CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-494

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-494	Brand Name	Axid®
OCPB Division (I, II, III)	II	Generic Name	Nizatidine
Medical Division	DGICDP	Drug Class	H_2 blockers
OCPB Reviewer	Suliman AlFayoumi	Indication(s)	Acid related disorders
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	15 mg/ml
		Dosing Regimen	150 mg BID
Date of Submission	4/10/02	Route of Administration	Oral
Estimated Due Date of OCPB Review	1/6/03	Sponsor	Reliant Pharmaceuticals, LLC
PDUFA Due Date	2/10/03	Priority Classification	Standard
Estimated Division Due Date	2/10/03		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	---			
HPK Summary	---			
Labeling	X			
Reference Bioanalytical and Analytical Methods	---			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	---			
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	1	1	1	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	Not needed at this time	
QBR questions (key issues to be considered)	**What is the bioavailability of the syrup formulation relative to the approved nizatidine capsule?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-494, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-180(Levine), HFD-870(AlFayoumi, Doddapaneni, Malinowski, Hunt), CDR

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-494

Trade Name: Axid®

Generic Name: Nizatidine Syrup, 15 mg/ml

Sponsor: Reliant Pharmaceuticals, LLC

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Original NDA

Stamp Date: 4/10/02

ORM Division: GI & Coagulation

OCPB Division: DPE II

Team Leader: Suresh Doddapaneni

I. Executive Summary

Axid® (nizatidine) immediate release 150 mg capsules is currently approved for the treatment of acid-related disorders. The recommended oral dosage is 150 mg twice daily & 300 mg once daily at bedtime.

The absolute bioavailability of nizatidine after oral administration exceeds 70%. Over 90% of an oral dose of nizatidine (including 60% unchanged drug) is excreted in the urine within 12 hrs. Accumulation is not expected with BID dosing in adult individuals with normal renal function as nizatidine is rapidly cleared with a half-life of 1-2 hrs. The primary metabolite excreted in urine is N-desmethyl-nizatidine (~7% of P.O. nizatidine dose).

In the current NDA, Nizatidine Syrup, 15 mg/ml is proposed as a new alternative administration option in adult & pediatric patients. A single relative bioavailability study has been submitted in support of the safety and efficacy of the nizatidine syrup formulation. In this study, the syrup was found to be bioequivalent to the approved capsules.

Recommendation

NDA 21-494 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/DPE II), and from the view point of OCPB, the submission is acceptable provided that a satisfactory agreement is reached on the package insert between the Agency and the sponsor. See Appendix 1 for the Agency's proposed revisions to the Clinical Pharmacology-related sections of Axid® package insert. Any additional revisions to the Axid® labeling will be included in an addendum to the current review

II. Summary of CPB Findings

The currently approved nizatidine formulation is Axid® IR capsule 150 mg (NDA 19-508).

NDA 21-494 seeks approval of the syrup formulation, which was originally developed as an age appropriate formulation for use in pediatric patients, and is supported by the same relative bioavailability study (study

In study AX9006, the relative bioavailability of the capsule contents administered in apple juice and in infant formula, as well as the new oral syrup formulation was determined relative to that of the intact capsule in a four-way crossover study in healthy adult subjects. The study demonstrated that the syrup and the capsule contents administered in infant formula were bioequivalent to the intact capsule (Table 1). However, administration of the capsule contents in apple juice resulted in a significantly reduced bioavailability (27% lower AUC & 44% lower Cmax) relative to the intact capsule. The sponsor has hypothesized that apple juice inhibits an Organic Cation Transporter, which might be involved in the absorption of nizatidine. Based on this comparative bioavailability study, the new nizatidine syrup is an appropriate alternative administration option for use in pediatric & adult patients.

Table 1. Summary of the geometric means and 95% confidence intervals for the primary PK parameters of the four administration options studied in study AX9006

	Syrup	Infant Formula	Apple Juice	Capsule
$AUC_{0-\tau}$ (ng·hr/ml)	3445.2 CI: 95-101	3356.9 CI: 92-98	2531.8 CI: 69-76	3538.2 ---
$AUC_{0-\infty}$ (ng·hr/ml)	3550.8 CI: 95-101	3455.2 CI: 93-98	2653.3 CI: 70-77	3460.6 ---
Cmax (ng/ml)	1290.0 CI: 94-109	1135.1 CI: 83-96	738.9 CI: 54-64	1297.9 ---

II. Table of Contents

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III. Question-Based Review

A. General Attributes

Axid® (nizatidine), a competitive inhibitor of histamine at the H_2 receptor, was first approved in the US in 1988. Axid® has been shown to significantly inhibit nocturnal gastric acid secretion for up to 12 hours. Axid® also significantly inhibits gastric acid secretion stimulated by food, caffeine, betazole, and pentagastrin. It currently is being marketed at 150 mg BID & 300 mg QD for the treatment of a variety of acid-related conditions.

The absolute bioavailability of nizatidine after oral administration of Axid® exceeds 70%. Over 90% of an oral dose of nizatidine (including 60% unchanged drug) is excreted in urine within 12 hrs. Accumulation is not expected with BID dosing in individuals with normal renal function as nizatidine is rapidly cleared with a half-life of 1-2 hrs. The primary metabolite excreted in urine is N-desmethyl-nizatidine (~7% of P.O. nizatidine dose).

B. General Biopharmaceutics

1. What is the nature of the formulation?

Nizatidine syrup, 15 mg/ml is a new formulation originally developed by the sponsor to serve as a bona fide age-appropriate pediatric formulation. The composition of the syrup formulation is shown in Table 1.

Table 1. Qualitative composition of the nizatidine syrup

Component, Grade Quality	Function	% w/v
Nizatidine, USP	Active ingredient	1.50
Methylparaben, NF		
Propylparaben, NF		
Glycerin, USP		
Sodium Alginate, NF		
Purified Water, USP		
Sodium Chloride, USP		
Saccharin Sodium, USP		
Sodium Citrate Dihydrate, USP		
Citric Acid Anhydrous, USP		
Sucrose, NP		
Flavor, Bubble Gum		
Artificial Sweetness Enhancer		
Sodium Hydroxide, NF		

2. How do nizatidine syrup & Axid® 150 mg capsules compare on the bioavailability of nizatidine?

In study AX9006, the relative bioavailability of the capsule contents administered in apple juice and in infant formula, as well as the new oral syrup formulation was determined relative to that of the intact capsule in a four-way crossover study in healthy adult subjects. The study demonstrated that the syrup and the capsule contents administered in infant formula were bioequivalent to the intact capsule (Table 1). However, administration of the capsule contents in apple juice resulted in a significantly reduced bioavailability (27% lower AUC & 44% lower Cmax) relative to the intact capsule. The sponsor has hypothesized that apple juice inhibits an Organic Cation Transporter, which might be involved in the absorption of nizatidine. However, with the availability of syrup formulation, this is not an issue from a practical point of view.

Table 1. Summary of the geometric means and 95% confidence intervals for the primary PK parameters of the four administration options studied in study AX9006

	Syrup	Infant Formula	Apple Juice	Capsule
$AUC_{0-\tau}$ (ng·hr/ml)	3445.2 CI: 95-101	3356.9 CI: 92-98	2531.8 CI: 69-76	3538.2 ---
$AUC_{0-\infty}$ (ng·hr/ml)	3550.8 CI: 95-101	3455.2 CI: 93-98	2653.3 CI: 70-77	3460.6 ---
Cmax (ng/ml)	1290.0 CI: 94-109	1135.1 CI: 83-96	738.9 CI: 54-64	1297.9 ---

Appendix 1

Proposed Package Insert

11 Page(s) Withheld

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

__✓__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1 of 1

Appendix 2

Individual Study Reviews

Study #: AX 9006 **Study Date: Jan 2002**

Type of Study: Bridging Relative Bioavailability Study

Study AX9006 is entitled,

"AN OPEN-LABEL, SINGLE-DOSE, RANDOMIZED, FOUR-WAY CROSSOVER STUYD TO EVALUATE THE BIOEQUIVALENCE OF NIZATIDINE FROM EXTEMPORANEOUS ORAL SOLUTIONS USED IN PEDIATRIC CLINICAL TRIALS WITH A PROTOTYPE NIZATIDINE LIQUID FORMULATION INTENDED FOR PEDIATRIC USE AND TO ASSESS THE RELATIVE BIOAVAIALBILITY OF THE ORAL SOLUTIONS AND PROTOTYPE LIQUID FORMULATION TO A 150 mg AXID® CAPSULE IN HEALTHY SUBJECTS"

Objectives

- To evaluate the relative bioavailability of 150 mg of the oral preparations in apple juice and formula, and 150 mg of the prototype syrup formulation to a 150 mg capsule.

Study Design

Open-label, randomized, single-dose, 4-way crossover relative bioavailability study

Subjects 24 healthy adults

Treatment Subjects were randomized to receive 150 mg nizatidine dissolved in infant formula, apple juice, or prototype syrup, or as intact capsule.

PK Sampling Samples were collected for determination of nizatidine and its N-desmethyl metabolite in plasma at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 & 24 hrs post-dose.

Pharmacokinetics/Pharmacodynamics

The following pharmacokinetic parameters were determined for nizatidine and its desmethyl metabolite: **T_{max}, C_{max}, $t_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$, CL/f and V_d/f.**

Results & Conclusions

Table 2. Summary of the primary PK parameters following administration of the four oral nizatidine formulations

Parameter	Treatment			
	Syrup	Apple Juice	Formula	Capsule
C_{max} (ng/mL)	1340.6 ± 378.6 (0.28)	762.8 ± 195.7 (0.26)	1178.4 ± 327.4 (0.28)	1367.6 ± 452.9 (0.33)
T_{max} (h)	0.77 ± 0.40 (0.52)	1.31 ± 0.41 (0.31)	0.94 ± 0.39 (0.42)	1.02 ± 0.48 (0.47)
AUC_{0-T} (ng•h/mL)	3510.0 ± 689.4 (0.20)	2578.1 ± 491.3 (0.19)	3410.9 ± 634.0 (0.19)	3605.0 ± 713.6 (0.20)
$AUC_{0-\infty}$ (ng•h/mL)	3610.9 ± 674.7 (0.19)	2694.1 ± 472.8 (0.18)	3506.6 ± 626.9 (0.18)	3703.1 ± 702.0 (0.19)
Kel (1/h)	0.518 ± 0.099 (0.19)	0.428 ± 0.085 (0.20)	0.526 ± 0.083 (0.16)	0.531 ± 0.119 (0.22)
T½ (h)	1.38 ± 0.26 (0.19)	1.69 ± 0.39 (0.23)	1.35 ± 0.25 (0.18)	1.37 ± 0.29 (0.21)
Cl/F (L/h)	43.0 ± 8.2 (0.19)	57.5 ± 10.8 (0.19)	44.0 ± 7.5 (0.17)	41.9 ± 8.0 (0.19)
Vd/F (L)	86.4 ± 26.5 (0.31)	142.3 ± 49.8 (0.35)	86.5 ± 25.0 (0.29)	83.4 ± 26.9 (0.32)

Table 3. Summary of the results of bioequivalence assessment following administration of the four oral nizatidine formulations

Parameter/Statistic	Syrup[a]	Apple Juice[a]	Formula[a]	Capsule[b]
AUC_{0-T} (ng•hr/mL)				
Adjusted Mean	3445.2	2531.8	3356.9	3538.2
Ratio	0.97	0.72	0.95	-
90% CI	95-101	69-76	92-98	-
$AUC_{0-\infty}$ (ng•hr/mL)				
Adjusted Mean	3550.8	2653.3	3455.2	3640.6
Ratio	0.98	0.73	0.95	-
90% CI	95-101	70-77	93-98	-
C_{max} (ng/mL)				
Adjusted Mean	1290.0	738.9	1135.1	1297.9
Ratio	0.99	0.57	0.87	-
90% CI	94-109	54-64	83-96	-

[a] Test
[b] Reference
CI: Confidence Interval

- As shown by Tables 2 & 3, the syrup formulation as well as the infant formula preparation was bioequivalent to the intact capsule. However, the apple juice preparation was deemed bioinequivalent to the intact capsule on both Cmax (reduced by 43%) and AUC (reduced by 27%). The sponsor hypothesizes that this might be due to apple juice inhibiting the organic cation transporter, for which nizatidine is a substrate. Irrespective of the mechanism involved, the same observation has been reported earlier in literature (Sullivan *et al.*, 1995).

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