

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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

**CORRESPONDENCE**

NDA 20-555/S-003

*Michael Folkendt*

Whitehall-Robins Healthcare  
Attention: Elle Barbo  
Director, Regulatory Affairs  
5 Giralda Farms  
Madison, NJ 07940-0871

JAN - 9 1997

Dear Ms. Barbo:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Axid® AR (nizatidine) Tablets, 75 mg

NDA Number: NDA 20-555

Supplement Number: S-003

Therapeutic Classification: Standard

Date of Supplement: December 16, 1996

Date of Receipt: December 17, 1996

This supplement provides for the treatment of heartburn, acid indigestion, and sour stomach.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 15, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: DOCUMENT CONTROL ROOM  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

*IS/1/8/97*

Michael Folkendt  
Project Manager  
Division of Gastrointestinal and Coagulation  
Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

NDA 20-555/S-004

APR - 8 1997

Whitehall-Robins Healthcare  
Attention: Elle Barbo  
Director, Regulatory Affairs  
5 Giralda Farms  
Madison, NJ 07940-0871

Dear Ms. Barbo:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Non-prescription Axid® AR (nizatidine) Tablets, 75 mg

NDA Number: NDA 20-555

Supplement Number: S-004

Therapeutic Classification: Standard

Date of Supplement: March 31, 1997

Date of Receipt: April 1, 1997

This supplement provides for a revision to the DIRECTIONS section of the labels and labeling to change the time to take the drug prior to a meal to prevent meal-induced heartburn symptoms from "...one-half hour to one hour before eating..." to "...right before eating or up to one hour before consuming..." as well as a revision to the graphical representations of the study results in the package insert concerning the prevention of heartburn symptoms.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 31, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: DOCUMENT CONTROL ROOM  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

ISI 4/8/97

Michael Folkendt  
Project Manager  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

HFD-180

MEMORANDUM

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

DATE:

FROM: <sup>DEC 10 1997</sup>  
Director  
Division of OTC Drug Products (HFD-560)  
Office of Drug Evaluation V

SUBJECT: Labeling Review  
Axid AR (nizatidine) Tablets, 75 mg  
NDA 20-555/S-003

TO: Director  
Division of Gastrointestinal & Coagulation Drug Products (HFD-180)  
Office of Drug Evaluation III

Attached is the labeling review of NDA 20-555/S-003, Axid AR (nizatidine) Tablets, 75 mg for OTC use by Whitehall-Robins Healthcare.

*Debra Bowen*  
Debra Bowen, M.D.

Attachment





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

December 12, 1997

NDA 20-555 (S-003)  
Axid<sup>®</sup> AR : Nizatidine Tablets, 75 mg (OTC)

**AMENDMENT TO A PENDING SUPPLEMENTAL APPLICATION (S-003)**  
**Chemistry, Manufacturing and Controls - Environmental Assessment**

Lilia Talarico, M.D., Acting Director  
Division of Gastrointestinal and  
Coagulation Drug Products (HFD-180)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
ATTN: Document Control Room 6B-24  
5600 Fishers Lane  
Rockville, MD 20857-0001

Dear Dr. Talarico:

Reference is made to new drug application (NDA) 20-555 sponsored by Whitehall-Robins Healthcare ("Whitehall-Robins") for Axid<sup>®</sup> AR (nizatidine, 75 mg) tablets. Specific reference is made to supplemental application S-003, submitted on December 16, 1996, which provides for an additional indication for the subject drug product -- relief of heartburn, acid indigestion, and sour stomach. The original supplement submission included an updated environmental assessment that reflected revised production forecasts and maximum expected emitted concentration (MEEC) calculations relative to the new indication. In subsequent communications with Ms. Elle Barbo from Whitehall-Robins, Mr. Michael Folkendt from the Division of Gastrointestinal and Coagulation Drug Products ("the Division") requested that the environmental assessment be withdrawn from the referenced supplement, and replaced with a claim for a categorical exclusion pursuant to 21CFR 25.31(b).

NDA 20-555 (S-003)  
Axid<sup>®</sup> AR : Nizatidine Tablets, 75 mg (OTC)

December 12, 1997  
Page 2

Whitehall-Robins hereby requests that the environmental assessment report included in the original supplement submission be withdrawn. In lieu of the withdrawn report, Whitehall-Robins is enclosing a claim for a categorical exclusion from the requirements to prepare an environmental assessment report with respect to the pending supplement.

We trust that the enclosed information satisfactorily addresses all outstanding issues relative to NDA 20-555, S-003. If you have any further questions or comments, please feel free to contact the undersigned at (201) 660-6160 [telefax: (201) 660-7162] or Ms. Elle Barbo at (201) 660-5751 [telefax (201) 660-7187]. Thank you for your prompt attention to this submission.

Sincerely,

WHITEHALL-ROBINS HEALTHCARE



Vin Milano  
Sr. Director, Regulatory Affairs

cc: M. Folkendt (CSO) [HFD-180]

**NDA 20-555; S-003**

**Axid<sup>®</sup> AR Tablets (nizatidine, 75mg)**

**Categorical Exclusion for Preparation of an Environmental Assessment**

Whitehall-Robins claims a categorical exclusion from the requirements to prepare an environmental assessment report relative to the NDA 20-555, supplement S-003 for Axid<sup>®</sup> AR (nizatidine, 75mg) Tablets. This claim is made pursuant to 21CFR 25.31(b) which states that a categorical exclusion is permitted for "action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below [redacted]"

[redacted] Whitehall-Robins hereby certifies that NDA 20-555, supplement S-003 qualifies for a categorical exclusion under the provisions of 21CFR 25.31(b) and, that to the best of our knowledge, no extraordinary circumstances exist relative to the proposed action.



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Kenneth Warner  
Associate Director, Regulatory Affairs  
Whitehall-Robins Healthcare

**MEMORANDUM**

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

DATE: December 15, 1997

FROM: Michael Folkendt *MF 12/15/97*  
Regulatory Health Project Manager  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: Lilia Talarico, M.D. *LT 12-15-97*  
Director  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

TO: NDA 20-555/SE1-003

SUBJECT: Comments on 12/9/97 labeling review for NDA 20-555/SE1-003

NDA 20-555 is currently approved for nonprescription use "for prevention of heartburn, acid indigestion and sour stomach brought on by consuming food and beverages". This supplemental application provides for a new indication for the treatment of episodic heartburn, acid indigestion and sour stomach.

The labeling review for this application was completed by the Division of Over-The-Counter Drug Products, HFD-560, on December 9, 1997 and recommends a number of labeling revisions. One of the recommendations (item 1b) was to revise the statement (called "riser" in the labeling review) "Relieves and Prevents: Heartburn, Acid Indigestion & Sour Stomach" to "Relieves and Prevents: Heartburn associated with Acid Indigestion & Sour Stomach." This revision, however, is not consistent with the usage of these terms as stated in the OTC Antacid Monograph.

Originally, because the nonprescription class of drugs labeled "Acid Reducer" treat the same symptoms, except via a different mechanism, as antacids (i.e., heartburn caused by reflux of gastric fluids in the esophagitis), it was decided that these drugs would have the same indication as the antacid monograph under 21 CFR 331.30(b):

"For the relief of" (optional, any of the following:) "heartburn," "sour stomach," and/or "acid indigestion" (which may be followed by the optional statement:) "and upset stomach associated with" (Optional, as appropriate) "this symptom" or "these symptoms."

The terms "heartburn", "acid indigestion" and "sour stomach" were intended in the OTC antacid monograph to be synonymous terms relating to the burning distress felt in the upper

abdomen or in the throat that may be related to the regurgitation of acid gastric contents into the esophagus (see 38 FR 3714, 38 FR 31258, & 51 FR 16258). The proposed revision, however, implies that "acid indigestion" and "sour stomach" are symptoms of "heartburn. Therefore, this recommendation will not be forwarded to the firm.

[N.B., It was also decided that, because heartburn is a symptom of esophageal distress rather than of the stomach, the phrase "and upset stomach associated with these symptoms" was considered misleading (because it implies that this drug will treat all symptoms of upset stomach) and should not be part of the indication for the "Acid Reducer" drugs.]

Another set of recommendations (items 1d - 1i) was to reformat the labeling according to the Over-The-Counter Human Drugs; Proposed Labeling Requirements: Proposed Rule (21 CFR 201, 330, and 358) published in the Federal Register on February 27, 1997. Because this proposed rule has not been finalized, it would be inappropriate to require revision of the labeling as a requirement for approval. Therefore, all of these requested revisions will not be forwarded to the firm.

cc: Archival NDA 20-555  
HFD-560/Division Files  
HFD-180/M.Folkendt  
HFD-180/L.Talarico  
HFD-560/S.Walther  
HFD-560/R.Neuner  
HFD-560/D.Bowen  
HFD-560/L.Katz

drafted by: mf/December 15, 1997

initialed by: K.Johnson 12/15/97

L.Talarico 12/15/97

finalized: 12/15/97

MEMORADUM