

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-555/S-003/S-004

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ITEM 2. SUMMARY

H. Clinical Data Summary and Results of Statistical Analysis

TABLE OF CONTENTS

I. OVERVIEW OF CLINICAL STUDIES.....	1
II. DESIGN FEATURES OF THE PIVOTAL CLINICAL TRIALS	6
A. STUDY SETTING	6
B. NUMBER OF TREATED EPISODES PER DAY	6
C. COMPONENTS OF EFFICACY	6
D. LENGTH OF EPISODE ASSESSMENT	8
E. DOSE RATIONALE	8
F. SINGLE-BLIND ANTACID QUALIFYING PERIOD.....	8
G. DOUBLE-BLIND TREATMENT PERIOD.....	9
H. USE OF RESCUE ANTACID	9
I. SAMPLE SIZE	9
III. CONTROLLED PIVOTAL CLINICAL STUDIES	10
A. NARRATIVE SUMMARY OF PIVOTAL STUDIES	10
B. SUMMARY OF CROSS STUDY EFFICACY ANALYSES.....	14
1. Overall Analyses	14
2. Subset Analyses.....	18
IV. CONTROLLED NON-PIVOTAL STUDY.....	20
V. SUMMARY OF CROSS STUDY SAFETY ANALYSES.....	22
A. DEMOGRAPHIC CHARACTERISTICS	23
B. EXTENT OF EXPOSURE.....	24
C. ADVERSE EXPERIENCES	25
1. Cross-study Adverse Experience Analysis.....	26

2. Premature Discontinuations Due to Adverse Experiences	27
3. Deaths and Serious Adverse Experiences	28
4. Adverse Experiences in Subpopulations	30
D. CLINICAL LABORATORY DATA	32
VI. OVERDOSE.....	33
VII. ABUSE POTENTIAL.....	33
VIII. WORLDWIDE SAFETY SURVEILLANCE.....	34
A. WORLDWIDE LITERATURE REVIEW.....	34
B. SPONTANEOUS PRESCRIPTION ADVERSE EXPERIENCE REPORTS.....	37
C. SPONTANEOUS NONPRESCRIPTION ADVERSE EXPERIENCE REPORTS	37
1. Overview	37
2. Serious Adverse Experiences	38
D. DRUG INTERACTIONS	39
E. SPECIAL POPULATIONS.....	39
1. Pregnancy	39
2. Nursing Mothers.....	40
3. Pediatric.....	40
4. Elderly	41
F. PRESCRIPTION PACKAGE INSERT CHANGES.....	41
IX. DISCUSSION AND CONCLUSIONS.....	43

TABLE OF IN-TEXT TABLES

Table 1. Table of Controlled Clinical Studies	3
Table 2. Demographic Characteristics of Pivotal Clinical Studies.....	13
Table 3. Summary of Efficacy Parameters Pooled Across NZ-95-01 and NZ-95-04 (Intent-to-treat Subjects)	15
Table 4. Demographic Characteristics of Subjects in WM-505	21
Table 5. Demographic Characteristics for the Safety Analysis Population: All Studies.	24
Table 6. Extent of Exposure: Mean and Range of Number of Doses per Subject Over 2- Week Double-Blind Period	25
Table 7. Number (%) Subjects Reporting Adverse Experiences that Occurred in $\geq 1\%$ of Nizatidine-Treated Subjects: All Studies	27
Table 8. Discontinuations Due to Adverse Experiences: Double-Blind Period: All Studies	28
Table 9. Deaths and Serious Adverse Experience: All Studies	29
Table 10. List of Published Articles (October 1994 to June 1996).....	35
Table 11. Nizatidine: Number of Nonprescription Adverse Experience Reports by Body System (June 1996 through August 1996).....	38

TABLE OF IN-TEXT FIGURES

Figure 1. Proportion of Episodes with Adequate Relief at Each Timepoint Based on the First Four Episodes: Studies NZ-95-01 and NZ-95-04.....	18
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I. OVERVIEW OF CLINICAL STUDIES

The results of three studies are presented in this submission, two identical pivotal efficacy and safety studies NZ-95-01, NZ-95-04, and a nonpivotal study WM-505. Table 1 lists the clinical investigators, design features and demographic characteristics of the populations for these studies. The two pivotal efficacy studies were multicenter, multiple-dose, placebo-controlled, randomized, parallel group design trials with a 1-week single-blind antacid qualifying period and a 2-week double-blind treatment period. These studies evaluated the efficacy of nizatidine 75mg versus placebo in the treatment of heartburn in men and women 16 years of age or older with at least a 3-month history of heartburn responsive to antacids or nonprescription histamine H₂-receptor antagonists. During the 2-week double-blind treatment period, subjects treated up to two episodes of heartburn of at least moderate severity per day with nizatidine 75mg or placebo and evaluated the adequacy of their relief at 15, 30, and 45 minutes and 1, 2, and 3 hours after taking study medication. Subjects also evaluated the completeness of their relief during the 3-hour treatment period at 180 minutes. Subjects were permitted to take rescue antacid after the 2-hour assessment timepoint, if they needed additional medication to obtain adequate relief from their heartburn.

WM-505, a non-pivotal study, was a multicenter, multiple-dose, placebo-controlled, randomized, parallel group design trial with a 2-week single-blind antacid qualifying period and a 2-week double-blind treatment period that evaluated the efficacy of nizatidine 75mg, antacid (magnesium hydroxide/aluminum hydroxide), and placebo in the alleviation of heartburn. The efficacy and safety results for WM-505 can be found in the abbreviated final clinical study report in this submission (*Vol 1.28, p08-09921*). For that report, only the primary

efficacy variable was analyzed. The data are summarized in Section IV of this item. Safety data from this study have been incorporated into the Integrated Summary of Safety. The efficacy data were not incorporated in the Integrated Summary of Efficacy because the clinical efficacy endpoints, study populations, and dosing regimen were different from those of the pivotal clinical studies. The primary efficacy variable for WM-505, the proportion of episodes for which at least "moderate" relief was achieved by 60 minutes, differed from that of the pivotal studies, the mean sustained adequate relief score (SARS) for the first four episodes. The WM-505 study population was required to have a history of at least six heartburn episodes per week of mild or greater severity to qualify at screening and at least 12 episodes during the 2-week single blind antacid qualifying period. This frequency of episodes was higher than the frequency of three episodes per week required for the pivotal studies and the minimum severity of episodes required (mild) was less than that required for the pivotal studies (moderate). Additionally, subjects in WM-505 were permitted to use up to twice as much nizatidine per day and remedicate after 1 hour for any single episode.

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Nizatidine 75mg

Table 1. Table of Controlled Clinical Studies

NZ-95-01 Treatment of Episodic Heartburn (Vol 1.03, p 08-00065)	Study Design and Duration	Treatment/ Dose	Number Entered DB	Age Range (mean)	Gender % M/F^a	Race (%) C/B/A/H/O^b
Investigators	Multicenter, multiple dose, placebo-controlled, randomized, balanced parallel group study with 1-week single-blind antacid qualifying period and 2-week double-blind treatment period	Total	537	16-81 (42)	44/56	83/13/0/3/1
		Placebo	265	16-78 (42)	45/55	84/11/1/4/1
		Nizatidine 75mg	272	16-81 (42)	42/58	82/16/0/2/0
		Up to two doses/day				

^aM/F = Male/Female

^bC/B/A/H/O = Caucasian/Black/Asian/Hispanic/Other

Nizatidine 75mg

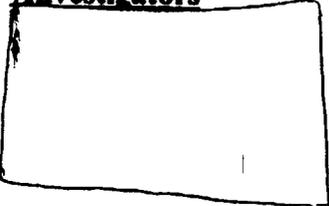
Supplement to NDA 20-555
Item 2H. Clinical Data Summary

NZ-95-04 Treatment of Episodic Heartburn <i>(Vol 1.17, p 08-05351)</i>	Study Design and Duration	Treatment/ Dose	Number Entered DB	Age Range (mean)	Gender % M/F^a	Race % C/B/A/H/O^b
	Multicenter, multiple dose, placebo-controlled, randomized, balanced parallel group study with 1-week single-blind antacid qualifying period and 2-week double-blind treatment period	Total	457	16-81 (44)	48/52	80/8/2/9/1
		Placebo	231	16-81 (45)	49/51	79/8/3/10/1
		Nizatidine 75mg	226	17-81 (43)	47/53	81/8/1/9/1
		Up to two doses /day				

^a M/F = Male/Female^b C/B/A/H/O = Caucasian/Black/Asian/Hispanic/Other

Nizatidine 75mg

Supplement to NDA 20-555
Item 2H. Clinical Data Summary

WM-505 Treatment of Episodic Heartburn (Vol 1.28, p 08-09921)	Study Design and Duration	Treatment/ Dose	Number Entered DB	Age Range (mean)	Gender % M/F*	Race %C/B/A/H/O^b
Investigators 	Multicenter, multiple dose, placebo-controlled, randomized, balanced parallel group study with a 2-week single-blind antacid qualifying period, and a 2-week double-blind treatment period,	Total	95	19-79 (49)	47/53	85/1/0/14/0
		Placebo	32	19-79 (45)	50/50	88/0/0/13/0
		Nizatidine 75 mg	31	25-76 (52)	52/48	81/0/0/19/0
		Antacid	32	21-71 (50)	41/59	88/3/0/9/0
		Up to four doses/day				

*M/F = Male/Female

^bC/B/A/H/O = Caucasian/Black/Asian/Hispanic/Other

II. DESIGN FEATURES OF THE PIVOTAL CLINICAL TRIALS

Both pivotal clinical trials were identical in design.

A. Study Setting

The clinical investigations were conducted as "at-home" studies to evaluate efficacy of nizatidine 75mg in the same environment where consumers would be treating their heartburn with nizatidine 75mg when it will be indicated for nonprescription use for the relief of episodic heartburn.

B. Number of Treated Episodes per Day

Subjects were permitted to treat up to two heartburn episodes per day, allowing nizatidine to be taken at a total daily dose 150mg, i.e., half the maximum daily prescription dose. This daily dose is also the maximum dose approved for nonprescription use for the prevention of heartburn.

C. Components of Efficacy

For the pivotal studies of this submission, a subject's response comprised the following two components of efficacy into a response profile: 1) whether adequate relief was attained and sustained until the 3-hour timepoint, and 2) the rapidity with which relief was attained. For any individual episode, a Sustained Adequate Relief Score (SARS), a categorical score from 0 to 4, was assigned, based on how rapidly sustained adequate relief was achieved. A score of 0 was assigned to episodes when sustained adequate relief was not attained or rescue medication was taken. A score of 4 denoted sustained adequate relief attained within 30 minutes of taking study medication. Scores from 1 to 3

were assigned based on increasing amounts of time taken to achieve sustained adequate relief.

These categorical values were planned to be averaged across the first *five* episodes within a subject to provide a more precise estimate of the components of efficacy for each subject. Since less than 90% of subjects had five episodes, the SARS was averaged over the largest number of episodes for which 90% of the subjects had data, as provided in the protocol. This was *four* episodes for both pivotal trials. The mean SARS for the first four episodes was the primary efficacy variable for these studies. Secondary variables included the SARS averaged across all episodes within a subject, the proportion of each subject's first four episodes and all episodes with sustained adequate relief regardless of time, the proportion of each subject's episodes and all episodes with complete relief reported at the 3-hour assessment timepoint, the proportion of subjects with sustained adequate relief at all episodes, the proportion of subjects with complete relief at all episodes, and SARS for the first episode. The parameter of complete relief at all episodes was an endpoint retrospectively identified after the studies had been initiated. It nevertheless represents a valid treatment effect assessment, because reliability of a product to produce complete relief is a meaningful efficacy parameter to consumers.

These endpoints allowed the efficacy of nizatidine 75mg to be evaluated in terms of speed, consistency, and completeness of response to medication, which are relevant issues for the consumer.

D. Length of Episode Assessment

Assessments of adequacy of heartburn relief were carried out to 180 minutes. Relief of heartburn was expected to last for at least 3 hours, based upon the length of time the 75mg dose maintained gastric pH above 4 in clinical pharmacology studies (*NDA 20-555, Vol 1.16, p 08-00122; Vol 1.18, p 08-01013*) and the timeframe thought to be relevant to consumers' needs for heartburn relief.

E. Dose Rationale

A dose of 75mg was selected for the pivotal efficacy trials of nizatidine in the relief of episodic heartburn. Clinical pharmacology studies conducted for the original NDA (*NDA 20-555, Vol 1.16, p 08-00122; Vol 1.18, p 08-01013*), monitored gastric pH in addition to plasma nizatidine concentrations following administration of nizatidine 225mg, 75mg or 25mg to subjects with recurrent heartburn in both the fed and fasted state. In these studies, both nizatidine 75mg and nizatidine 225mg inhibited meal-induced gastric acid secretion and maintained gastric pH above 4 for 2 to 3 hours. Nizatidine 25mg had little effect on gastric pH. As such, nizatidine 75mg was the lowest tested dose likely to prove efficacious in relieving episodic heartburn related to the esophageal reflux of gastric acid.

F. Single-blind Antacid Qualifying Period

A single-blind antacid qualifying period was used to select subjects whose heartburn was of at least moderate severity, was responsive to neutralization of gastric acid and was sufficiently frequent to obtain a good assessment of efficacy during the 2-week double-blind treatment period. Subjects had to treat at least three episodes of heartburn of moderate or

greater severity during this 1-week period and at least 50% of those episodes had to have responded to antacid, either as the single-blind antacid or the rescue medication. Subjects whose heartburn responded to neutralization of gastric acid by antacid were also expected to respond to suppression of acid secretion by nizatidine 75mg during the double-blind period.

G. Double-blind Treatment Period

Clinical investigations were conducted as double-blind, placebo-controlled studies to reduce bias. Since no active comparator has been accepted as the standard against which it would be necessary to show efficacy, these studies were placebo-controlled. The double-blind treatment period lasted 2 weeks in order for subjects to treat and assess a sufficient number of episodes to estimate an individual subject's response to nizatidine 75mg more accurately.

H. Use of Rescue Antacid

To avoid a high dropout rate for treatment failure, the use of rescue antacid was permitted for those subjects who did not obtain sufficient relief with study medication. The relative frequency of rescue antacid use in the two treatment groups also provided a secondary efficacy endpoint for differentiating nizatidine 75mg from placebo.

I. Sample Size

The hypotheses for these trials was that nizatidine 75mg was superior to placebo in providing faster and/or more consistent relief from heartburn. In each pivotal trial, an estimated sample size of approximately 250 subjects per treatment group was needed to achieve 80% power for a two-

Nizatidine 75mg

sided null hypothesis test at the 0.05 level. The sample size calculation assumed a σ equal to 2.0 (based on the standard deviation being approximately bounded by half the range of the SARS scale of 0 to 4) and Δ equal to 0.4. If only the response for one episode were to be evaluated, the required sample size would have been about 400 subjects per group. The primary efficacy analysis was to have been based on the average SARS for the first five episodes within a subject. Assuming an intraclass correlation of ρ equal to 0.5, the estimated sample size was reduced by 40% to approximately 250 per group. The protocol stated that if fewer than 90% of subjects had five episodes, the highest number of episodes recorded by at least 90% of subjects would be used. For both studies, this was four episodes.

III. CONTROLLED PIVOTAL CLINICAL STUDIES

The efficacy and safety data from two identical pivotal controlled clinical studies of nizatidine 75mg and placebo in the relief of episodic heartburn, NZ-95-01 and NZ-95-04, are being reported in this submission. The safety and efficacy data from WM-505, a non-pivotal study of nizatidine 75mg, placebo, and antacid are summarized in Section IV of this item. The safety data from WM-505 has been incorporated into the Integrated Summary of Safety.

A. Narrative Summary of Pivotal Studies

Two identical clinical studies were performed to assess the safety and efficacy of nizatidine 75mg, taken as needed up to twice daily, compared to placebo in episodic heartburn relief. Both trials were multicenter, randomized, double-blind, placebo-controlled balanced-parallel-group design studies lasting approximately three weeks. Subjects were men and

women 16 years of age or older, in generally good health, with at least a 3-month history of episodic heartburn of moderate or greater intensity occurring at least 3 times per week, usually treated with nonprescription antacids or nonprescription histamine H₂-receptor antagonists.

Subjects treated up to two episodes of moderate to severe heartburn daily for one week in the single-blind antacid qualifying period and for two weeks with nizatidine 75mg or matching placebo up to two times daily as needed in the double-blind treatment period. Each treated episode was evaluated over three hours at 15, 30, 45 minutes, 1, 2, and 3 hours after dosing. Subjects who had insufficient relief were permitted to take rescue medication after the 2-hour post-dose assessment. A 4-hour interval from the start of study medication and resolution of the previous episode were required before treating a second episode on any one day of the study. Completeness of heartburn relief was also assessed at the 3-hour timepoint. Adverse experiences were recorded at the end of the single-blind and double-blind treatment periods.

A sample size of approximately 500 subjects (250 per treatment group) was needed to achieve 80% power for rejecting a two-sided null hypothesis test at the 0.05 level. A subject's response profile comprised two components: 1) whether sustained adequate relief was attained, and 2) the rapidity with which it was attained. For any individual episode of heartburn, the Sustained Adequate Relief Score (SARS), a categorical score of 0 to 4, was assigned based on the time taken to achieve sustained adequate relief for that particular episode. The primary unit of statistical analysis was the subject and efficacy was based on the average score

across the first four episodes to provide an analysis of whether sustained adequate relief of heartburn was attained more frequently and/or sooner in the nizatidine-treated group than in the placebo-treated group. Cochran-Mantel-Haenszel tests and generalized estimating equations were used to analyze the data. All analyses were performed using SAS® Version 6.11 and SUDAAN Version 7.0.

Data from two sets of subjects were analyzed for efficacy. The primary analysis was an intent-to-treat (ITT) analysis using all available data from all randomized subjects who took study medication and provided efficacy data. The secondary analysis, Evaluable Subjects/Evaluable Episodes, included randomized subjects without major protocol violations who took study medication and had at least one evaluable episode.

Demographics

In both studies, the treatment groups were comparable for demographic characteristics as shown in Table 2.

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Table 2. Demographic Characteristics of Pivotal Clinical Studies

Study	Number entered	Age range (mean)	Gender % M/F ^a	Race % C/B/A/H/O ^b
NZ-95-01	Total: 537	16-81 (42)	44/56	83/13/0/3/1
	Placebo: 265	16-78 (42)	45/55	84/11/1/4/1
	Nizatidine: 272	16-81 (42)	42/58	82/16/0/2/0
NZ-95-04	Total: 457	16-81 (44)	48/52	80/8/2/9/1
	Placebo: 231	16-81 (45)	49/51	79/8/3/10/1
	Nizatidine: 226	17-81 (43)	47/53	81/8/1/9/1

^aM/F = Male/Female^bC/B/A/H/O = Caucasian/Black/Asian/Hispanic/Other**Results**

Efficacy: Nizatidine 75mg demonstrated a significant advantage over placebo in both studies with a mean SARS of 2.45 compared to 2.15 for placebo in NZ-95-01 and 2.39 compared to 2.11 for placebo in NZ-95-04 for the first four episodes and including all episodes, indicating that subjects received faster and/or more consistent heartburn relief when treated with nizatidine. Nizatidine 75mg also exhibited a significant advantage over placebo for all secondary efficacy endpoints except efficacy for the first episode alone in NZ-95-04.

Safety: There were no significant differences between the treatment groups for the incidence of any adverse experience in either study. Headache was the most commonly reported adverse experience among nizatidine-treated subjects, followed by diarrhea, dyspepsia, and nausea. Headache was reported by 21 (8.0%) and 11 (4.9%) of nizatidine-treated subjects and 12 (5.0%) and 11 (4.3%) of placebo-treated subjects ($p=0.151, 0.826$) in NZ-

95-01 and NZ-95-04, respectively. There were no deaths reported in NZ-95-01. One subject, a 44-year old man enrolled in study NZ-95-04, died before taking any nizatidine. Two serious adverse events, atrial fibrillation and hospitalization secondary to intraoperative arterial laceration, were reported for two placebo-treated subjects. No serious treatment-related adverse events were reported for nizatidine-treated subjects. Four placebo-treated subjects and one nizatidine-treated subject discontinued for adverse experiences.

Conclusion

The clear benefit of nizatidine in the treatment of episodic heartburn was demonstrated in these adequate and well-controlled studies. The efficacy 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.

B. Summary of Cross Study Efficacy Analyses

1. Overall Analyses

The cross study analysis of pivotal clinical trials, NZ-95-01 and NZ-95-04, can be found in the Integrated Summary of Efficacy in this submission (*Vol 1.30, p 08-10866*). Analysis of pooled data was performed to determine whether the effects of nizatidine versus placebo were consistent across both pivotal efficacy trials with respect to the key efficacy parameters. Results of the key parameters are presented in Table 3, followed by a summary of the proportion of episodes adequately relieved at each timepoint for the first four episodes. The Cochran-Mantel-Haenszel (CMH) test

was used to compare nizatidine to placebo while controlling for investigational site. The statistical methods used for this analysis and the detailed results are presented in the Appendices of the Integrated Summary of Efficacy (*Vol 1.30, p 08-10878*).

Table 3. Summary of Efficacy Parameters Pooled Across NZ-95-01 and NZ-95-04 (Intent-to-treat Subjects)

EFFICACY PARAMETER	Placebo (n=496)	Nizatidine 75mg (n=498)	Treatment p-value	Treatment by-study p-value
Mean SARS				
First four episodes	2.14	2.43	<0.001	0.923
All episodes	2.12	2.41	<0.001	0.559
Proportion of subject's episodes with sustained adequate relief				
First four episodes	0.66	0.75	<0.001	0.590
All episodes	0.66	0.75	<0.001	0.374
Proportion of subject's episodes with complete relief reported at three hours				
First four episodes ^a	0.64	0.74	<0.001	0.992
All episodes ^b	0.64	0.73	<0.001	0.695
Proportion of subjects with sustained adequate relief at all episodes	0.25	0.37	<0.001	0.364
Proportion of subjects with complete relief at all episodes^b	0.24	0.37	<0.001	0.536
SARS for first episode	2.18	2.47	0.005	0.163

^an=495 for placebo and n=497 for nizatidine since one subject in each group failed to indicate the presence or absence of complete relief for each of the first 4 episodes.

^bn=497 for nizatidine since one subject failed to indicate the presence or absence of complete relief for all the episodes.

Results of the key efficacy parameters show that the nizatidine group was consistently superior to the placebo group with strong

statistical significance, even when considering only the first treated episode of heartburn. These results were consistent across studies, as evidenced by the non-significant treatment-by-study interactions. The mean SARS averaged over the first four episodes for subjects who took nizatidine was 2.43 compared to 2.14 for subjects who took placebo, a highly significant difference ($p < 0.001$). This difference of 0.29 represents a 14% improvement over placebo, thus demonstrating that subjects taking nizatidine had heartburn relief that was achieved faster and/or more reliably than did subjects taking placebo. When the SARS was calculated over all episodes within subjects this same significant advantage for nizatidine-treated subjects persisted. It is noteworthy that this clear advantage of nizatidine was demonstrable even for the first episode, where the nizatidine group had significantly better results (SARS=2.47) than the placebo group (SARS=2.18) in the pooled analysis.

When efficacy was assessed as a proportion of episodes for which sustained adequate relief was attained, regardless of time, both among the first four and over all episodes, subjects taking nizatidine attained relief for 75% of their episodes, significantly more often than subjects taking placebo, who attained relief for 66% of their episodes.

Nizatidine not only provided adequate relief more often than placebo averaged over for a majority of episodes, it was also significantly better than placebo at providing relief at *all* episodes.

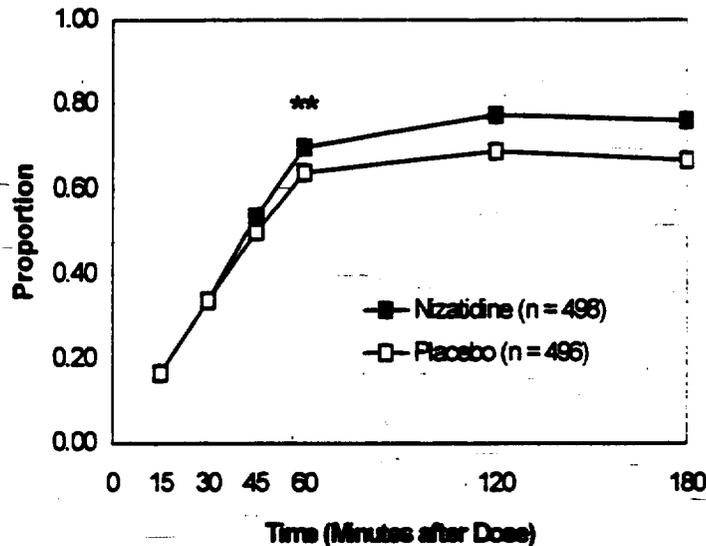
Over one-third (37%) of the nizatidine-treated subjects experienced sustained adequate relief at all episodes, while this was true for only one fourth (25%) of placebo-treated subjects, a significant difference.

Nizatidine's effectiveness was not limited to just adequate relief of heartburn. It also provided complete relief significantly more often than did placebo, both in terms of the mean proportion of episodes completely relieved, 74% for nizatidine-treated subjects compared to 64% for placebo-treated subjects, and in the proportion of subjects with complete relief at all their episodes. Over one-third (37%) of the nizatidine-treated subjects experienced complete relief at all episodes, while this was true for less than one fourth (24%) of placebo-treated subjects, also a significant difference.

As shown in Figure 1, for the first four episodes, nizatidine-treated subjects had significantly more episodes adequately relieved than did placebo-treated subjects at 60 minutes through 180 minutes. This was also shown when all episodes were considered.

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Figure 1. Proportion of Episodes with Adequate Relief at Each Timepoint Based on the First Four Episodes: Studies NZ-95-01 and NZ-95-04



* $p \leq 0.05$ vs Placebo, ** $p \leq 0.01$ vs Placebo, *** $p \leq 0.001$ vs Placebo

2. Subset Analyses

The key efficacy variables were analyzed within subsets to determine whether any differences in response occurred in subgroups of the study populations in terms of the following characteristics: (1) gender, (2) race, (3) age, (4) caffeine use, (5) alcohol use, (6) tobacco use, and (7) frequency of heartburn episodes. In addition, heartburn episodes were subgrouped according to their initial severity to assess whether there were any response differences for treated heartburn episodes of moderate severity as compared to more severe episodes. The full results pooled across the two pivotal studies are given in Appendix III of the Integrated Summary of Efficacy (*Vol 1.30, p 08-109v7*).

Nizatidine was generally effective across the various subgroups. Nizatidine remained effective even with the more severe episodes of heartburn. When considering only the more severe episodes of heartburn, nizatidine was significantly favored over placebo for not only the SARS, but also for all the other key efficacy parameters, except for the SARS at the first episode. In fact, 40% of the nizatidine-treated subjects had complete relief at *all* their more severe heartburn episodes compared to only 26% of placebo-treated subjects.

Two of the subgroupings do result in notable differences. First, nizatidine's efficacy was not evident among non-Caucasians compared to Caucasians. The explanation for this is unclear and it may in fact be simply a random deviant finding. However, nizatidine 75mg prevented meal-related heartburn among both Caucasians and non-Caucasians in the studies conducted as part of the original NDA (*NDA 20-555, Vol 1.69, p 08-19927*), indicating that nizatidine 75mg does have pharmacologic activity in non-Caucasians. It is therefore unlikely that nizatidine's lack of efficacy in relieving heartburn in non-Caucasians was due to lack of pharmacologic activity.

Second, nizatidine's efficacy was more apparent among subjects who used caffeine on a daily basis than among those who did not. Although there is no obvious explanation for this difference, the relevant finding is that nizatidine's effectiveness is not diminished

in the presence of caffeine or other potentially confounding substances such as tobacco or alcohol.

IV. CONTROLLED NON-PIVOTAL STUDY

WM-505 was a non-pivotal study that evaluated the safety and efficacy of nizatidine 75mg or antacid (magnesium hydroxide 400mg/aluminum hydroxide 400mg) taken up to four times per day (qid) as needed (prn) for two weeks compared to placebo in the alleviation of symptoms of heartburn. The study was designed as a multicenter, multiple-dose, placebo-controlled, randomized, balanced-parallel-group study with a 2-week, single-blind antacid qualifying period and a 2-week double-blind treatment phase. Subjects were men and women, 18 years of age or older, with a history of episodic heartburn of at least 3 months' duration, occurring at least 6 times per week, responsive to antacids and lasting for a period of at least 2 hours in the absence of antacid therapy. A sample size of 120 subjects (40 per treatment group) was planned for the study. Due to difficulty in obtaining qualified subjects, the study was terminated prematurely and did not meet its enrollment objectives. A total of 95 subjects was entered into the double-blind treatment period.

In the double-blind period, subjects were randomly assigned to receive either nizatidine 75mg qid prn, antacid qid prn, or placebo qid prn. During the 2-week double-blind treatment phase, subjects took one dose of study medication initially to treat each episode of heartburn. An additional dose could be taken after one hour. Use of rescue antacid was also permitted starting one hour after dosing with study medication, if necessary to obtain adequate relief.

The primary efficacy endpoint was the proportion of heartburn episodes for which at least moderate relief was achieved within 60 minutes of the first dose of study medication. Safety measures consisted of liver chemistry tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transpeptidase [GGTP], and total bilirubin), physical examinations before and after study medications and adverse experiences.

Statistically significant treatment differences were declared if the probability of random occurrence among or between the treatment groups was ≤ 0.05 (two-tailed test). All computations were performed using SAS ® version 6.09. The primary efficacy variable was analyzed via the Cochran-Mantel-Haenszel test.

Demographics

The treatment groups were comparable for all demographic variables as shown in Table 4.

Table 4. Demographic Characteristics of Subjects in WM-505

Treatment/ Dose	Number Entered DB	Age Range (mean)	Gender % M/F ^a	Race % C/B/A/H/O ^b
Total	95	19-79 (49)	47/53	85/1/0/14/0
Placebo	32	19-79 (45)	50/50	88/0/0/13/0
Nizatidine 75mg	31	25-76 (52)	52/48	81/0/0/19/0
Antacid	32	21-71 (50)	41/59	88/3/0/9/0

^a M/F = male/female

^b C/B/A/H/O = Caucasian/Black/Asian/ Hispanic/Other

Results

Efficacy: There was no significant difference among treatment groups in the mean proportion of episodes within a subject for which at least "moderate" relief was achieved within 60 minutes of the first dose of study medication. While the nizatidine group had a notable proportion of episodes (80%) with moderate or greater relief, the placebo group had an equally large proportion, making it difficult to demonstrate a statistically significant effect of nizatidine.

Safety: No serious, unexpected adverse experiences related to study medication administration occurred. A significant difference among the treatment groups in the adverse experience incidence was seen for the Body as a Whole System, where the placebo treatment group had the highest incidence. The most common adverse experience in the nizatidine treatment group was headache. No clinically meaningful alterations in liver chemistry tests before and after nizatidine treatment were detected. No serious adverse events or deaths were reported for this study.

Conclusion

Nizatidine 75mg is safe and well-tolerated when taken up to 300mg daily for the treatment of episodic heartburn.

V. SUMMARY OF CROSS STUDY SAFETY ANALYSES

The safety data presented here are from the double-blind periods of the three controlled trials, NZ-95-01, NZ-95-04, and WM-505. Subjects are identified by their study number, double-blind randomization number and treatment group denoted as follows: NZ - nizatidine 75mg, AA - antacid, and PL - placebo. Subjects from WM-505 were not included in the subset analysis for effect of

alcohol, tobacco and caffeine because this data was not collected during that study.

A. Demographic Characteristics

The demographic characteristics of the 1089 subjects in the Integrated Summary of Safety are summarized in Table 5. There were 500 (46%) men and 589 (54%) women. The study population included 890 (82%) Caucasians, 108 (10%) Blacks, 12 (1%) Asians, 70 (6%) Hispanics, and nine (1%) subjects of other racial or ethnic background. The mean age was approximately 43 years; the youngest subject was 16 years of age and the oldest subject was 81 years of age. There were 99 subjects (9%) \geq 65 years of age, including 22 subjects (2%) \geq 75 years of age. There were no significant differences among the treatment groups with respect to demographic characteristics.

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**Table 5. Demographic Characteristics for the Safety Analysis Population:
All Studies**

Demographic Characteristic		Treatment Group			
		Overall n=1089	Placebo n=528	Nizatidine 75mg n=529	Antacid n=32
		N (%)	N (%)	N (%)	N (%)
Gender	Men	500 (46%)	250 (47%)	237 (45%)	13 (41%)
	Women	589 (54%)	278 (53%)	292 (55%)	19 (59%)
Race	Caucasian	890 (82%)	432 (82%)	430 (81%)	28 (88%)
	Black	108 (10%)	46 (9%)	61 (12%)	1 (3%)
	Asian	12 (1%)	9 (2%)	3 (1%)	0 (0%)
	Hispanic	70 (6%)	36 (7%)	31 (6%)	3 (9%)
	Other	9 (1%)	5 (1%)	4 (1%)	0 (0%)
Age (yr)	Mean	43.4	43.6	42.9	50.0
	Range	(16-81)	(16-81)	(16-81)	(21-71)
	≥65 yr	99	45	49	5
	≥75 yr	22	13	9	0
Weight (lb)	Mean	186.0	186.2	186.3	177.6
	Range	(92-384)	(92-384)	(100-348)	(111-227)
Height (in)	Mean	66.9	67.0	66.9	66.4
	Range	(52-80)	(54-80)	(52-76)	(60-72)
Tobacco use ^a	No	751 (76%)	374 (75%)	377 (76%)	NA
	Yes	243 (24%)	122 (25%)	121 (24%)	
Alcohol use ^a	No	909 (91%)	454 (92%)	455 (91%)	NA
	Yes	85 (9%)	42 (8%)	43 (9%)	
Caffeine use ^a	No	233 (23%)	110 (22%)	123 (25%)	NA
	Yes	761 (77%)	386 (78%)	375 (75%)	

^aThese data were not collected for WM-505. Therefore the percentages are of a total of n=994 subjects (n=496 for placebo and n=498 for nizatidine-treated subjects) from studies NZ-95-01 and NZ-95-04 combined.

B. Extent of Exposure

The mean number and range of doses taken were similar for nizatidine 75mg for the two pivotal trials as shown in Table 6. On average, subjects were exposed to approximately ten 75mg doses or 750mg of nizatidine

over the 2-week double-blind treatment period. Exposures ranged from 75mg (one dose) to 2100mg (28 doses) over two weeks. The protocol allowed a maximum of two doses (150mg) per day.

The mean number of doses of nizatidine 75mg taken in WM-505 was 16.7 or 1253 mg. Exposures ranged from 150mg (two doses) to 2700mg (36 doses) over two weeks. The protocol allowed a maximum of four doses (300mg) per day over 14 days (4200mg) and provided for an additional four days (16 doses, 1200mg) to allow for delayed return to the study center.

Table 6. Extent of Exposure: Mean and Range of Number of Doses per Subject Over 2-Week Double-Blind Period

Study	Nizatidine 75mg	
	No. Subjects	Mean No. Doses (range) Mean total # mg
NZ-95-01	272	10.3 [] 772.5
NZ-95-04	226	10.4 [] 780
WM-505	31	16.7 [] 1253

C. Adverse Experiences

For summary purposes, the in-text table reporting adverse experience incidences presents only those adverse experiences that occurred in 1% or more of the nizatidine-treated population.

1. Cross-Study Adverse Experience Analysis

The number and percent of subjects reporting any adverse experience by frequency of adverse experience using COSTART terminology is summarized by treatment group in Table 7. Overall, the percentage of subjects reporting any adverse experience was similar across treatment groups: nizatidine, (18.1%), placebo, (16.5%), and antacid, (18.8%). Headache was the most frequently reported adverse experience for subjects in the nizatidine treatment group; 38 (7.2%) subjects reported headache, 16 (3.0%) reported diarrhea, 10 (1.9%) reported dyspepsia, and eight (1.5%) reported nausea. For subjects in the placebo treatment group, headache was most frequently reported; 30 (5.7%) subjects reported headache, followed in frequency of reporting by diarrhea (11, 2.1%), dyspepsia (8, 1.5%), and flatulence and nausea (5, 0.9%). Four subjects (12.5%) in the antacid group reported headaches and three (3.9%) reported diarrhea.

The incidence of adverse experiences within body systems was similar for both the nizatidine and placebo treatment groups in each of the individual pivotal studies NZ-95-01 and NZ-95-04. The incidence of adverse experiences was higher in study WM-505, possibly as a result of the smaller treatment group size. There was no significant difference between treatment groups within any body system or individual adverse experience with the exception of flatulence, which occurred more often among placebo-treated subjects.

Most of the adverse experiences were rated mild or moderate. Severe adverse experiences were reported by 24 (4.5%) nizatidine-treated subjects, 22 (4.2%) placebo-treated subjects, and 3 (3.2%) antacid-treated subjects. None of these severe adverse experiences was serious.

Table 7. Number (%) Subjects Reporting Adverse Experiences that Occurred in $\geq 1\%$ of Nizatidine-Treated Subjects: All Studies

Adverse experience	Treatment Group		
	Placebo n= 528	Nizatidine 75mg n=529	Antacid n=32
Any adverse experience	87 (16.5)	96 (18.1)	6 (18.8)
Headache	30 (5.7)	38 (7.2)	4 (12.5)
Diarrhea	11 (2.1)	16 (3.0)	3 (9.4)
Dyspepsia	8 (1.5)	10 (1.9)	0 (0.0)
Nausea	5 (0.9)	8 (1.5)	0 (0.0)

2. Premature Discontinuations Due to Adverse Experiences

The number and percent of subjects with adverse experiences leading to premature discontinuation during the double-blind period are summarized in Table 8. Subjects #10702-PL (NZ-95-01) and #201-NZ (WM-505), who discontinued for serious adverse experiences, are discussed in Section IV.C.3 of this item.

Table 8. Discontinuations Due to Adverse Experiences: Double-Blind Period: All Studies

Study	Subject No. Treatment Group ^a	Adverse Experience	Number of Episodes Treated Before AE	Relationship to Study Medication ^b
NZ-95-01	#10413-PL	Sinusitis/Cough	1	None/None
	#10702-PL	Atrial Fibrillation	3	None
	#11509-PL	Dyspepsia	6	None
	#12413-PL	Back Pain	3	Possible
	#12303-NZ	Headache	3	Probable
NZ-95-04	None	-	-	-
WM-505	#201-NZ	Severe chest pain	7	None

^a PL=placebo; NZ=nizatidine 75mg^b Relationship attributed by Investigator

3. Deaths and Serious Adverse Experiences

Table 9 summarizes information on the one death and three serious adverse experiences reported during these studies. Subject #16807-NZ (NZ-95-04), who died of a probable myocardial infarction, did not take any study medication before his death. Three additional subjects reported serious adverse experiences: one nizatidine-treated subject and two placebo-treated subjects. None of the serious adverse experiences was considered to be drug related. Summaries of these case histories follow Table 9.

Table 9. Deaths and Serious Adverse Experience: All Studies

Subject Number Treatment Group ^a	Age/gender	Adverse Experience	Outcome	Relationship to Study Medication ^b
NZ-95-01				
#10702-PL	68 yr M	Chest pain, hospitalization	Recovered	None
#11532-PL	29 yr F	Arterial laceration, laparotomy	Recovered	None
NZ-95-04				
#16807-NZ	44 yr M	Death (probable myocardial infarction)	Died	None
WM-505				
#201-NZ	66 yr M	Severe chest pain	Recovered	None

^a PL=placebo; NZ=nizatidine 75mg^b Relationship attributed by Investigator

Subject #10702-PL, a 68-year old man with a history of myocardial infarction 10 years ago, atherosclerotic coronary artery disease, and mitral valve prolapse, had chest pain associated with palpitations. He was diagnosed with atrial fibrillation and had successful cardioversion.

Subject #11532-PL, a generally healthy 29-year old woman, entered the hospital for an elective tubal ligation. During the procedure, the surgeon accidentally lacerated an artery, which was repaired during subsequent exploratory abdominal surgery. The incident required extended hospitalization; the subject was discharged as fully recovered.

Subject #16807-NZ, a 44-year old man with a history of an unspecified sleep disorder, was found dead at home of probable cardiac-related causes (apparent myocardial infarction). According

to his brother, he had not taken any of the study medication. He was on no other medications at the time of his death.

Subject #201-NZ, a 66-year old man, experienced severe chest pain resulting in study discontinuation after treating seven heartburn episodes. This subject had a coronary artery bypass graft without complications.

4. Adverse Experiences in Subpopulations

Adverse experiences were evaluated for the subpopulations of elderly subjects age 65 or older and age 75 or older, men and women, users of alcohol, tobacco, and caffeine, subjects taking angiotensin-converting enzyme inhibitors, beta-adrenergic bronchodilators, beta-adrenergic antagonists, calcium channel blockers, inhaled corticosteroids, selective serotonin reuptake inhibitors or theophylline, and subjects with hypertension, asthma, or depression. The incidence of adverse experiences among the various subpopulations was similar to that of the study population as a whole with the exception of subjects taking beta-adrenergic bronchodilators or selective serotonin reuptake inhibitors and subjects with depression.

For these two medications and for depression, there was a notable (more than double the incidence in placebo-treated subjects) but not statistically significant increase in percent of nizatidine-treated subjects reporting adverse experiences. None of these adverse experiences was severe or serious. In the group of nizatidine-

treated subjects taking bronchodilators, there were three reports of headache, and one report each of dyspepsia, nausea, eructation, myalgia, and pruritus. There were no respiratory adverse experiences reported. In the group of nizatidine-treated subjects taking SSRIs, there was one report each of headache, diarrhea, dyspepsia and neck pain. No drug interactions for any of these medications are listed in the nizatidine prescription package insert. No specific adverse experience had a statistically significant increase in frequency and there was no pattern of adverse experiences apparent when nizatidine and any of these medications were used in combination.

In the group of nizatidine-treated subjects with depression, five subjects reported 11 diverse adverse experiences. Six of these (back pain, headache, neck pain, diarrhea, rash, and dysmenorrhea) were reported by one female subject.

With the exception of theophylline and hypertension, none of the individual medications and concomitant illnesses chosen for subset analysis were evaluated in the original *NDA (NDA 20-555, Vol 1.70, p 08-20332)*. Antihypertensive medications, which would encompass angiotensin-converting enzyme inhibitors, beta-adrenergic antagonists, and calcium channel blockers, were evaluated as a group. No increase in the incidence of adverse experiences for nizatidine-treated subjects taking antihypertensive medications was noted in that submission. Additionally, there was no increase in the incidence of adverse experiences noted for

nizatidine-treated subjects with hypertension. There were no placebo-treated subjects taking theophylline in the population of the original NDA. None of the seven nizatidine-treated subjects taking theophylline reported an adverse experience.

D. Clinical Laboratory Data

No laboratory evaluations were done in NZ-95-01 and NZ-95-04. In WM-505, a comprehensive laboratory evaluation consisting of hematology, blood chemistries and urinalysis was done at screening. Post-study assessments were obtained for the liver chemistries (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transpeptidase [GGTP] and total bilirubin) at the end of the study, up to six weeks post-randomization.

There were no clinically or statistically significant differences among or between the three treatment groups in changes in any of the liver chemistry tests.

Four subjects, who had normal values for GGTP before taking study medication (#207-NZ, #238-NZ, #203-AA, #304-PL), had values above the normal range at the post-study evaluation. Likewise, four subjects, who had normal values for ALT before taking study medication (#229-NZ, #401-NZ, #408-AA, #304-PL), had values above the normal range at the post-study evaluation. None of these abnormalities were considered clinically meaningful by the Investigator or the Sponsor.

VI. OVERDOSE

A detailed discussion of overdose and abuse potential can be found in Item 8I of this submission (*Vol 1.30, p 08-11121*). Nizatidine exhibits a wide safety margin in cases of overdose, whether alone or in combination with other drugs. Since the submission of the overdose information for the original NDA (*NDA 20-555, Vol 1.70, p 08-20564*), no deaths or incidences of nizatidine overdose resulting in serious sequelae have been reported. Twenty-seven incidences of overdose with nizatidine were reported to the Spontaneous Reporting System (SRS) of the Food and Drug Administration (FDA) during the period May 1988 to August 1996. Approximately [redacted] prescriptions were written during this same period.

The American Association of Poison Control Centers reported 2,081 exposures to nizatidine with or without other medications from 1988 to 1995. In this group, no deaths were reported. There were 835 exposures in children 12 years old or younger. Of these, 595 were in children less than 2 years old. No deaths or serious sequelae have been reported for pediatric exposures to nizatidine. Since initial marketing of nizatidine 75mg for nonprescription use in June 1996, one asymptomatic overdose case was spontaneously reported to Whitehall-Robins Healthcare. Approximately [redacted] nizatidine 75mg tablets have been sold since June 1996. Nizatidine's profile in overdose indicates minimal risk with continued non-prescription availability.

VII. ABUSE POTENTIAL

There is no known abuse potential or addiction liability associated with nizatidine. Nizatidine was not a "frequently mentioned medication", i.e., there were less than 10 citations in the 24,999 drug abuse case counts in 1992-1994 or in the 994,403

emergency room episodes in 1992-1993 reported to the Drug Abuse Warning Network.

VIII. WORLDWIDE SAFETY SURVEILLANCE

The full Worldwide Safety Surveillance report can be found in Item 8F2 of this submission (*Vol 1.30, p08-10769*). The safety overview presented here covers new information that has become available since the submission of the original NDA (*NDA 20-555, Vol 1,68, p 08-19256*) for the worldwide literature review, spontaneous adverse experience reports from both the prescription (Eli Lilly and Company, FDA SRS) and nonprescription data bases (Whitehall-Robins Healthcare) drug interaction, and safety in special populations, and changes in the prescription package insert.

A. Worldwide Literature Review

Table 10 summarizes the salient information from the eleven articles that appeared between October 1994 and June 1996. The published literature articles report only one adverse experience (subfulminant hepatic failure) not listed in the prescription package insert; however, hepatocellular injury with jaundice and cholestasis is listed in the labeling. No increased frequency of known adverse experiences, new drug interactions, or new safety concerns in pregnant or nursing women, children or the elderly have been reported for the prescription product. The two case reports of serious adverse events (Mira-Perceval *et al*, 1996, anaphylaxis, and Chey *et al*, 1995, subfulminant hepatic failure) are summarized in Table 10. Copies of these articles and the prescription package insert can be found in the full Worldwide Safety Surveillance Report (*Vol 1.30, p 08-10769*).

Nizatidine 75mg

Supplement to NDA 20-555
Item 2H. Clinical Data Summary

Table 10. List of Published Articles (October 1994 to June 1996)

Reference			Adverse experience /safety parameter	Comments
No.	Author	Citation		
1	Mira-Perceval <i>et al</i>	J Allergy Clin Immunol 1996; 97(3):855-6	anaphylaxis	59-yr old woman had acute anaphylactic reaction 30-40 min after first dose of NZ 300mg. Recovered after emergent care
2	Chey <i>et al</i>	J Clin Gastroenterol 1995;20(2):164-7	subfulminant hepatic failure	39-yr old man developed jaundice progressing to subfulminant hepatic failure one month after end of 4-6 weeks course of NZ (dose unspecified). Recovered with residual histopathologic hepatic changes
3	Kubota <i>et al</i>	Intern J Clin Pharm Ther 1995;33(4):219-25	rash	Retrospective study of drugs causing rash during first month of administration. NZ showed potential to cause rash. Prescription package insert labeled for AE
4	Lundberg, Biriell	Therapie 1993; 48:457-9	sexual dysfunction	Retrospective study of sexual dysfunction reported for histamine H ₂ blockers, low incidence of reports for NZ
5	Garcia Rodriguez <i>et al</i>	Lancet 1995;345:1059-60	ocular safety	Retrospective study of ocular safety of H ₂ -blockers. NZ had no risk for causing inflammatory ocular disorders
6	Bachmann <i>et al</i>	Brit J Clin Pharmacol 1993;36:380-2	phenytoin interaction	Study designed to test for drug interaction, none noted.

NZ = nizatidine

Table 10. List of Published Articles (cont'd)

Reference			Adverse experience /safety parameter	Comments
No.	Author	Citation		
7	Wells <i>et al</i>	Annals Intern Med 1994;121:676-83	warfarin interaction	Study designed to test for drug interaction, none noted.
8	Mikawa <i>et al</i>	Brit J Anaesthesia 1994;73:600-4	preoperative use in children	No AEs noted
9	Rao, Kirch	Clin Pharm Ther 1996, 59(2):193 (p III-22)	cardiovascular effects	Nizatidine 300mg lowered heart rate in healthy subjects
10	Leite <i>et al</i>	Am J Gastroent 1995; 90(10):1874-77	increased maximum dose	No AEs noted in patients who took 6 and 12 times the maximum recommended R _x dosage (300mg)
11	Saaresranta,, Terho	Clin Exp Allergy 1995; 25: 574	false negative histamine reaction	52-yr old man with history of positive response to skin prick tests failed to react to histamine 10mg/mL during a two month's daily regimen of NZ 300mg and cisapride 5mg

NZ = nizatidine

B. Spontaneous Prescription Adverse Experience Reports

For the period August 1993 to August 1996, 1,046 adverse experiences were reported to the FDA SRS database for 667 patients. Worldwide, during this period, [] prescriptions were written for nizatidine, resulting in an adverse experience reporting rate of [] prescriptions. This is less than the reporting rate ([] prescriptions) submitted with the original NDA (*NDA 20-555, Vol 1.68, p 08-19263*) covering the period May 1988 to August 1993. The largest reporting category for both periods was the Body as a Whole System.

C. Spontaneous Nonprescription Adverse Experience Reports**1. Overview**

Table 11 summarizes the number of adverse experiences reported for the nonprescription nizatidine 75mg product. Whitehall-Robins Healthcare received 157 spontaneous adverse experience reports between product introduction in June 1996 and August 31, 1996. During this period, approximately [] tablets were sold. All but two of the 157 reports were classified as non-serious. Two cases of acute allergic reactions were reported as serious but not unexpected. These cases are discussed in section VIII.C.2.

The profile of non-serious adverse experiences reported for the nonprescription product was similar to that of the prescription product.

Table 11. Nizatidine: Number of Nonprescription Adverse Experience Reports by Body System (June 1996 through August 1996)

Body system	Number of Reports	Number of Specific Adverse Experiences ^a
Body as a Whole	86	Lack of drug effect - 57 Headache - 12 Abdominal pain - 8
Digestive	45	Diarrhea - 13 Nausea - 12 Dyspepsia - 5 Dry mouth - 5
Nervous	26	Dizziness - 10 Insomnia - 6 Somnolence - 5
Skin and Appendages	23	Pruritus - 10 Rash - 8 Urticaria - 7
Respiratory	10	-----
Cardiovascular	9	-----
Special Senses	5	-----
Urogenital	5	-----
Metabolic and Nutritional	2	-----
Musculoskeletal	2	-----
Endocrine	0	-----
Hemic and Lymphatic	0	-----
Hepatic	0	-----

^a Specific adverse experiences listed only when number of reports received was ≥ 5 .

2. Serious Adverse Experiences

The two cases of acute allergic reaction reported as serious are summarized as follows:

Report 96-2400-103: A 49-year old male patient took one nizatidine 75mg tablet for heartburn prevention, developed facial edema, pruritus and urticaria, and went to the emergency room. He was treated with

diphenhydramine and prednisone, with improvement of symptoms, and discharged. Three days later he was admitted overnight due to not feeling well. The symptoms were felt to be secondary to prednisone.

Report 96-2400-118: A 53-year old female patient took one nizatidine 75mg tablet for heartburn prevention and developed laryngismus and urticaria within five minutes. She went to the emergency room and was treated with epinephrine and diphenhydramine, with resolution of symptoms, and discharged.

D. Drug Interactions

The information in the published literature, FDA SRS and Whitehall-Robins Healthcare databases indicates no drug interactions for nizatidine as stated in the prescription product package insert.

E. Special Populations

There is no information in the literature, the FDA SRS database or the Whitehall-Robins Healthcare database that suggests there has been a change in nizatidine's safety profile for pregnant or nursing women, children, or elderly subjects.

1. Pregnancy

The nonprescription package insert states that nizatidine should not be used by pregnant or nursing women without the advice of health professional. No reports of pregnancy, congenital anomaly or stillbirth have appeared in the medical literature, and none have

been received by Whitehall-Robins Healthcare. One congenital anomaly (unspecified) was reported to the nizatidine FDA SRS database.

2. Nursing Mothers

The nizatidine FDA SRS database, the Whitehall-Robins Healthcare database, and the published literature contained no reports of adverse experiences relating to nursing mothers or their infants.

3. Pediatric

Neither the prescription nor the nonprescription product is labeled for use in children. The review of the nizatidine FDA SRS database from the period August 1993 to August 1996 identified one report of accidental overdose in which the child was asymptomatic. The American Association of Poison Control Centers data covering the period from prescription product introduction in May 1988 through the end of 1995 (the last available data) reported 835 cases of exposure to nizatidine, alone or in combination with other substances, in children 12 years of age or younger. No major adverse effects or fatalities were reported in these cases. Item 8I, Overdose and Abuse Potential Information, (Vol 1.30, p 08-11121) provides more detailed information on pediatric exposures to nizatidine.

The Whitehall-Robins Healthcare nonprescription nizatidine spontaneous adverse experience database contained no reports of adverse experiences occurring in children.

4. Elderly

Of the 667 patients in the nizatidine FDA SRS database for the period August 1993 to August 1996, a total of 152 (22.8%) were individuals 65 years of age or older. There have been neither any newly published reports of adverse experiences in the elderly nor any newly published reports of clinical studies in the elderly.

Of the 157 reports in the Whitehall-Robins Healthcare nonprescription spontaneous adverse experience database as of August 31, 1996, sixty (38%) occurred in elderly patients. All reports in elderly patients were classified as non-serious.

The profile of nizatidine safety remains consistent with prior experience and supports its continued suitability for nonprescription use.

F. Prescription Package Insert Changes

The changes in the prescription product labeling made since the original nonprescription NDA are as follows:

- The Actions and the Clinical Pharmacology sections were revised on October 22, 1993, *to add the benign gastric ulcer indication.*
- The Precautions section was revised on July 25, 1994, *to change the pregnancy risk category to B from C.*

Nizatidine 75mg

**Supplement to NDA 20-555
Item 2H. Clinical Data Summary**

- The Adverse Reactions section was revised on July 25, 1994, to add the adverse experience term "*Vasculitis*" in the *Integumental* category.

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IX. DISCUSSION AND CONCLUSIONS

The two pivotal symptom treatment studies, NZ-95-01 and NZ-95-04, were both adequate and well-controlled clinical trials that provided clinically relevant information about the safety and effectiveness of nizatidine 75mg as a nonprescription treatment for episodic heartburn. The data from studies NZ-95-01 and NZ-95-04 individually and the pooled data from both studies consistently demonstrated the significant superiority of nizatidine 75mg over placebo in providing sustained adequate relief of heartburn. Nizatidine-treated subjects achieved relief from their heartburn faster and/or more reliably than did subjects treated with placebo. Furthermore, complete relief was reported significantly more often by subjects who had taken nizatidine 75mg than by those who had taken placebo.

The key efficacy parameters from the two pivotal efficacy trials were analyzed to determine whether subjects responded differently based on age, gender, race, initial severity of heartburn, heartburn frequency, or use of alcohol, tobacco or caffeine. No meaningful differences in response were seen for any of these subsets, except for a lack of efficacy among non-Caucasians, which was probably a random deviant finding since nizatidine 75mg has previously been shown to be effective in preventing heartburn among non-Caucasians. Nizatidine 75mg was even shown to be effective for the relief of more frequent and more severe heartburn, which is of clinical importance to the general population of subjects who experience heartburn on a regular basis.

The integrated safety assessment of nizatidine 75mg for nonprescription use included data from 1089 subjects from three controlled clinical studies, NZ-95-01,

NZ-95-04 and WM-505. In these studies, 529 subjects took at least one dose of nizatidine 75mg. The safety data support the conclusion that nizatidine is well tolerated. The percentage of subjects reporting any adverse experience was similar for nizatidine, placebo, and antacid treatment groups. No specific adverse experience occurred significantly more frequently in nizatidine-treated subjects than in placebo-treated subjects. There were no treatment related serious adverse experiences. Nizatidine was well tolerated in elderly subjects. The frequency of adverse experiences was similar for men and women. Daily use of alcohol, tobacco, or caffeine did not affect the frequency of adverse experiences. Addition of nizatidine to angiotensin-converting enzyme inhibitors, beta-adrenergic antagonists, calcium channel blockers, inhaled corticosteroids, or theophylline did not substantially affect the frequency of adverse experiences.

Nizatidine-treated subjects who were also taking beta-adrenergic bronchodilators or selective serotonin reuptake inhibitors had a notable, but not statistically significant, increase in frequency of adverse experiences, none of which was serious or severe. The frequency of adverse experiences among nizatidine-treated subjects was not affected by the presence of the chronic medical conditions hypertension or asthma. Nizatidine-treated subjects who also had a diagnosis of depression had a notable, but not statistically significant, increase in frequency of adverse experiences, none of which was serious. Nizatidine did not cause consistent or clinically meaningful changes in liver chemistry tests. The safety profile of nizatidine in these studies was entirely consistent with the safety profile in the application for the approved NDA for use of nizatidine 75mg for the prevention of heartburn.

Nizatidine exhibited a wide safety margin in cases of overdose, whether alone or in combination with other drugs. Nizatidine's profile in overdose indicated minimal risk with continued nonprescription availability. There is no known abuse potential or addiction liability associated with nizatidine. The literature articles published from August 1993 to June 1996 reported only one adverse experience (subfulminant hepatic failure) not specifically listed in the prescription labeling; however, hepatocellular injury is listed. No increased frequency of known adverse experiences, new drug interactions, or new safety concerns in pregnant or nursing women, children or the elderly have been reported in the literature.

The spontaneous adverse experience reporting rate for the prescription product ([redacted] prescriptions) for the period August 1993 to August 1996 decreased from the rate ([redacted] prescriptions) covering the period May 1988 to August 1993. From June 1996 through August 1996, 157 adverse experiences were reported for the nonprescription product. Of the 157 reports, all but two (acute allergic reactions) were classified as non-serious. These two cases were reported as serious but not unexpected since this adverse experience is listed in the prescription package insert.

In summary, the safety and efficacy profile of nizatidine 75mg supports its use up to twice a day as a nonprescription treatment for episodic heartburn.

ITEM 2: SUMMARY

I. Benefits and Risks

Nizatidine 75mg has a favorable benefit-to-risk profile as a nonprescription drug for relieving heartburn. Consumers can expect to attain adequate relief of their heartburn within an hour after taking nizatidine and have that relief sustained for three hours beyond dosing. Nizatidine 75mg offers therapeutic benefit not provided by antacids, the other class of nonprescription heartburn relief medication. Antacids are efficacious for treating heartburn symptoms once they have occurred, as is nizatidine, but do not reduce production of acid in the stomach, as does nizatidine, to provide long-lasting relief. The clinical trials in this supplemental application have demonstrated the effectiveness of nizatidine to relieve heartburn and to sustain that relief over three hours.

Nizatidine is a member of one of the safest classes of drug available and its safety is confirmed by prescription use at up to 300mg daily for extended treatment durations in patients with significant medical conditions. The rate of adverse experiences involving prescription nizatidine reported to the FDA Spontaneous Reporting System database is [redacted] prescriptions written during the period from initial prescription marketing in May 1988 through August 1996, an interval during which [redacted] prescriptions were written for nizatidine. In lower-dose, short-term nonprescription use, this excellent safety profile is further confirmed by the safety data generated from clinical studies with nizatidine 75mg in the original NDA 20-555 for OTC prevention of heartburn and the present supplemental application for relief of episodic heartburn. The pivotal studies in the

present supplemental application reveal no differences in the safety profile of nizatidine 75mg in men compared to women or in elderly subjects compared to the general study population. There have been only 157 spontaneous adverse experience reports, with two reported as serious (non 15-Day Reports) from the time of OTC product launch on June 24, 1996 through August 31, 1996, an interval during which [redacted] were sold.

Nizatidine's wide therapeutic window, coupled with its OTC dosage strength of 75mg, intended episodic dosing frequency, and informative labeling make the drug's availability as an OTC product highly unlikely to be associated with any significant risks. The additional indication proposed, relief of heartburn, poses no additional risk. The risk of harm from potentially masking serious disease, such as gastric carcinoma, is minimized by the dosing regimen on the labeling which instructs the consumer not to exceed two weeks of daily therapy and to consult a physician if symptoms do not respond to treatment. Nizatidine 75mg does not appear to present special concerns among the elderly, pregnant or lactating women, or among individuals with renal or hepatic impairment. The risks of clinical sequelae from inadvertent overdosing appear minimal. There are no pharmacokinetic interactions of nizatidine with prescribed drugs of concern such as theophylline, warfarin, [redacted]. The proposed additional indication for relief is consistent with a self-diagnosable, self-treatable condition appropriate for nonprescription use. In summary, the benefits provided by nonprescription nizatidine 75mg for both relieving and preventing episodic heartburn substantially outweigh any corresponding risks.