

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-494

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-494

MAY 25 2004

Reliant Pharmaceuticals, Inc.
Attention: Robert Mandetta
Director, Regulatory Affairs
110 Allen Road
Liberty Corner, NJ 07938

Dear Mr. Mandetta:

Please refer to your new drug application (NDA) dated April 10, 2002, received April 10, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axid[®] (nizatidine) Oral Solution, 15mg/ml. We determined this application to be approvable in our letter dated February 10, 2003.

We acknowledge receipt of your submissions dated October 10, 17, 24; November 24, 25; and December 03, 2003; and February 18; March 11, 12, 30; and April 06, 08, 12, 13, 14, 16, 19, 29; and May 06, 17, and 24, 2004.

The November 24, 2004 submission, received November 25, 2004, constituted a complete response to our February 10, 2003, Approvable letter

This new drug application provides for the use of Axid[®] (nizatidine) Oral Solution, 15mg/ml for the following indications:

In Adults:

1. For up to 8 weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within 4 weeks.
2. For maintenance therapy for duodenal ulcer patients at a reduced dosage of 150 mg h.s. after healing of an active duodenal ulcer. The consequences of continuous therapy with nizatidine for longer than 1 year are not known.
3. For up to 12 weeks for the treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn due to GERD.
4. For up to 8 weeks for the treatment of active benign gastric ulcer. Before initiating therapy, care should be taken to exclude the possibility of malignant gastric ulceration.

In Pediatric Patients 12 years of age and older:

1. For up to 12 weeks for the treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn due to GERD.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor revisions indicated in the enclosed labeling.

In addition, we would like for you to change the term "children" to "pediatric patients" in your 05/24/04 label prior to your first printing.

We remind you of your Chemistry, Manufacturing, and Controls postmarketing study commitments listed in your submission dated April 14 and 29, 2004. These commitments are listed below.

1. To provide information on degradation controls as requested in the Chemistry, Manufacturing, and Controls (CMC) Deficiency Letter, dated March 11, 2004. Specifically, to submit summaries and copies of all relevant chemical literature of paraben and drug substance degradants in similar dosage forms.

Final Report Submission:.....August 24, 2004

2. Study Protocol Entitled "Isolation and Identification, Through Structural Characterization Techniques, the Degradant Products of Nizatidine and Paraben Excipients in the Drug Product"

Protocol Submission date3rd Quarter 2004
Study start date1st Quarter 2005
Final report submission date4th Quarter 2005

3. Study Protocol Entitled "Investigation of Complexation Reactions of Nizatidine with Excipients in the Drug Product"

Protocol submission date3rd Quarter 2004
Study start date1st Quarter 2005
Final report submission date4th Quarter 2005

Based upon the findings and results of the above investigations, the existing analytical test method and specifications will be reviewed and reassessed. Additional proposed tests and specifications may be generated based on the scientific understanding of the collected data/information to be submitted as a supplement to the NDA. Beforehand, a request may be placed to the Division to have an opportunity for an open dialog with the chemistry reviewers in order to reach a consensus on setting specifications that meet FDA's expectations.

Submit your Chemistry, Manufacturing, And Controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently

labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit final printed labeling (FPL) identical to the enclosed labeling (text for the package insert, immediate container labels, and carton labels). These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

You may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-494". Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product to the NDA when it is available.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Paul E. Levine, Jr., R.Ph., J.D., Regulatory Health Project Manager, at (301) 443-8347.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and

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Reliant Pharmaceuticals, LLC
Attention: Robert Mandetta
Director, Regulatory Affairs
110 Allen Road
Liberty Corner, NJ 07938

Dear Mr. Mandetta:

Please refer to your new drug application dated April 10, 2002, received April 10, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axid® nizatidine.

This new drug application proposes a new oral liquid formulation of nizatidine for use in pediatric patients for treatment of the signs and symptoms of erosive esophagitis and gastroesophageal reflux disease.

We acknowledge receipt of your submissions dated June 17; and July 12 and 25; September 11; and October 23 and 30, 2002.

We refer to our December 18, 2002, Chemistry, Manufacturing, and Controls (CMC) Deficiency Review letter.

We also refer to our proposed draft labeling sent to you by facsimile on January 30, 2003, and to the labeling meeting held with you on February 03, 2003 to discuss the draft labeling.

We have completed our review of this new drug application (NDA), and it is approvable. Before the application may be approved, however, you must resolve the following deficiencies:

Clinical:

Adult Patients

1. Adequate labeling for the use of Axid® (nizatidine) — in adults.

Pediatric Patients 12 to 18 years of age

1. Adequate labeling for the use of Axid® (nizatidine) — in pediatric patients 12 to 18 years of age.

In order resolve these clinical deficiencies, the following must be submitted.

Adult Patients

1. Adequate draft labeling must be submitted for this age group.

Pediatric Patients 12 to 18 years of age

1. Adequate draft labeling must be submitted for this age group.

Chemistry, Manufacturing, and Controls

1. Provide justification for the acceptance criteria for individual and total impurities in the drug product.
2. Amend the drug product specifications so that they contain tests and acceptance criteria for specific degradation products in the drug product (which are described in the NDA).
3. Amend the drug product specifications so that they are adequate to demonstrate the identity, homogeneity, and certain other important physical properties (e. g. viscosity) of the dosage form; alternatively, provide data to justify why this is not necessary.

In addition, we remind you that you must submit a complete response to all of the deficiencies listed in our December 18, 2002, CMC Deficiency Review letter.

It will be necessary for you to submit draft labeling with revisions that adequately address our comments. We will defer final review of the labeling until the deficiencies are resolved.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Health Project Manager, at (301) 443-8347.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Robert Justice
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