CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-555/S-003/S-004

ADMINISTRATIVE DOCUMENTS

EXHIBIT A

Patent/Exclusivity Information

1)	Active Ingredient:	Nizatidine
2)	Strength:	75 mg
3)	Trade Name:	AXID® AR
4)	Dosage Form, Route of Administration:	Tablet, Oral
5)	Applicant Firm Name:	Whitehall-Robins Healthcare, Division of American Home Products Corporation
6)	NDA Number:	20-555
7)	Approval Date:	May 9, 1996
8)	Exclusivity - Date first ANDA could be approved and length of exclusivity period:	Pursuant to clause (III) of Section 505 (j)(4)(D) and clause (iii) of Section 505 (c)(3)(D) of the Federal Food, Drug and Cosmetic Act, as amended, no ANDA may be approved and made effective prior to three (3) years after the date of approved of this NDA. This NDA contains "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application" included in the data submitted to support indications for the drug in treating (relieving) the symptoms of heartburn, acid indigestion and sour stomach.
9)	Applicable Patent Information:	U.S. Patent 4,375,547 (nizatidine) Expires: October 2, 2002 Type: Composition Owner: Eli Lilly and Company

EXHIBIT A

Patent/Exclusivity Information

1)	Active Ingredient:	Nizatidine
2)	Strength:	75 mg
3)	Trade Name:	AXID® AR
4)	Dosage Form, Route of Administration:	Tablet, Oral
5)	Applicant Firm Name:	Whitehall-Robins Healthcare, Division of American Home Products Corporation
6)	NDA Number:	20-555
7)	Approval Date:	May 9, 1996
8)	Exclusivity - Date first ANDA could be approved and length of exclusivity period:	Pursuant to clause (III) of Section 505 (j)(4)(D) and clause (iii) of Section 505 (c)(3)(D) of the Federal Food, Drug and Cosmetic Act, as amended, no ANDA may be approved and made effective prior to three (3) years after the date of approved of this NDA. This NDA contains "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application" included in the data submitted to support indications for the drug in treating (relieving) the symptoms of heartburn, acid indigestion and sour stomach.
9)	Applicable Patent Information:	U.S. Patent 4,375,547 (nizatidine) Expires: October 2, 2002 Type: Composition Owner: Eli Lilly and Company

ITEM 14: PATENT CERTIFICATION

Paragraph IV Certification

Whitehall-Robins certifies that Patent No. 4,375,547 will not be infringed by the manufacture, use, or sale of AXID® AR for which this application is submitted. Whitehall-Robins will comply with the requirements of 21 CFR §314.552(a) with respect to providing a notice of this certification to the patent owner, Eli Lilly and Company. Whitehall-Robins has been granted a patent license by the patent owner.

ITEM 14: PATENT CERTIFICATION

Paragraph IV Certification

Whitehall-Robins certifies that Patent No. 4,375,547 will not be infringed by the manufacture, use, or sale of AXID® AR for which this application is submitted. Whitehall-Robins will comply with the requirements of 21 CFR §314.552(a) with respect to providing a notice of this certification to the patent owner, Eli Lilly and Company. Whitehall-Robins has been granted a patent license by the patent owner.

EXCLUSIVITY SUMMARY for NDA # 20-555 SUPPL # SE1-003

Trade Name nonprescription Axid® AR Tablets, 75 mg Generic Name nizatidine tablets

Applicant Name Whitehall-Robins Healthcare HFD-180/560

Approval Date April 1, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA?

   YES /___/ NO /_X_/

   b) Is it an effectiveness supplement?

   YES /_X_/ NO /___/

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

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

   YES /_X_/ NO /___/

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

   N/A

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

   N/A

   d) Did the applicant request exclusivity?

   YES /_X_/ NO /___/

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

   3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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

1. Single active ingredient product.

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

YES /_X_/ NO /___/

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

NDA # 19-508 Axid Pulvules (nizatidine) Capsules, 150 mg

NDA # 20-555 nonprescription Axid® AR (nizatidine) Tablets, 75 mg

2. Combination product.

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

YES /___/ NO /___/

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

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

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

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

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

YES /_X_/ NO /___/

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

YES /___/ NO /_X_/

If yes, explain: _____

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

YES /___/ NO /_X_/

If yes, explain: _____

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

Investigation #1, Study # NZ-95-01

Investigation #2, Study # NZ-95-04

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

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

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/

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

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

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

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

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

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

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

Investigation #1, Study # NZ-95-01

Investigation #2, Study # NZ-95-04

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

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

Investigation #1

IND #[redacted] YES /_X_/ ! NO /___/ Explain: _____

Investigation #2

IND #[redacted] YES /_X_/ ! NO /___/ Explain: _____

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

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

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

YES /___/ NO /_X_/

If yes, explain: _____

/S/

Signature / Date 3/31/98

Title: Project Manager

/S/

Signature of Division Director Date 4-1-98

cc: Original NDA 20-555/SE2-003 HFD-560/Division File HFD-85 Mary Ann Holovac

EXCLUSIVITY SUMMARY for NDA # 20-555 SUPPL # SE2-004

Trade Name nonprescription Axid® AR Tablets, 75 mg Generic Name nizatidine tablets

Applicant Name Whitehall-Robins Healthcare HFD-180/560

Approval Date April 1, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA?

   YES /___/ NO /_X_/

   b) Is it an effectiveness supplement?

   YES /_X_/ NO /___/

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

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

   YES /_X_/ NO /___/

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

   N/A

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

   N/A

   d) Did the applicant request exclusivity?

   YES /_X_/ NO /___/

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

   3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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

1. Single active ingredient product.

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

YES /_X_/ NO /___/

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

NDA # 19-508 Axid Pulvules (nizatidine) Capsules, 150 mg

NDA # 20-555 nonprescription Axid® AR (nizatidine) Tablets, 75 mg

2. Combination product.

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

YES /___/ NO /___/

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

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

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

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

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

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

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

   YES /_X_/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

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

YES /_X_/ NO /___/

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

YES /___/ NO /_X_/

If yes, explain: _____

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

YES /___/ NO /_X_/

If yes, explain: _____

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

Investigation #1, Study # NZ-95-02

Investigation #2, Study # NZ-95-03

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

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

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/

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

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

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

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

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

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

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

Investigation #1, Study # NZ-95-02

Investigation #2, Study # NZ-95-03

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

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

Investigation #1

IND # _____ YES /_X_/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /_X_/ ! NO /___/ Explain: _____

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

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

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

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____

/S/

Signature 3/31/98
Date

Title: Project Manager

/S/

Signature of Division Director 4-1-98
Date

cc: Original NDA 20-555/SE2-004 HFD-560/Division File HFD-85 Mary Ann Holovac

EXHIBIT A

DEBARMENT STATEMENT

Whitehall-Robins Healthcare, to the best of its knowledge, did not and will not use in any capacity, the services of any person debarred under section 306 of the act in connection with said application.

Rich Cuprys
Assistant Vice President,
Regulatory Affairs
Whitehall-Robins Healthcare

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT A

DEBARMENT STATEMENT

Whitehall-Robins Healthcare, to the best of its knowledge, did not and will not use in any capacity, the services of any person debarred under section 306 of the act in connection with said application.

Eleanor F. Barbo
Director, Regulatory Affairs
Whitehall-Robins Healthcare

Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940-0871
Telephone (201) 660-5500

WHITEHALL ROBINS

December 16, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
ATTN: Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

Subject: Supplement to NDA 20-555
AXID® AR, Nizatidine Tablets 75 mg
Patent and Exclusivity Information

Dear Sir/Madam:

Reference is made to our supplemental NDA submission herewith for AXID® AR, Nizatidine tablets 75 mg, the requirements of the Federal Food, Drug and Cosmetic Act ("Act") to submit patent and exclusivity information and the Food and Drug Administration (FDA) interpretations of those sections of the Act. This supplemental new drug application also refers in part to original NDA 20-555 for AXID AR (approved May 9, 1996) sponsored by Whitehall-Robins Healthcare and NDA 19-508[redacted] The purpose of this submission is to obtain a new indication for the relief (treatment) of heartburn symptoms. This product has been previously approved for over-the-counter use in the prevention of heartburn symptoms.

Patent Information

The undersigned declares that Patent Number 4,375,547 covers the composition of nizatidine. This product is presently approved under section 505 of the Federal Food, Drug, and Cosmetic Act. Whitehall-Robins has a license agreement with Eli Lilly with regard to this patent. Whitehall-Robins is hereby updating the patent information previously provided (Exhibit A) and making the following certification statement.

Paragraph IV Certification

Whitehall-Robins certifies that Patent No. 4,375,547 will not be infringed by the manufacture, use, or sale of AXID® AR for which this application is submitted. Whitehall-Robins will comply with the requirements of 21 CFR §314.552(a) with respect to providing a notice of this certification to the patent owner, Eli Lilly and Company. Whitehall-Robins has been granted a patent license by the patent owner.

Exclusivity Information

- New Clinical Investigations -

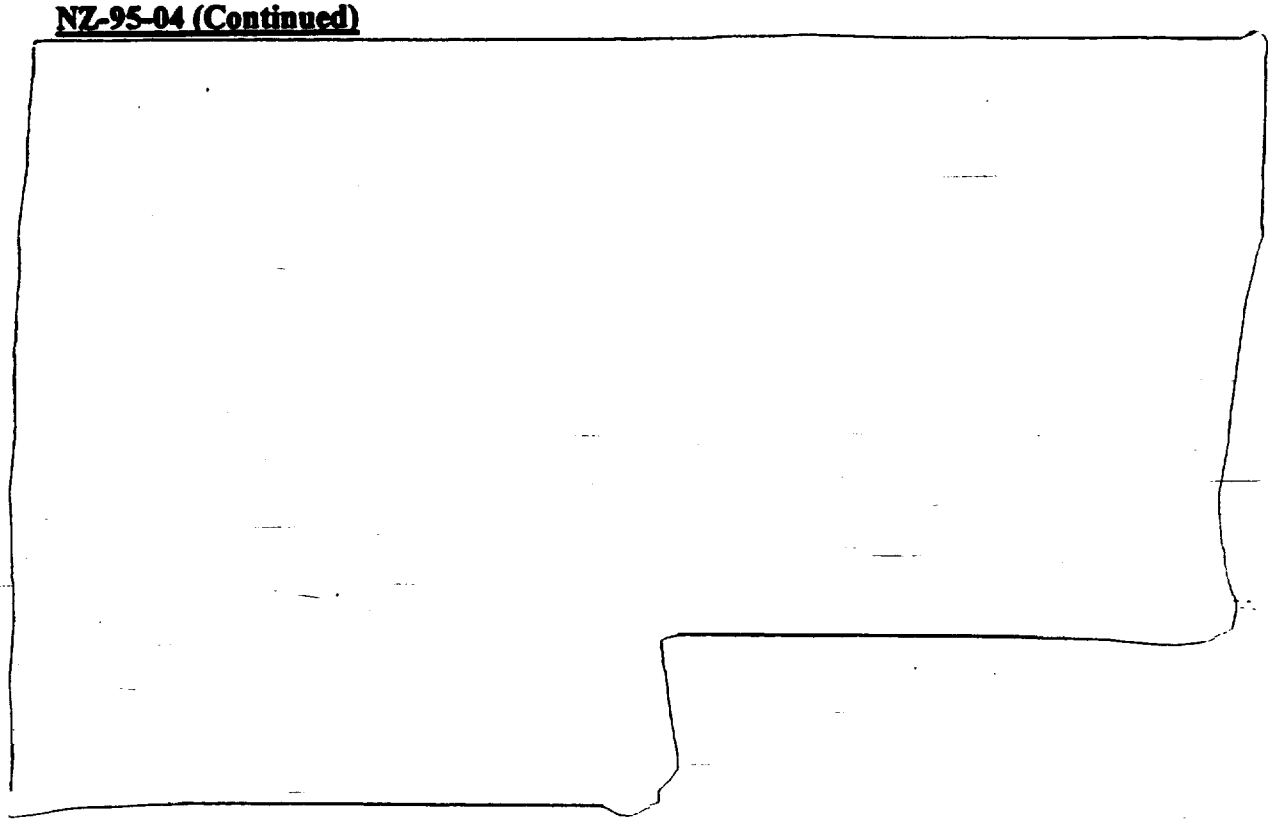
1) This submission relies primarily on new clinical investigations in humans conducted under Whitehall-Robins [redacted] These studies are:

NZ-95-01 Relief of Episodic Heartburn
Investigators:

[redacted]

2 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

NZ-95-04 (Continued)



With respect to the above-identified investigations,

The undersigned certifies, that to the best of his knowledge, none of the investigations identified hereinabove have formed part of the basis of a finding of substantial evidence of effectiveness for this indication in a previously approved new drug application.

- Essential to Approval -

2) With respect to the FDA's interpretation that the new clinical investigation(s) is (are) essential to approval,

The undersigned certifies that the scientific literature has thoroughly been searched and, to the best of the undersigned's knowledge, attached as Exhibit B is a complete and accurate list (as of October 10, 1996) of published studies or publicly available reports generated with respect to the active ingredient, the product, which is the subject of this supplemental new drug application.

In the opinion of the undersigned, there are not sufficient published or publicly available reports of clinical evaluations to support the approval of AXID AR, Nizatidine tablets 75 mg, for relieving the symptoms of heartburn, acid indigestion and sour stomach, other than those conducted or sponsored by the applicant.

- Conducted or Sponsored By the Applicant -

3) The undersigned sponsored the studies identified in paragraph 1) above,

The undersigned certifies, that applicant sponsored each study identified above in paragraph 1) by providing more than 50% of the cost of conducting each said study.

Applicant is the sponsor named in each Form FDA 1571 for each study identified in paragraph 1) as well as the sponsor named in the IND.

- Exclusivity Rationale -

Whitehall-Robins is seeking a three year period of exclusivity (as provided in the Act) for AXID AR, Nizatidine Tablets 75 mg, for the indication of relief (treatment) of heartburn symptoms. This drug product has been previously approved for the indication of prevention of heartburn symptoms at this dosage strength. A drug product containing nizatidine at higher dosage strengths has been approved for prescription use under NDA 19-508.

The studies outlined above, sponsored by the applicant, include significant, new clinical investigations "other than bioavailability studies" as required for NDA approval, and are precisely what are referred to in the statute as "essential to the approval of the application."

Sincerely,
WHITEHALL-ROBINS HEALTHCARE

Rich Cuprys
Assistant Vice President,
Regulatory Affairs

MEMORANDUM OF 45-DAY FILING MEETING

February 4, 1997

Application Number: NDA 20-555/SE1-003; Non-prescription Axid AR (nizatidine) Tablets, 75 mg

Attendees:

Stephen B. Fredd, M.D.; Director, HFD-180
Hugo Gallo-Torres, M.D.; Clinical Reviewer, HFD-180
Eric Duffy, Ph.D.; Chemistry Team Leader, HFD-180
W. Mike Adams, M.S.; Chemistry Reviewer, HFD-180
A.J. Sankoh, Ph.D.; Statistical Reviewer, HFD-720
Michael Folkendt; Project Manager, HFD-180

BACKGROUND

This application, submitted on December 16, 1996, provides for a new claim for the treatment of heartburn acid indigestion, and sour stomach. Currently, this drug is approved for Over-The-Counter (OTC) use for the prevention of meal-induced heartburn when taken 30-60 minute prior to a meal. Appropriate user fees have been received. The 60-day filing date for this application is February 15, 1997.

MEETING

I. **Filing issues:**

1. Administrative: None. However, because this drug is intended for over-the-counter use (OTC), the new procedures as outlined in MaPP 6020.5, as applicable, will be applied to this application, including labeling being reviewed by the Division of OTC drug products and dual divisional sign off on action letters. Additional copies of volume 1 (summary volume) will be requested from the firm and consulted to the Division of OTC drug products.

2. Clinical: Dr. Gallo-Torres stated that there no clinical filing issues.

3. Preclinical: None. No new preclinical information was submitted nor required for this type of application.

4. Statistical: Dr. Sankoh stated that there no statistical filing issues. However, Dr. Sankoh later requested that the firm submit new diskettes containing the SAS files/datasets not in SAS transport file format.

5. Chemistry, Manufacturing, and Controls (CMC):

   Mr. Adams, the assigned chemistry reviewer, stated that the application is fileable with regards to the chemistry, manufacturing, Controls (CMC) sections, specifically the Environmental Assessment portion of the application. No other CMC information was submitted.

6. Biopharmaceutics: None. No new human biopharmaceutical information was submitted.

II. Request for information:

The following was requested of the firm:

1. Three additional copies of volume 1 of this application.
2. Statistical data on diskette in SAS 6.10 for Windows format (not SAS transport files).

III. Projected completion of reviews:

Although the PDUFA Goal Date for this application is December 17, 1997, it was agreed that reviews will be targeted for completion by mid summer, 1997. There will be no regular team meetings pre-scheduled for this application.

IV. Conclusion:

It was agreed that the application will be filed. The firm, however, will be requested by phone to submit the items cited in item II above

/S/ 2/14/97

Michael Folkendt
Project Manager

cc:
Original NDA 20-745
HFD-180/Div. Files
HFD-180/M.Adams
HFD-180/M.Folkendt
HFD-180/H.Gallo-Torres
HFD-720/A.J. Sankoh

drafted: MF/February 13, 1997
final: 2/14/97

MEETING MINUTES

MEMORANDUM OF 45-DAY FILING MEETING

May 16, 1997

Application Number: NDA 20-555/SE1-004; Non-prescription Axid AR (nizatidine) Tablets, 75 mg

Attendees:

H. Gallo-Torres, M.D.; Clinical Reviewer, HFD-180
K. Robie-Suh, M.D.; Clinical Reviewer, HFD-180
E. Duffy, Ph.D.; Chemistry Team Leader, HFD-820
W. Mike Adams, M.S.; Chemistry Reviewer, HFD-820
M. Rashid, Ph.D.; Statistical Reviewer, HFD-720
A.J. Sankoh, Ph.D.; Statistical Reviewer, HFD-720
M. Folkendt; Project Manager, HFD-180
L. Katz, M.D.; Deputy Director, HFD-560
R. Cook; Supervisory CSO, HFD-560
R. Neuner; Clinical Reviewer, HFD-560
S. Walther; CSO, HFD-560
H. Cothran; Interdisplinary Scientist, HFD-560
M. Robinson; Interdisplinary Scientist, HFD-560

BACKGROUND

This application, submitted on March 31,1997, provides for a revision to the DIRECTIONS section of the labeling to change the time to take the drug prior to a meal to prevent meal-induced heartburn symptoms from "30 minute to one hour prior to a meal..." to "...right before eating or up to one hour before consuming...". Appropriate user fees have been received and the 60-day filing date for this application is May 31, 1997.

MEETING

I. Filing issues:

1. Administrative: None. However, because this drug is intended for over-the-counter use (OTC), the new procedures as outlined in MaPP 6020.5 will be applied to this application, including labeling being reviewed by the Division of OTC drug products and dual divisional sign off on action letters. Copies of volume 1 (summary volume) have been consulted to the Division of OTC drug products on April 9, 1997. Copies of all completed reviews done by HFD-180 will be immediately sent to HFD-560.

2. Clinical: Dr. Gallo-Torres stated that there no clinical efficacy filing issues.

3. Labeling: Dr. Neuner requested that the firm submit copies of full color mock-ups of all labeling, both hard copy and on diskette readable by WordPerfect 6.1. Dr. Neuner also informed the attendees that a draft of the new labeling template for non-prescription drugs will be in draft the week of the May 19, 1997.

4. Preclinical: None. No new preclinical information was submitted nor required for this type of application.

5. Statistical: Dr. Rashid stated that there no statistical filing issues.

6. Chemistry, Manufacturing, and Controls (CMC):

Dr. Duffy and Mr. Adams stated that there are no filability issues concerning the chemistry, manufacturing, Controls (CMC) sections, specifically the Environmental Assessment (EA) portion of the application. It was noted by Dr. Duffy that because there is no increase in drug use expected from the approval of this application, an A is not needed. No other CMC information was submitted.

7. Biopharmaceutics: None. No new human biopharmaceutical information was submitted.

II. Request for information:

The firm will be requested to submit full color mock-ups of the labeling, both on paper and on diskette readable by WordPerfect 6.1 for Windows.

III. Projected completion of reviews:

Although the PDUFA Goal Date for this application is April 1, 1998, it was tentatively agreed that reviews will be targeted for completion by the first week in September and that a team meeting to discuss this application would be held the week of September 8, 1997. All agreed that Drs. Bowen (Division Director, HFD-560) and Talarico (Acting Division Director, HFD-180) should attend this team meeting. In addition, to increase review efficiency and because the proposed labeling submitted in this application incorporate the proposed changes submitted in supplement 20-555/SE1-003 (with a User Fee Goal Date of December 17, 1997), supplements 20-555/SE1-003 and 20-555/SE2-004 will be reviewed concurrently.

IV. Conclusion:

It was agreed that the application will be filed. The firm, however, will be requested by phone to submit the full color mock-up of the labeling cited in item II above.

/S/ 6/30/97

Michael Folkendt
Regulatory Health Project Manager
HFD-180

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

ADMINISTRATIVE REVIEW
of
NDA 20-555/SE1-003

JAN 10 1997

Axid® AR (nizatidine) Non-prescription Tablets, 75 mg

Date Submitted: December 16, 1996
Date Received: December 17, 1996
Sponsor: Whitehall-Robins Healthcare

BACKGROUND

Axid® AR (nizatidine) Non-prescription Tablets, 75 mg, is currently approved for non-prescription use for the prevention of meal-induced heartburn when taken 30-60 minutes prior to a provocative meal. This application provides for a new indication for the treatment of heartburn, acid indigestion, and sour stomach. In support of this indication, the firm has submitted results from two identical pivotal, multi center, multiple-dose, placebo-controlled, randomized , parallel group, 2-week (with a 1 week single blind antacid qualifying period) clinical efficacy and safety studies [NZ-95-01 and NZ-95-04] and a non-pivotal study [WM-505] conducted in the United States. This application consists of 70 volumes.

A 45 day filing meeting is scheduled for February 4, 1997.

REVIEW

A. Regarding the indices & pagination of the application:

This application has up to three overlapping pagination schemes. The main pagination for this application, located in the lower right corner of each page, is by item number in the format NN-XXXXX, where NN refers to the item number listed on the back of the FDA form 356h and XXXXX refers the page number within that item number. Each item number begin with page NN-00001. If an item number encompasses multiple volumes, each volume is preceded with an item specific index before continuing on with the next page number for that item from the previous volume. Therefore, to locate any specific page within this application, the volume number (1.1 through 1.70) and complete page number (NN-XXXXX) must be referenced. The application index using this pagination scheme appears to be accurate and detailed enough to permit a review of this application.

It should be noted that self-contained documents within any section (e.g., study reports , integrated summaries, etc.) have a secondary page number usually located in the upper

center of the page. This secondary page number appears to be solely as a page counter since no index can be found that refers to these page numbers.

Further, study protocols have a third pagination located in the upper left corner under the protocol ID and date. This page number is referred to only by the Table of Contents located at the beginning of that protocol.

B. Regarding the summary volume:

The summary volume appears to contain all the required information necessary for this efficacy supplement. Draft labeling in both black and white and full color mock-up were submitted, each with and without changes indicated. Annotation to all of the labeling changes are done in tabular format on pages 04-00011 through 04-00016 of volume 1.

C. Regarding the clinical and statistical sections:

These sections appear complete and adequately indexed. The respective reviewers will evaluate the reviewability of these sections.

D. Regarding the nonclinical pharmacology/toxicology and human pharmacokinetics/bioavailability sections of the application:

No new information was submitted to these sections.

E. Regarding the Chemistry, Manufacturing, and Controls (CMC) section and environmental assessment:

There were no new chemistry, manufacturing, and controls information submitted in this application. However, because this supplement is for a different indication, an environmental assessment is required for this application under 21 CFR 25.24(c)(2) (see also MaPP 5015.1). An updated environmental assessment, including the FOI copy, was included in this application in volume 1, page 03-00001.

F. Regarding the Case report forms (CRF) and tabulations (CRT):

The case report tabulations (CRT), known in this application as "Data Listings", are in located in the clinical and statistical sections (Items 8 and 10, respectively). Volume 1.67 page 11-00001 cites specifically where the case report tabulations can be found. The case report forms are located in volume 1.67 through volume 1.70 and are sorted by study. The beginning of each volume contains a complete table of contents for this section (Item number).

G. Requested information: None.

CONCLUSION

The application appears to be administratively complete and adequately indexed to permit a review.

/S/ 1/10/97

Michael Folkendt
Project Manager, HFD-180

cc:
Original NDA 20-555/S-003
HFD-180/Div. Files
HFD-180/M.Folkendt
HFD-180/S.Fredd

1/10/97 /S/

drafted by: mf/January 9, 1997
final: 1/10/97

ADMINISTRATIVE REVIEW

Gol/Kindt

MEMORANDUM

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

DATE: MAR 19 1998

FROM: Director
Division of OTC Drug Products (HFD-560)

SUBJECT: Labeling Review
Axid® AR 75 mg Tablets
NDA 20-555/SE2-004

TO: Director
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)

Attached is OTC's review of the draft labeling submitted by Whitehall-Robbins Healthcare for the subject supplement.

Debra Bowen, M.D.

Division of Over-the-Counter Drug Products
Labeling Review

NDA #: 20-555/SE2-004
TYPE OF SUBMISSION:
SPONSOR: Whitehall Robins Healthcare
DRUG PRODUCT: Axid® AR Tablets
INDICATIONS: For relief of Heartburn, Acid Indigestion and Sour Stomach
For prevention of these symptoms brought on by consuming food and beverages.
ACTIVE INGREDIENT: Nizatidine tablets, 75 mg
SUBMISSION DATE: March 31,1997
REVIEWER: Mary S. Robinson, MS
REVIEW DATE: January 25, 1998
PM: Al Rothschild

Background:

Axid ® AR (nizatidine) 75 mg Tablets, manufactured by Whitehall-Robins Healthcare, was approved for OTC marketing on May 9, 1996 for the prevention of heartburn, acid indigestion and sour stomach when taken one-half hour to one hour before eating. The manufacturer has submitted this application in support of a change in the time of dosing to "right before a meal to up to one hour before consuming food and beverages." This review is based on xeroxed copies of draft labels and labeling. (i.e., carton label, package insert, container label (12 tablets bottle, and pouch label) for Axid ® AR. [NOTE: This submission was submitted on March 31, 1997, before the approvable letter of December 17, 1997 was issued for S-003. (See Attachment 1.)]

Reviewer's Comments-and Recommendations on the Proposed Revised Axid AR Tablets Labeling

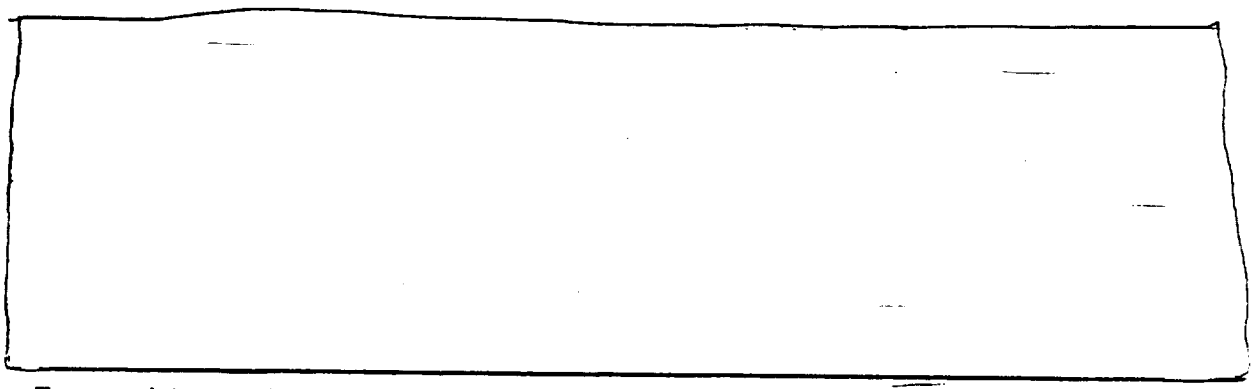
(Please refer to the attached proposed labeling for the carton, container, package insert, and pouch reference in the comments below.) (See Attachment 2.)

1. The statement of Identity "Acid reducer, Nizatidine tablets 75 mg" is not in conformity with 21 CFR 201.61 and needs to be corrected to read: "Nizatidine tablets 75 mg, Acid Reducer." In addition to the carton, this change should also be made on the container, package insert, and pouch.

2. The sponsor's deletion of the phrase "Now in non-prescription strength" on the front riser is acceptable.

3. On the front riser the word "completely" (new addition) needs to be removed from the statement "Relieves and Prevents Heartburn, Acid Indigestion and Sour Stomach Completely."

4.

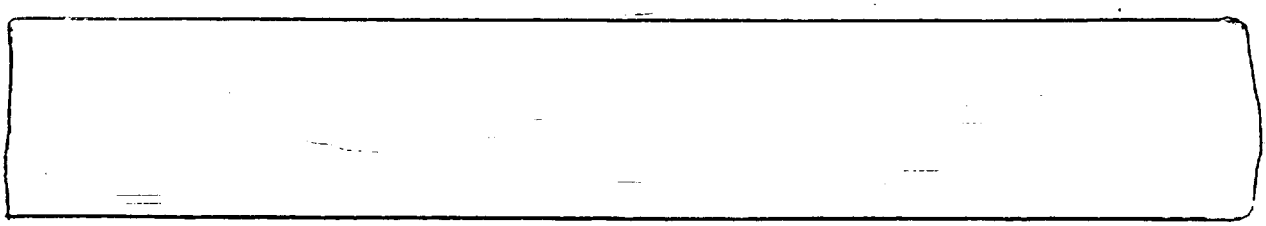


5. For consistency, the relief statement should also be modified under the directions section on the carton (first bullet), package insert (first bullet), container (first sentence) and on the pouch (first bullet). The directions should read:

"For **Relief** of symptoms, 1 tablet with a full glass of water."

6. Under "Warnings" on the carton back(second bullet), the package insert (second bullet), container (second sentence), and pouch (second bullet), the "pregnancy-nursing" warning should be placed before the **"Keep out of reach"** warning.

7. Although it is not required at this time, it is suggested that the sponsor revise this labeling so that it is in compliance with the February 27, 1997 Proposed Labeling Requirements for OTC Drug Products. A prototype label is attached. (See Attachment 3.) The labeling information is presented in the following specific order **Active Ingredient(s), Purpose(s), Uses(s), Warnings, Directions, Other Information,** and **Inactive Ingredients.** No other information should precede the "Active Ingredient" section. Additional format and wording changes from the currently approved label are included in the prototype label. (See Attachment 3.) Note that as part of the acid reducer class consumer labeling: The **"Uses"** section is revised to denote heartburn as the primary symptom, with other symptoms being secondary. The **Uses** section reads: "For relief of heartburn acid indigestion and sour stomach," and "For prevention brought on by consuming certain food and beverages."

8 

9 On the carton side, the Tamper Resistant/Tamper Evident Statement "DO NOT USE IF FOIL IS TORN" should be revised to conform with other acid reducer drug product labeling. The statement should read: "DO NOT USE IF FOIL IS OPEN OR TORN." The word "OPEN" should also be inserted in the Tamper Resistant/Tamper Evident

Statements as follows:

a. on the package insert (side 1 bottom right) for bottles - "Do not use if foil is open or torn."
b. on the package insert (side 1 bottom right) for packets - "Do not use if seal is open or torn."
c. on the pouch (first statement) - "Do not use if foil is open or torn."

10. The following changes need to made as stated in the approvable letter of December 17, 1997 (see attachment 1):

a. Package insert, side 2, first bullet. The statement "AXID AR contains an ingredient, nizatidine, that doctors have prescribed millions of times and has been taken safely with many frequently prescribed medications" should be revised or data should be submitted to support this statement, or use the statement in the currently approved labeling.
b. Package insert, side 2, third bullet. The word "completely" should be deleted from the text.
c. Package insert, side 2, right side, under the heading "Heartburn: a problem that can interfere with your lifestyle," second sentence, the statement "This pain and discomfort, commonly known as heartburn, can interfere with everyday activities," should be revised to "This pain and discomfort is commonly known as heartburn."
d. Package insert, side 2, response rate graphs, bottom. The "% better" should be deleted from all of the graphs.
e. Package insert, side 2, response rate graph for the relief of heartburn. The rate graph should display only the results from a single study, i.e., study NZ-95-01, because it is more convincing than study NZ-95-04. NOTE: The study numbers were inadvertently switched in the December 17, 1997 approvable letter.

11. Package insert, side 2, rate graphs. The sponsor has made the following changes to the 3 rate graphs:

a. The 3 rate graphs showing "PREVENTION, PREVENTION, and RELIEF" have been revised to display "COMPLETE PREVENTION, PREVENTION/REDUCTION, and COMPLETE RELIEF," respectively. The title "PREVENTION/REDUCTION" is confusing and is not acceptable.
b. The 3 rate graphs headers "Study A–Pills taken 60 minutes before eating, Study B–Pills taken 30 minutes before eating, and Combined Studies C and D–Pills taken after symptoms occur," are revised to "Multiple Studies, Multiple Studies, and Combined Studies–Pills Taken after Symptoms Occur," respectively. The new headers "Multiple Studies" are not acceptable because the headers imply that the information displayed in a single bar graph resulted from several studies. The header "Combined Studies" is not acceptable because only one study (NZ-95-01) should be displayed.
c. A new bar graph has been added to rate graphs 1 and 2 indicating "Pills Taken Immediately Before." This information should be displayed on a

separate response rate graph and not displayed as multiple studies.

d. Rate graph 3. The bar graph showing "Subjects with complete relief of all episodes," is deleted.

12. Package insert, side 1, right side, under tips for managing heartburn, please refer to the "Tips for Managing Heartburn" in prototype label (see Attachment 3). We recommend that the prototype label language be used in this section.

Conclusions and Recommendations:

1. The sponsor should be advised that their labeling needs revision. We suggest that they refer to the prototype label attached (see Attachment 3). Further, it should be pointed out to the sponsor that, although not required at this time, the agency has proposed Labeling Requirements for OTC Drug Products in the FEDERAL REGISTER of February 27, 1997, pages 9024-9062. (See paragraph 7.)

2. The sponsor should be advised that the statement of identity is not in conformity with 21 CFR 201.61 and needs to be corrected on all parts of the labeling to read: Nizatidine tablets 75 mg, Acid Reducer.

3. The sponsor should remove the word "completely" on the front riser and the package insert, side 2. (See paragraphs 3 and 9a, above.)

4. [redacted]

5. The phrase "[redacted]1 tablet with a full glass of water" should be added to the "relief and prevention statements in the "Directions" sections on the carton, package insert, container and pouch as outlined in paragraph 4,above.

6. The "warnings" sections on the carton, package insert, container and pouch need to be revised so that the "pregnancy-nursing warning is placed before the **"Keep out of reach"** warning. (See paragraph 6, above.)

7. The words "OPEN OR" should be inserted in the Tamper Resistant/Tamper Evident Statements in the labeling before the word "TORN" so that the phrase reads: "OPEN OR TORN." (See paragraph 8, above.)

8. The sponsor needs to make the changes as listed in the approvable letter of December 17, 1997 (see Attachment 1 and paragraph 9, above).

9. Response rate graphs Package insert, side 2, See paragraph 10, above. Although the sponsor made several changes in the display of the 3 response rate graphs, the information conveyed remains confusing and may be misleading. The sponsor needs to

revise the response rate graphs as follows:

a. As stated in the December 17, 1997, approvable letter, the "% Better" located at the top of the bar graphs must be deleted.

b. The response rate graph for relief of heartburn should display only the results from a single study, i.e., study NZ-95-01, because it is more convincing than study NZ-95-04. NOTE: The study numbers were inadvertently switched in the December 17, 1997 approvable letter. (See Attachment 1 and paragraph 9, above.)

c. The response rate graphs titles and headers need to be changed to reflect more accurately the results of the studies. The headings "Multiple Studies" and "Combined Studies" should not be used because they imply that the information displayed in a single bar graph resulted from several studies. The results from each study should be placed on a separate response rate graph. A fourth graph may be added to display the results "Pills taken immediately before eating."

/S/

Mary S. Robinson, MS
Regulatory Review Chemist, HFD-560

/S/

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

/S/

Helen Cothran
Team Leader, HFD-560

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