (i.e., at 30 min.), and at 60, 90, 150 and 210 min. after the start of the meal, subjects evaluated the presence and severity of heartburn. Subjects reporting heartburn with a severity rating of  $\geq 50$  mm at least once during the 3-h post-meal follow-up period of the S-B qualifying meal were eligible to participate in the D-B treatment meal. Study procedures for the D-B treatment meal were identical to those of the S-B qualifying meal. At both meals, following the 90 min. evaluation, subjects complaining of severe HB could receive a rescue antacid [redacted] upon request.

In study NZ-95-03 the study population consisted of generally healthy subjects who had a Hx of at least moderate HB distress in relation to the types of food (spicy and hot) that were to be served at the study meals. These subjects suffered with meal-related HB and, in general, treated this symptom with OTC H<sub>2</sub>-receptor antagonists and/or non-prescription antacids. The most important efficacy assessments in this and study NZ-95-02 were the Heartburn Presence Scale (HBPS), based on a YES/NO question and the Heartburn Severity Scale (HBSS), based on a 0 to 100 mm VAS.

Also adequate were the efficacy endpoints. For HB Prevention, the primary efficacy endpoint was the proportion of subjects (%) with total HB absence assessed by both the HPSS and the HBSS. The two efficacy endpoints measuring HB reduction, both measured in the 0 to 100 mm VAS, were the Average HB

Severity and Maximum Severity of HB. The most important assumptions by the sponsor were a) that the proportion of PL-treated subjects likely not to develop HB was not expected to be greater than 5% and b) that the test med. would be considered superior of the proportion of subjects on NIZ that reported no HB was at least 15%. In other words, using the primary efficacy parameter (NO HB), a therapeutic gain of 10% of NIZ over PL was expected.

A detailed evaluation of the patients' baseline characteristics was carried out. This assessment demonstrated that the three Tx groups were essentially comparable in demographic, HB Hx, medical Hx and additional background characteristics. The exception was gender since the PL group had a greater percentage of women than did the NIZ groups. Although this imbalance was not expected to impact on efficacy results the summary efficacy endpoints were subgrouped according to gender to determine if the significant difference between the number of women and men had any effect on efficacy result (IT DID NOT). Since there were no clinically significant pre-drug differences among the Tx groups it was appropriate to assess comparative efficacy and safety analyses. Also it is worth mentioning that the randomized study population was similar to the broad screening populations and the population receiving single-blind medication.

Under the experimental conditions used in study NZ-95-03, single oral doses of NIZ 75 mg were found to be both effective and safe. NIZ 75 mg taken immediately before a meal, demonstrated a clinically and statistically significant [therapeutic gain 13%;  $p=0.001$ ] advantage over PL in the complete prevention of HB with 27% of NIZ subjects versus 14% of PL subjects being completely free of HB. NIZ 75 mg taken 15 min. before a meal completely prevented HB in 19% of subjects compared to 14% of subjects who took PL [therapeutic gain 5%;  $p=N.S.$ ]. The 15 min. result was not significant, largely due to a single site, which was the only one in which PL was numerically superior to NIZ. [Removing this site from the analysis results in a clinically meaningful and significant advantage for NIZ over PL]. The sponsor stated that, although the predetermined statistical convention to protect for multiple treatment comparisons required the -15 min. NIZ vs PL comparison to be significant before the 0 min. NIZ vs PL comparison was eligible for significance, the statistical result for the 0 min. NIZ group was so robust that even when the conservative Bonferroni adjustment to control for the three summary efficacy endpoints was applied, the comparison of 0 min NIZ to PL remained highly significant ( $p=0.003$  after the adjustment).

Study NZ-95-03 also showed that NIZ 75 mg taken 15 min. or immediately before a meal significantly reduced average HB severity compared to PL [(therapeutic gain 5 mm);  $p=0.002$ ]. Both NIZ treatment groups significantly reduced maximum HB severity compared to PL [therapeutic gain 9 and 10 mm, respectively;  $p<0.001$ ]. Both NIZ treatment groups had a significantly higher percentage of subjects free of HB compared to the PL group starting at the 90-min. time point and continuing throughout the remainder of the 3-h assessment period.

Single oral doses of NIZ 75 mg were well tolerated.

In summary, the MO agrees with the sponsor's conclusion. Single oral doses of NIZ 75 mg taken either 15 min. before or immediately prior to a heartburn-producing meal are safe and well-tolerated and provide complete prevention of HB in a significant proportion of subjects. This NIZ single dose also significantly reduced average and maximum HB severity.

**IV. RECOMMENDATIONS FOR REGULATORY ACTION**

The following is recommended.

1. Approval of AXID® AR [nizatidine 75 mg tablets], taken 15 minutes before or immediately before eating, for the prevention of heartburn, acid indigestion and sour stomach related to foods and beverages.

This recommendation is based on results of the two placebo-controlled studies (NZ-95-02 and NZ-95-03) conducted in the U.S. Both studies were well-designed and apparently well-executed. The efficacy results in these adequate studies indicate that NIZ 75 mg is significantly effective in the complete prevention of heartburn symptoms in patients 16y of age or older when administered either immediately (0-min) or 15 minutes prior to consuming food and beverages anticipated to provoke heartburn. Studies NZ-95-02 and NZ-95-03 also showed that NIZ 75 mg significantly reduced the average as well as the maximum heartburn severity when taken either immediately or 15 minutes prior to a provocative meal.

A previous review by the MO (NDA 20-555) resulted in the approval of AXID® (nizatidine) OTC mg tablets for the prevention of heartburn, acid indigestion, sour stomach and upset stomach associated with these symptoms when the medication was taken one-half to one hour before eating.

Based on the results of the studies reviewed here as well as in the already approved labeling, the sponsor proposes a labeling revision to consolidate all information regarding the effectiveness of the drug for the OTC prevention indication. The MO's second recommendation for regulatory action is therefore:

2. Approve the labeling revision proposed by the sponsor, so as to read.

**DIRECTIONS**

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- For Prevention of symptoms, take 1 tablet with water right before eating or up to one hour before consuming food and beverages that cause you heartburn.

*ISI* February 20, 1998

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:  
 NDA 20-555  
 HFD-180  
 HFD-180/LTalarico  
 HFD-180/HGallo-Torres  
 HFD-181/CSO  
 HFD-180/JChoudary  
 HFD-180/EDuffy  
 r/d 2/18/98 jgw  
 f/t deg: 2/20/98  
 MED\w\20555802.1HG

*ISI/c-25-98*