

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-494**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

### ITEM 13 PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

Time Sensitive Patent Information pursuant to 21 C.F.R. 314.53 for NDA # 19-508.

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

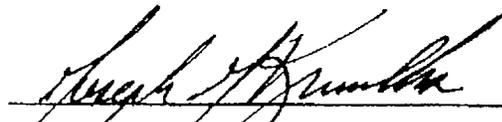
Trade Name: Axid®  
Active Ingredient(s): Nizatidine  
Strength(s): 150 mg capsules, 300 mg capsules  
Dosage Form: Capsule  
Approval Date of NDA # 19-508: April 12, 1988

The following is the patent information required to be submitted in accordance with 21 C.F.R. 314.53:

Patent Number: 4,375,547  
Expiration Date: April 12, 2002  
Type of Patent: Indicate all that apply  
Drug Substance (Active Ingredient)  Yes  No  
Method of Use  Yes  No  
Drug Product (Composition/Formulation):  Yes  No  
Name of Patent Owner: Reliant Pharmaceuticals, LLC

The undersigned declares that the above United States Patent Number 4,375,547 covers the active ingredient of the drug product subject to this application. This product is the subject of the application for which approval is being sought.

Signed:



Joseph J. Kriyulka

Title: President

Date: March 11, 2002

**ITEM 14 PATENT CERTIFICATION WITH RESPECT TO ANY  
PATENT WHICH CLAIMS THE DRUG**

This Section is not applicable to the applicant as the NDA is being filed pursuant to Section 505(b)(1) of the Federal Food Drug and Cosmetic Act.

Debarment Certification

Reliant Pharmaceuticals, LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signature: \_\_\_\_\_

Title: Keith Rotenberg, Ph.D.  
Vice President, Regulatory  
Reliant Pharmaceuticals, LLC

Date: \_\_\_\_\_

EXCLUSIVITY SUMMARY for NDA # 21-494 SUPPL #

Trade Name: Axid® Oral Solution 15mg/ml Generic Name: nizatidine

Applicant Name Reliant Pharmaceuticals, Inc. HFD- 180

Approval Date: \_\_\_\_\_

**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 / X / NO / \_\_\_ /

b) Is it an effectiveness supplement? YES / \_\_\_ / NO / X /

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

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.

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:

d) Did the applicant request exclusivity?

YES /\_\_\_/ NO /\_X\_/

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

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /\_X\_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /\_\_\_/ NO /\_X\_/

If yes, NDA # \_\_\_\_\_ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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 9 (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 /  / NO /  /

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

NDA # 19-508, Axid® Capsules

NDA #

NDA #

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 9. 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 /  / NO /  /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9:

- (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 /\_\_\_/      NO /X/

- (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 /\_\_\_/

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 #AX 9000

Investigation #2, Study #AX 9005

Investigation #3, Study

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 #AX 9000 YES /\_\_\_/ NO /\_\_X\_/

Investigation #2 #AX 9005 YES /\_\_\_/ NO /\_\_X\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

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 #AX 9000 YES /\_\_\_/ NO /\_X\_/

Investigation #2 #AX 9005 YES /\_\_\_/ NO /\_X\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

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 #\_\_, Study # AX 9000

Investigation #\_\_, Study # AX 9005

Investigation #\_\_, Study #

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 # 18,975 YES / X / ! NO /     / Explain:

Investigation #2 !  
IND #        YES /     / ! 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: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Signature of  
Regulatory Health Project Manager

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of  
Medical reviewer

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Office or Division Director

\_\_\_\_\_  
Date

cc:  
Archival NDA

HFD- /Division File  
HFD- /RPM  
HFD-610/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Joyce Korvick  
6/9/04 12:44:34 PM

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-494	Efficacy Supplement Type SE-	Supplement Number
Drug: <b>Axid (nizatidine) Oral Solution, 15mg/ml</b>		Applicant: <b>Reliant Pharmaceuticals, Inc.</b>
RPM: <b>Paul E. Levine, Jr. R.Ph., J.D.</b>		HFD-180 <span style="float: right;">Phone # 301-443-8347</span>
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 19-508
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3S
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
		May 25, 2004
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
❖ Exclusivity Summary (approvals only)		
		X
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		
		X – (See Project Management section)

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	Approvable (AE)
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	May 24, 2004
• Original applicant-proposed labeling	April 10, 2002
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	See Discipline Reviews
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	April 20, 2004
• Reviews	See CMC Review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	CMC Review dated 03/05/04 and IR letter dated 03/11/04
• Documentation of discussions and/or agreements relating to post-marketing commitments	See CMC Review dated 04/28/04 and letters from sponsor dated 04/19/04 and 04/29/04
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	DR Letters: 03/11/04, 03/30/04, 04/13/04 and 04/16/04
❖ Memoranda and Telecons	N/A (for cycle-2)
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	N/A
❖ Clinical review(s) (indicate date for each review)	April 15, 2004
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) (indicate date for each review)	March 05, 2004 April 28, 2004
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See CMC Reviews dated 03/05/04 & 04/28/04
• Review & FONSI (indicate date of review)	NA
• Review & Environmental Impact Statement (indicate date of each review)	See CMC Reviews dated 03/05/04 & 04/28/04
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	August 12, 2002
❖ Facilities inspection (provide EER report)	Date completed: 04/27/04 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	April 01, 2004
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
❖ CAC/ECAC report	NA

Additional Comments:

[ \_\_\_\_\_ ]

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-494	Efficacy Supplement Type SE-	Supplement Number
Drug: Nizatidine Syrup, 15mg/ml		Applicant: Reliant Pharmaceuticals, LLC
RPM: Paul E. Levine, Jr. R.Ph.		HFD-180 <span style="float: right;">Phone # 301-443-8347</span>
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
<b>❖ Application Classifications:</b>		
<input type="checkbox"/> Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<input type="checkbox"/> Chem class (NDAs only)		3S
<input type="checkbox"/> Other (e.g., orphan, OTC)		
<b>❖ User Fee Goal Dates</b>		
		February 10, 2003
<b>❖ Special programs (indicate all that apply)</b>		
		<input type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
<b>❖ User Fee Information</b>		
<input type="checkbox"/> User Fee		<input checked="" type="checkbox"/> Paid
<input type="checkbox"/> User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
<input type="checkbox"/> User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
<b>❖ Application Integrity Policy (AIP)</b>		
<input type="checkbox"/> Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<input type="checkbox"/> This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<input type="checkbox"/> Exception for review (Center Director's memo)		
<input type="checkbox"/> OC clearance for approval		
<b>❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.</b>		
		<input checked="" type="checkbox"/> Verified
<b>❖ Patent</b>		
<input type="checkbox"/> Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
<input type="checkbox"/> Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<input type="checkbox"/> For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
<b>❖ Exclusivity Summary (approvals only)</b>		
		NA
<b>❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)</b>		
		See Project Management section

## General Information

❖ Actions		
• Proposed action		( ) AP ( ) TA ( ) AE (X) NA
• Previous actions (specify type and date for each action taken)		
• Status of advertising (approvals only)		( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications		
• Press Office notified of action (approval only)		( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated		(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))		
• Division's proposed labeling (only if generated after latest applicant submission of labeling)		January 27, 2003
• Most recent applicant-proposed labeling		April 10, 2002
• Original applicant-proposed labeling		April 10, 2002
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)		See Discipline Reviews Labeling Mtg: 01/28/03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)		
Labels (immediate container & carton labels)		
• Division proposed (only if generated after latest applicant submission)		
• Applicant proposed		April 10, 2002
• Reviews		
❖ Post-marketing commitments		
• Agency request for post-marketing commitments		NA
• Documentation of discussions and/or agreements relating to post-marketing commitments		
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)		Micro – DR Letter: 10/07/02 CMC – DR Letter: 12/18/02
❖ Memoranda and Telecons		September 19, 2001
❖ Minutes of Meetings		
• EOP2 meeting (indicate date)		NA
• Pre-NDA meeting (indicate date)		August 02, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)		NA
• Other		
❖ Advisory Committee Meeting		
• Date of Meeting		NA
• 48-hour alert		
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)		NA

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	MTL: 01/22/03
❖ Clinical review(s) (indicate date for each review)	NA
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	NA
❖ Statistical review(s) (indicate date for each review)	NA
❖ Biopharmaceutical review(s) (indicate date for each review)	January 09, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) (indicate date for each review)	December 16, 2002
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See CMC Review
• Review & FONSI (indicate date of review)	NA
• Review & Environmental Impact Statement (indicate date of each review)	NA
• Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	August 12, 2002
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	NA
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
❖ CAC/ECAC report	NA

Additional Comments:

[ \_\_\_\_\_ ]

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research**

---

**DATE:** 5/20/2004

**FROM:** Joyce A Korvick, MD, MPH  
DGCDP/ODE III

**SUBJECT:** **Director (Deputy) Summary Approval Comments  
NDA 21-494**

**APPLICANT:** Reliant Pharmaceuticals, LLC.

**DRUG:** Axid® (nizatidine) Oral solution, 15mg/ml

**DIVISION RECOMMENDATION:**

The Division recommends approval of Axid Oral Solution, 15 mg/ml in adults for the following indications:

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.

It is recommended that Axid also be approved in pediatric patients 12 years of age and older for the treatment of erosive esophagitis and gastroesophageal reflux disease. Efficacy in pediatric patients less than 12 years of age has not been established.

In addition the following Chemistry, Manufacturing, and Controls postmarketing phase 4 commitments are listed below.

1. 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 date .....3rd Quarter 2004

Study start date .....1st Quarter 2005

Final report submission date .....4th Quarter 2005

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

Protocol submission date .....3rd Quarter 2004

Study start date .....1st Quarter 2005

Final report submission date .....4th 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.

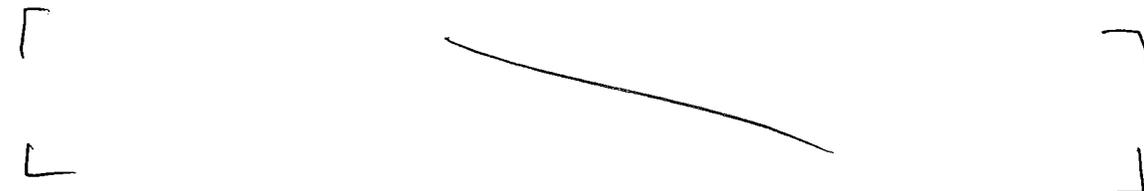
**BACKGROUND:**

Currently Axid is approved in a 150-mg capsule preparation for the treatment of active duodenal ulcer, for maintenance therapy for duodenal ulcer patients, for endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn due to GERD, and for the treatment of active benign gastric ulcer. The current NDA submission proposed this new oral liquid formulation of nizatidine (15mg/mL syrup) for use in pediatric patients for the treatment of erosive esophagitis and gastroesophageal reflux disease in pediatric patients 12 to 18 years of age at a nizatidine dosage of 150 mg bid.

On 2/10/03 an approvable letter was sent to Reliant regarding this formulation requesting adequate clinical labeling and resolution of Chemistry and Manufacturing issues. The applicant has proposed new labeling in this second review period and has addressed many of these issues. The Chemistry group has recommended approval with phase 4 commitments (see Chemistry review for specific details).

**LABELING ISSUES:**

1. Adult use is recommended for the same indications approved under the capsule formulation of Axid. Specific wording was agreed upon by the division and Reliant (see labeling text attached to the approval letter).
2. Pediatric labeling in patients 12 to 18 years of age was agreed upon by the division and Reliant.



Joyce Korvick, MD, MPH  
Deputy Division Director  
Division of Gastrointestinal and Coagulation Drug Products  
CDER/FDA

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Joyce Korvick  
5/25/04 12:14:56 PM  
MEDICAL OFFICER



NDA 21-494

**DISCIPLINE REVIEW LETTER**

Reliant Pharmaceuticals, LLC  
Attention: Robert J. Mandetta  
Director, Regulatory Affairs  
110 Allen Road  
Liberty Corner, New Jersey 07938

Dear Mr. Mandetta:

Please refer to your April 10, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nizatidine —

We refer to your submission dated November 24, 2003 (received November 25, 2003) providing a complete, class-2 response to our February 10, 2003, Approvable letter.

We further refer to your submission dated March 11, 2004. This submission contains a request for a trade name review of the name "AXID —

The review of the proposed proprietary name, AXID — for the new oral solution formulation for nizatidine is complete. Be advised that your proposed proprietary name AXID — is unacceptable. The proposed proprietary name is unacceptable for the following reasons.

[ — ]

We recommend that the dosage form be presented in conjunction with the established name (e.g., Axid Oral Solution). We request that you submit a new proprietary name to the Agency for review prior to its implementation.

If you have any questions, call Paul E. Levine, Jr., R.Ph., J.D., Regulatory Health Project Manager, at 301-827-7310.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.  
Director  
Division of Gastrointestinal and  
Coagulation Drug Products, HFD-180  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Robert Justice  
4/16/04 04:43:46 PM



Reliant Pharmaceuticals, LLC  
110 Allen Road  
Liberty Corner, NJ 07938  
908-580-1200  
Fax: 908-542-9405  
www.ReliantRx.com

April 14, 2004

Robert Justice, MD, Director  
Division of Gastrointestinal and  
Coagulation Drug Products, HFD-180  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

RECEIVED  
APR 15 2004  
FDR/CDER

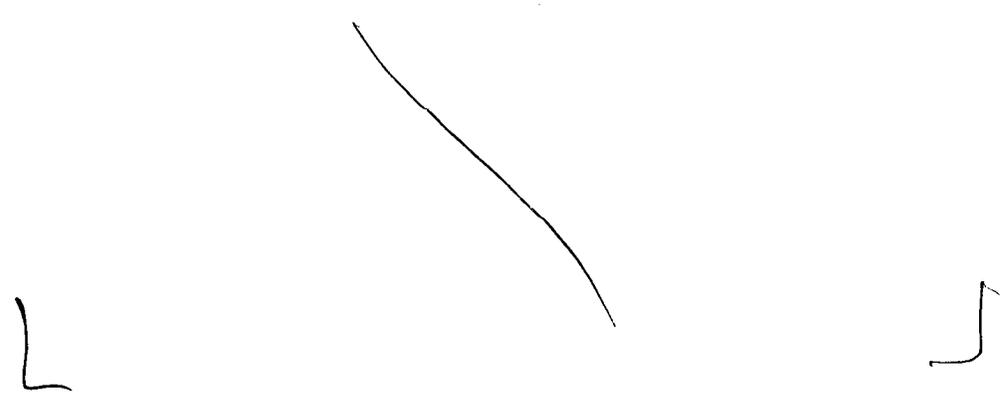
Re: **NDA 21-494**  
**Axid® — (nizatidine) Oral Solution 15 mg/mL**  
**Phase 4 Commitments – CMC Information**

Dear Dr. Justice:

Reference is made to the Reliant Pharmaceuticals, Inc. pending NDA 21-494 for Axid® — (nizatidine) Oral Solution. In addition, specific references are made to the March 11, 2004 Discipline Review (DR) Letter, the March 18, 2004 teleconference between FDA and Reliant, and the April 5, 2004 amendment to the pending NDA. In the amendment, Reliant voluntarily committed to address the issues raised in Point 1.b. of the DR Letter as Phase 4 studies.

As a condition of approval under 21 CFR 314, Subpart H, we are responding to requests from FDA to conduct post-approval research and studies. At this time, we are providing the proposed study information along with a completion schedule to identify and provide controls for degradants in the drug product (FDA's Category Code 016) for points 1.b. and 2 in the DR Letter. For convenience purposes, the FDA requests are repeated in **bold** type with the corresponding response directly following.

For the remaining subcomponent issues of point 1.b., we are providing preliminary responses and information with a commitment to submit relevant updates for complete fulfillment when information becomes available.



In order to address the above requests for degradation controls, a series of research studies will be conducted as follows:

Post Approval Commitment and Schedule

- A. Summaries and copies of all relevant chemical literature of paraben and drug substance degradants in similar dosage forms will be submitted to the Division within 90 days from the approval date of this drug product.
- B. Protocols for the following two studies will be submitted to the Division within 90 days from the approval date of this drug product:
  - 1. A study to isolate and identify, through structural characterization techniques, the degradant products of nizatidine and paraben excipients in the drug product.
  - 2. A study to investigate complexation reactions of nizatidine with excipients in the drug product.
- C. Study reports will be submitted to the Division within 12 months following review and approval of these protocols by the Division.

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.

1   Page(s) Withheld

  ✓   § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Should there be any comments or question regarding this submission or any other Chemistry, Manufacturing, and Controls issues, please contact me directly by telephone at 908-542-4403, by telefax at 908-542-4460, or by email at [pkosmoski@reliantrx.com](mailto:pkosmoski@reliantrx.com).

For ease of review, three personal desk copies of this submission are provided.

Sincerely,



Paulette F. Kosmoski  
Senior Director, Regulatory Affairs

Submitted in duplicate

Desk copies:

P. Levine

Dr. L. Zhou

Dr. R. Frankewich



NDA 21-494

**DISCIPLINE REVIEW LETTER**

Reliant Pharmaceuticals, LLC  
Attention: Robert J. Mandetta  
Director, Regulatory Affairs  
110 Allen Road  
Liberty Corner, New Jersey 07938

Dear Mr. Mandetta:

Please refer to your April 10, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nizatidine —

We refer to your submission dated November 24, 2003 (received November 25, 2003) providing a complete, class-2 response to our February 10, 2003, Approvable letter.

We further refer to your submission dated March 11, 2004. This submission contains a request for a trade name review of the names "AXID —" and "AXID —"

The review of the proposed proprietary names, AXID — and AXID — for the new oral solution formulation for nizatidine is complete. Be advised that your proposed proprietary names AXID — and AXID — are unacceptable. The proposed proprietary names are unacceptable for the following reasons.

[ \_\_\_\_\_ ]  
We recommend that the dosage form be presented in conjunction with the established name (e.g., Axid Oral Solution). We request that you submit a new proprietary name to the Agency for review prior to its implementation.

If you have any questions, call Paul E. Levine, Jr., R.Ph., J.D., Regulatory Health Project Manager, at 301-827-7310.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.  
Director  
Division of Gastrointestinal and  
Coagulation Drug Products, HFD-180  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Robert Justice  
4/13/04 01:40:24 PM



NDA 21-494

**DISCIPLINE REVIEW LETTER**

Reliant Pharmaceuticals, LLC  
Attention: Robert J. Mandetta  
Director, Regulatory Affairs  
110 Allen Road  
Liberty Corner, New Jersey 07938

Dear Mr. Mandetta:

Please refer to your April 10, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nizatidine: —

We further refer to your submissions on October 10, 17; and November 24, 2003. We considered your November 24, 2003 (received November 25, 2003) a complete, class-2 response to our February 10, 2003, Approvable letter.

We have completed the clinical review of your October 17, 2003, submission and have the following comments and recommendations:

⌈ \_\_\_\_\_ ⌋  
⌋

If you have any questions, call Paul E. Levine, Jr., R.Ph., J.D., Regulatory Health Project Manager, at 301-827-7310.

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  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Joyce Korvick  
3/30/04 04:08:29 PM  
for Dr. Robert Justice



NDA 21-494

**DISCIPLINE REVIEW LETTER**

Reliant Pharmaceuticals, LLC  
Attention: Robert J. Mandetta  
Director, Regulatory Affairs  
110 Allen Road  
Liberty Corner, New Jersey 07938

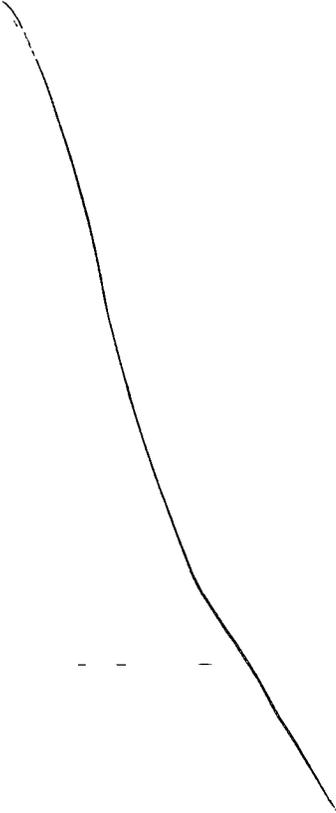
Dear Mr. Mandetta:

Please refer to your April 10, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nizatidine —

We further refer to your submissions on October 10, 17; and November 24, 2003. We considered your November 24, 2003 (received November 25, 2003) a complete, class-2 response to our February 10, 2003, Approvable letter.

Our review of the Chemistry, Manufacturing, and Control (CMC) section of your submission is complete, and we have identified the following deficiencies:

[Handwritten signature area with a large diagonal line and corner brackets]



If you have any questions, call Paul E. Levine, Jr., R.Ph., J.D., Regulatory Health Project Manager, at 301-827-7310.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.  
Chemistry Team Leader for the  
Division of Gastrointestinal and  
Coagulation Drug Products, HFD-180  
DNDC DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Liang Zhou  
3/11/04 11:56:45 AM

9 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process



NDA 21-494

**DISCIPLINE REVIEW LETTER**

Reliant Pharmaceuticals, LLC  
Attention: Robert J. Mandetta  
Director, Regulatory Affairs  
110 Allen Road  
Liberty Corner, New Jersey 07938

Dear Mr. Mandetta:

Please refer to your April 10, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nizatidine —

We also refer to your submissions dated July 12, and September 11, 2002.

Our review of the Microbiology section of your submission is complete, and we have the following identified deficiencies:

[ \_\_\_\_\_ ]

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Health Project Manager, at 301-827-7310.

Sincerely,

Liang Zhou, Ph.D.  
Chemistry Team Leader for the  
Division of Gastrointestinal & Coagulation Drug  
Products, HFD-180  
DNDC DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Liang Zhou  
10/7/02 03:53:18 PM



Reliant Pharmaceuticals, LLC  
110 Allen Road  
Liberty Corner, NJ 07938  
908-580-1200  
Fax: 908-542-9405  
www.ReliantRx.com

April 10, 2002

Via Hand Delivery

Food and Drug Administration  
Central Document Room  
12229 Wilkins Avenue  
Rockville, Maryland 20852-1833

Re: **NEW DRUG APPLICATION**  
NDA Number 21-494, Nizatidine Syrup, 15 mg/mL  
User Fee Identification Number 4306

Dear Sir or Madam:

In accordance with 21CFR 314.50, Reliant Pharmaceuticals, LLC ("Reliant") herewith submits an original new drug application for Nizatidine Syrup, 15 mg/mL. Nizatidine is indicated for the treatment of esophagitis, including erosive and ulcerative esophagitis and associated heartburn due to GERD.

Please be advised that the submission herewith is to be cross-referenced with prior Nizatidine/Axid® submissions made by \_\_\_\_\_ and by Reliant on behalf of \_\_\_\_\_, namely:

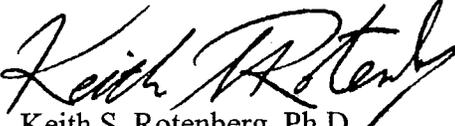
NDA Number \_\_\_\_\_  
IND Number \_\_\_\_\_

Reliant considers the information contained in this application to be confidential, and its contents are not to be disclosed without express written consent. Please address any questions or comments on this application to:

Robert J. Mandetta, Director, Regulatory Affairs  
Phone: 908-542-4429  
[rmandetta@reliantrx.com](mailto:rmandetta@reliantrx.com)

Thank You.

Sincerely,

  
Keith S. Rotenberg, Ph.D.  
Vice President, Regulatory

KSR:rw

Enclosures

4 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-\_\_\_\_\_