CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-494

MEDICAL REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	21-494
DRUG NAME:	Axid Oral Solution (Nizatidine)
ROUTE OF ADMINISTRATION:	Oral
INDICATION:	treatment of the signs and symptoms of erosive esophagitis and gastroesophageal reflux disease in adults and children aged 12 to 18 years old.
SPONSOR:	Reliant Pharmaceuticals, LLC
DATE SUBMITTED:	November 24, 2003
DATE RECEIVED:	November 25, 2003
REVIEW COMPLETED:	April 15, 2004
REVIEWER:	Ann Marie Trentacosti, M.D.

INTRODUCTION:
NDA # 21-494 (Axid ___) was originally submitted by the sponsor on April 10, 2002. The proposed indication in this submission was for use in pediatric patients for the treatment of the signs and symptoms of erosive esophagitis and gastroesophageal reflux disease.
An approvable letter sent by DGCDP on February 10, 2003 delineated the following clinical deficiencies:

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, DGCDP stated that 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.

On October 14, 2003, the sponsor submitted a response to the Division's approvable letter. The submission included labeling for adult and pediatric patients 12 to 18 years of age.

Sponsor's Proposed Labeling and Review Comments:
The proposed draft labeling submitted by the sponsor was compared to the recommended draft-labeling revision which DGCDP sent to the sponsor on January 30, 2003 concerning nizatidine

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Ann Marie Trentacosti
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MEDICAL OFFICER

Hugo Gallo Torres
4/15/04 03:43:20 PM
MEDICAL OFFICER

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	21-494 N000(C)
DRUG NAME:	Axid® Oral Solution (Nizatidine)
ROUTE OF ADMINISTRATION:	Oral
INDICATION:	Treatment of the signs and symptoms of erosive esophagitis and gastroesophageal reflux disease in adults and children aged 12 to 18 years old.
SPONSOR:	Reliant Pharmaceuticals, LLC
DATE SUBMITTED:	October 17, 2003
REVIEW COMPLETED:	March 9, 2004
REVIEWER:	Ann Marie Trentacosti, M.D.

INTRODUCTION:
NDA # 21-494 (Axid® , —— was originally submitted by the sponsor on April 10, 2002. The proposed indication in this submission was for use in pediatric patients for the treatment of the signs and symptoms of erosive esophagitis and gastroesophageal reflux disease.
An approvable letter sent by DGCDP on February 10, 2003 delineated the following clinical deficiencies:

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.

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_____ § 552(b)(5) Deliberative Process

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Ann Marie Trentacosti
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MEDICAL OFFICER

Hugo Gallo Torres
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MEDICAL OFFICER

Memorandum

DATE: January 9, 2003

FROM: Medical Team Leader (GI Drugs)
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

SUBJECT: Recommendations for Regulatory Action: NDA 21-494 / Pediatric Supplement
Axid (nizatidine) ___ formulation, 15 mg/ml
Sponsor: Reliant Pharmaceuticals, Liberty Corner, NJ
Date Submitted: April 10, 2002

TO: Division File, NDA 21-494

I. BACKGROUND/INTRODUCTION

Axid® (nizatidine) is an H2-receptor antagonist available in the US since 1988. Nizatidine capsules 150 mg bid and 300 mg qd are approved for the treatment of a variety of clinical conditions where inhibition of acid secretion is needed. Included among these adults indications are treatment of active duodenal ulcer (DU), maintenance therapy to prevent recurrence of DU, treatment of endoscopically diagnosed esophagitis and associated heartburn related to gastroesophageal reflux disease (GERD) and treatment of benign gastric ulcer (GU). The recommended oral dosage for the currently approved indications is 150 mg twice-a-day ans 300 mg once-a-day at bedtime.

It is to be noted that the absolute bioavailability of nizatidine after oral dosage (capsules) exceeds 70%. More than 90% of the orally administered drug, including 60% of non-metabolized nizatidine), is excreted in the urine within 24h. As pointed out by the Biopharm reviewer (Dr. S. Al-Fayoumi, accumulation is not expected with twice-a-day dosing in adult individuals with normal renal function in whom nizatidine is rapidly cleared with a half-life of 1 to 2 h.. The Biopharm reviewer also notes that the primary urinary metabolite is N-desmethyl-nizatidine (ca. 7% of the orally administered nizatidine dose).

- In the currently approved labeling, it is stipulated that safety and effectiveness in pediatric patients has not been established.

- In the current NDA submission, the sponsor proposes a change in the labeling that will instruct usage of a new oral formulation (~~~), 15 mg/ml, which is proposed as an alternative administration option in adult and pediatric patients.

- [redacted]

- In support of the safety and efficacy of the proposed Nizatidine syrup formulation, 15 mg/ml, the sponsor submitted a single bioavailability study designed to determine if the serum formulation is bioequivalent to the approved capsules.

II. SUCCINCT CONCLUSIONS FROM REVIEWS/PENDING ISSUES

- The materials submitted by the sponsor under NDA 21-494, were reviewed by Drs. S. Al-Fayoumi (Biopharm), R.P. Frankewich (Chemistry). . A consult Review on Microbiology, carried out by Dr. Stinavage, was included as part of the CMC deficiencies. The conclusions from these reviews are briefly summarized below.

- The Biopharm reviewer concluded that, from the viewpoint of OCPB, the submission is acceptable provided that a satisfactory agreement is reached on the package insert between the Agency and the sponsor. In Appendix 1 of the Biopharm review, Dr. Al-Fayoumi proposed revisions to the clinical Pharmacology-related sections of AXID® package insert.

  It is to be noted that the Biopharm recommendations for package insert revisions are considered in the current review (see Section IV).

- The Chemistry reviewer identified 28 CMC deficiencies. These were condensed to 20 (1 related to the drug substance and 19 to the drug product) and communicated to the sponsor in writing.. Although not all CMC deficiencies are major, in the final analysis, they are considered approvability issues that need to be resolved before approval of NDA 21-494 can be recommended.

- The current secondary review is concerned almost exclusively with labeling changes proposed by the sponsor, taking into considerations the revisions proposed by FDA reviewers.

III. REGULATORY RECOMMENDATION

- NDA 21-494 is approvable until the following two issues are resolved.

    1. The CMC deficiencies identified by the Chemistry reviewer.
    2. Agreement is reached between the Agency and Reliant Pharmaceuticals, LLC on the proposed labeling revisions.

IV. RECOMMENDED LABELING REVISIONS (Appendix 1)

As previously stated, the labeling revisions recommended in Appendix 1 include not only the MTL recommendations but also those from the reviewers from the other disciplines.

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Hugo Gallo Torres
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MEDICAL OFFICER
This secondary review incorporates the up to date recommendations for labeling revisions from all disciplines.