CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-494

CHEMISTRY REVIEW(S)

NDA 21-494

Axid (Nizatidine USP) Oral Solution

Reliant Pharmaceuticals, LLC

Raymond P. Frankewich, Ph.D.
Division of GI and Coagulation Drug Products (HFD-180)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-494

2. REVIEW #4

3. REVIEW DATE: 28-4-2004

4. REVIEWER:

Raymond P. Frankewich, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	10-04-2002
Amendment	12-07-2002
Amendment	11-09-2002
Amendment	23-10-2002
Amendment	30-10-2002
Amendment	11-02-2003
Amendment	10-10-2003
Amendment	16-02-2004
Amendment	05-04-2004
Amendment	14-04-2004
Amendment	19-04-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Reliant Pharmaceuticals, LLC
Address:	110 Allen Road Liberty Corner, NJ 07938
Representative:	Robert J. Mandetta, Director, Regulatory Affairs
Telephone:	(908) 542-4429

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Axid Oral Solution
b) Non-Proprietary Name (USAN): Nizatidine (USP) Oral Solution
c) Code Name/# (OGD only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Anti-ulcerative.

11. DOSAGE FORM: Solution (code 138)

12. STRENGTH/POTENCY: 15 mg/mL

13. ROUTE OF ADMINISTRATION: Oral (code 001)

14. Rx/OTC DISPENSED: __X__Rx ____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See page 9.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	1/31/02	LOA pg. 4-34, v. 1.2, 12/6/01.
	III			4	NA	-	-
	III			4	NA	-	-
	III			1	Adequate	1/28/03	LOA pg. 4-191 v. 1.4, 6/10/94.
	III			1	Adequate	1/24/03	LOA pg. 4-193 v. 1.4, 1/4/02.
	IV			1	Adequate	1/24/03	LOA pg. 4-63 v. 1.3, 3/4/02.
	IV			1	Adequate	1/24/03	LOA pg. 4-65 v. 1.3, 3/4/02.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Chemistry Review Data Sheet

IND	18,975	Referenced in this NDA
IND	22,422	Referenced in this NDA
NDA	19-508	Referenced in this NDA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	None	-	-
EES	Acceptable	27-4-2004	J. D'Ambrogio (HFD-324)
Pharm/Tox	None	-	-
Biopharm	None	-	-
LNC	None	-	-
Methods Validation	Pending	28-4-2004	Frankewich
OPDRA	None	-	-
EA	None	-	-
Microbiology	Recommended for approval	30-1-2003	Paul Stinavage

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-494

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
May be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
NA. For information on Phase 4 Commitment, see II.C (Basis for Approvability or Not-Approval Recommendation).

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
See CMC Review #1.

B. Description of How the Drug Product is Intended to be Used
See CMC Review #1.

C. Basis for Approvability or Not-Approval Recommendation
Resolution of the CMC concerns described in Reviews 1, 2, and 3. Phase 4 (Post - Marketing) Commitment has been provided so that, within one year, degradation products of the active substance (nizatidine) and the [redacted] (parabens) in the drug product will be isolated and identified. See comments under the heading List of Comments to be Communicated at the end of this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

12 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 1 of 4

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

/s/

Ray Frankewich
4/28/04 04:20:53 PM
CHEMIST

Liang Zhou
4/28/04 04:40:30 PM
CHEMIST
Paul: AP from a CMC point of view. However, the Phase 4 studies needs to be included in the action letter.

NDA 21-494

Axid (Nizatidine USP) Oral Solution

Reliant Pharmaceuticals, LLC

Raymond P. Frankewich, Ph.D.
Division of GI and Coagulation Drug Products (HFD-180)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-494

2. REVIEW #3

3. REVIEW DATE: 3-4-2004

4. REVIEWER:

Raymond P. Frankewich, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	10-04-2002
Amendment	12-07-2002
Amendment	11-09-2002
Amendment	23-10-2002
Amendment	30-10-2002
Amendment	11-02-2003
Amendment	10-10-2003
Amendment	16-02-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Reliant Pharmaceuticals, LLC
Address:	110 Allen Road Liberty Corner, NJ 07938
Representative:	Robert J. Mandetta, Director, Regulatory Affairs
Telephone:	(908) 542-4429

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Axid Oral Solution
b) Non-Proprietary Name (USAN): Nizatidine (USP) Oral Solution
c) Code Name/# (OGD only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Anti-ulcerative.

11. DOSAGE FORM: Solution (code 138)

12. STRENGTH/POTENCY: 15 mg/mL

13. ROUTE OF ADMINISTRATION: Oral (code 001)

14. Rx/OTC DISPENSED: __X__Rx ____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See page 9.
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
1	II	[redacted]		1	Adequate	1/31/02	LOA pg. 4-34, v. 1.2, 12/6/01.
1	III			4	NA	-	-
	III			4	NA	-	-
	III			1	Adequate	1/28/03	LOA pg. 4-191 v. 1.4, 6/10/94.
	III			1	Adequate	1/24/03	LOA pg. 4-193 v. 1.4, 1/4/02.
	IV			1	Adequate	1/24/03	LOA pg. 4-63 v. 1.3, 3/4/02.
	IV			1	Adequate	1/24/03	LOA pg. 4-65 v. 1.3, 3/4/02.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	18,975	Referenced in this NDA
IND	22,422	Referenced in this NDA
NDA	19-508	Referenced in this NDA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	None	-	-
EES	Pending (Resubmitted)	27-2-2004	J. D'Ambrogio (HFD-324)
Pharm/Tox	None	-	-
Biopharm	None	-	-
LNC	None	-	-
Methods Validation	Pending. Resolve issues concerning specification	13-12-2002	Frankewich
OPDRA	None	-	-
EA	None	-	-
Microbiology	Recommended for approval	30-1-2003	Paul Stinavage

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-494

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
See CMC Review #1.

B. Description of How the Drug Product is Intended to be Used
See CMC Review #1.

C. Basis for Approvability or Not-Approval Recommendation
Basis for the recommendation of approvable is as follows:

- Specific degradation products in the drug product, which are described in the submission, are not addressed by the drug product specifications. The components of the drug product degrade significantly when it is stored at room temperature. The degraded solution does not appear to posses toxicity (see Pharm/Tox review). However, demonstration of batch to batch consistency and product quality requires a more complete impurity profile. The applicant may choose to do this as a post-approval commitment.
- Alternatively, the applicant may choose to perform long-term storage at a refrigerated condition ———, at which the dosage for is more stable. The applicant will be asked to modify labeling, stability commitment, and the Regulatory Specification.

In a telephone conference held on February 3, 2003 (which addressed labeling), the firm proposed changing the name of the drug product from Axid® (Nizatidine USP) — to Axid® (Nizatidine USP) Oral Solution. This proposed change appears to be acceptable, based on the description of "Oral Solutions" in USP General Chapter <1151> (Pharmaceutical Dosage Forms).

The CMC issues will be communicated in a Discipline Review (DR) letter. The specific wording is provided in the List of Deficiencies to be Communicated, starting on pg. 43 of this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

34 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 24

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/s/

Ray Frankewich
3/5/04 02:31:52 PM
CHEMIST

Liang Zhou
3/5/04 03:19:32 PM
CHEMIST

NDA 21-494

Axid (Nizatidine USP) ——

Reliant Pharmaceuticals, LLC

Raymond P. Frankewich, Ph.D.
Division of GI and Coagulation Drug Products (HFD-180)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-494

2. REVIEW #2

3. REVIEW DATE: 3-2-2003

4. REVIEWER:

Raymond P. Frankewich, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	10-04-2002
Amendment	12-07-2002
Amendment	11-09-2002
Amendment	23-10-2002
Amendment	30-10-2002

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Reliant Pharmaceuticals, LLC
Address:	110 Allen Road Liberty Corner, NJ 07938
Representative:	Robert J. Mandetta, Director, Regulatory Affairs
Telephone:	(908) 542-4429

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Axid
b) Non-Proprietary Name (USAN): Nizatidine (USP)
c) Code Name/# (OGD only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Anti-ulcerative.

11. DOSAGE FORM:

12. STRENGTH/POTENCY: 15 mg/mL

13. ROUTE OF ADMINISTRATION: Oral (code 001)

14. Rx/OTC DISPENSED: __X__Rx ____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note28]:

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See page 9.
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
1	II			1	Adequate	1/31/02	LOA pg. 4-34, v. 1.2, 12/6/01.
1	III			4	NA	-	-
	III			4	NA	-	-
	III			1	Adequate	1/28/03	LOA pg. 4-191 v. 1.4, 6/10/94.
	III			1	Adequate	1/24/03	LOA pg. 4-193 v. 1.4, 1/4/02.
	IV			1	Adequate	1/24/03	LOA pg. 4-63 v. 1.3, 3/4/02.
	IV			1	Adequate	1/24/03	LOA pg. 4-65 v. 1.3, 3/4/02.

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2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	18,975	Referenced in this NDA
IND	22,422	Referenced in this NDA
NDA	19-508	Referenced in this NDA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	None	-	-
EES	Acceptable	29-1-2003	J. D'Ambrogio (HFD-324)
Pharm/Tox	None	-	-
Biopharm	None	-	-
LNC	None	-	-
Methods Validation	Pending. Resolve issues concerning specification	13-12-2002	Frankewich
OPDRA	None	-	-
EA	None	-	-
Microbiology	Recommended for approval	30-1-2003	Paul Stinavage

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-494

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
See CMC Review #1.

B. Description of How the Drug Product is Intended to be Used
See CMC Review #1.

C. Basis for Approvability or Not-Approval Recommendation
Basis for the recommendation of approvable is as follows:

- It is not clear whether specifications for individual and total impurities in the drug product are justified;
- Specific degradation products in the drug product, which are described in the submission, are not addressed by the drug product specifications;
- Drug product specifications do not appear to be adequate to demonstrate the identity, homogeneity, and certain other important physical properties (e. g. viscosity) of the dosage form;
- No recommendations are provided for the measurement of the doses.

Recommendation has been changed from Not Approvable to Approvable based on a teleconference with the applicant and evaluation of applicant's proposed responses to the concerns noted above.

In a telephone conference held on February 3, 2003 (which addressed labeling), the firm proposed changing the name of the drug product from Axid® (Nizatidine USP) —— to Axid® (Nizatidine USP) Oral Solution. This proposed change appears to be acceptable, based on the description of "Oral Solutions" in USP General Chapter <1151> (Pharmaceutical Dosage Forms).

The CMC issues will be communicated in the action letter as follows:

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.

4. Provide recommendations in the labeling (and, if necessary, supplement the container/closure system) of the drug product to facilitate the measurement of doses.

5. Address all issues discussed in the December 18, 2002 Discipline Review letter.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

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

/s/

Ray Frankewich
2/3/03 05:01:24 PM
CHEMIST

Liang Zhou
2/3/03 05:20:36 PM
CHEMIST

CHEMISTRY REVIEW

NDA 21-494

Axid (Nizatidine USP)

Reliant Pharmaceuticals, LLC

Raymond P. Frankewich, Ph.D.
Division of GI and Coagulation Drug Products (HFD-180)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-494

2. REVIEW #:1

3. REVIEW DATE: 13-12-2002

4. REVIEWER:

Raymond P. Frankewich, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	10-04-2002
Amendment	12-07-2002
Amendment	11-09-2002
Amendment	23-10-2002

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Reliant Pharmaceuticals, LLC
Address:	110 Allen Road Liberty Corner, NJ 07938
Representative:	Robert J. Mandetta, Director, Regulatory Affairs
Telephone:	(908) 542-4429

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Axid
b) Non-Proprietary Name (USAN): Nizatidine (USP)
c) Code Name/# (OGD only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Anti-ulcerative.

11. DOSAGE FORM:

12. STRENGTH/POTENCY: 15 mg/mL

13. ROUTE OF ADMINISTRATION: Oral (code 001)

14. Rx/OTC DISPENSED: __X__Rx ____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note28]:

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See page 9.
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			7	NA	-	LOA pg. 4-34, v. 1.2, 12/6/01. Review pending
	III			4	NA	-	-
	III			4	NA	-	-
	III			7	NA	-	LOA pg. 4-191 v. 1.4, 6/10/94. Review pending.
	III			7	NA	-	LOA pg. 4-193 v. 1.4, 1/4/02. Review pending.
	IV			7	NA	-	LOA pg. 4-63 v. 1.3, 3/4/02. Review pending.
	IV			7	NA	-	LOA pg. 4-65 v. 1.3, 3/4/02. Review pending.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	None	-	-
EES	Pending	13-12-2002	Frankewich
Pharm/Tox	None	-	-
Biopharm	None	-	-
LNC	None	-	-
Methods Validation	Pending. Resolve issues concerning specification	13-12-2002	Frankewich
OPDRA	None	-	-
EA	None	-	-
Microbiology	Approvable	1-8-2002	Paul Stinavage

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-494

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Axid (nizatidine) —— 15 mg/mL active. It is intended as an oral solution. It is packaged in two different configurations: a 16 fl. oz. (480 mL) — bottle with plastic closure for market [———] The drug product is a solution with — sucrose, sweetner, bubble-gum flavor, and preservatives. It has a slightly higher specific gravity than water —— The batch used for clinical trials contained slightly higher preservative concentrations than those intended for market (see pg. 17).

The drug substance is nizatidine. Nizatidine is described in USAN as an anti-ulcerative. Nizatidine is the active ingredient in one other currently marketed dosage form of Axid (capsules, which are known by the proprietary name pulvules). There is a USP monograph for Nizatidine. Nizatidine is described in DMF — for [—], its manufacturer and supplier. DMF —is currently under review.

B. Description of How the Drug Product is Intended to be Used

[———] The relationship between the dosage form and the amount of drug product dispensed to the patient is not clear, because doses described in the package insert are in terms of mg drug substance only (e. g. 150 mg per day), and no dispensing devise is described in the application. See comments in container/closure and labeling sections of this review. In the package insert, dosing schedules are provided per indication. For several, it is indicated that the dose must be individualized and calculated on a per kg basis for each patient. Recommended dose for some indications is 150 mg twice daily or 300 mg once daily. 300 mg once daily appears to be the highest recommended dose for any indication. Recommended storage conditions are similar to USP controlled room temperature (see comments in labeling section).

C. Basis for Approvability or Not-Approval Recommendation

Basis for the recommendation of not approvable is as follows:

- It is not clear whether specifications for individual and total impurities in the drug product are justified;
- Specific degradation products in the drug product, which are described in the submission, are not addressed by the drug product specifications;
- Drug product specifications deviate from the recommendations of ICH Q6A without apparent justification, potentially compromising the determinations of the identity and homogeneity of the drug product, and certain important physical properties (e. g. viscosity) of the dosage form;
- No recommendations are provided for the measurement of the doses.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

54 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 4 of 4

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

/s/

Ray Frankewich
12/13/02 08:27:34 PM
CHEMIST

The original submission of NDA 21-494, dated 10-April-2002, could not be located in "My Assignments" in DFS,
and is therefore not among the submissions listed.
This review is of the original submission and
those listed.

Liang Zhou
12/16/02 09:08:01 AM
CHEMIST