

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-327**

**PHARMACOLOGY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-327  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: July 16, 2008  
PRODUCT: Prevacid Lansoprazole delayed-release capsules  
15 mg  
INTENDED CLINICAL POPULATION: Frequent heartburn (occurs 2 or more days a  
week) in adults 18 years of age and older  
APPLICANT: Novartis Consumer Health, Inc  
DOCUMENTS REVIEWED: Vol. 1  
REVIEW DIVISION: Division of Nonprescription Clinical Evaluation  
(HFD-560)  
PHARM/TOX REVIEWER: Cindy Li, Ph.D.  
PHARM/TOX SECONDARY REVIEWER: Wafa Harrouk, Ph.D.  
PHARM/TOX SUPERVISOR: Paul Brown, Ph.D.  
DIVISION DIRECTOR: Andrea Leonard-Segal, M.D.  
PROJECT MANAGER: Mary Lewis, RPM

Date of review submission to Division File System (DFS): Mar 23, 2009

## ***EXECUTIVE SUMMARY***

### **A. Recommendation on approvability**

This is a 505(b)(1) application. The applicant is switching from prescription to OTC self medication status relying on data submitted under NDA 20-406, for which they have full rights to the supporting data. Based on the risk-benefit analysis and the experience of human use, NDA 22-327 can be approved from the nonclinical perspective.

### **B. Recommendation for nonclinical studies**

There are no outstanding pharmacology/ toxicology issues.

**Appears This Way  
On Original**

**PHARMACOLOGY/TOXICOLOGY REVIEW****NDA number:** 22-327**Review number:** 1**Sequence number/date/type of submission:** SN000/ 07/15/2008 /NDA**Information to sponsor:** Yes ( ) No (x)**Sponsor and/or agent:** Novartis Consumer Health, Inc.**Reviewer name:** Cindy Li, Ph.D.**Division name:** DNCE, Office of Nonprescription Products (ONP)**HFD #:** 560**Review completion date:** 3/13/2009**Drug:** Prevacid24HR (15mg lansoprazole) capsules**Drug class:** proton pump inhibitor**Intended clinical population:** Treatment of frequent heartburn**Route of administration:** Oral capsule**Proposed clinical protocol:** None**Drug:**

Trade name: Prevacid 24 HR

Generic name: Prevacid 24 HR(15mg lansoprazole) capsules

Synonyms: Abbott-65006, AG-1749, Prevacid

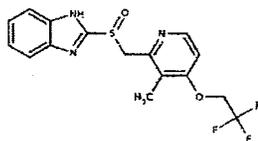
Chemical name: 1H-Benzimidazole, 2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)

CAS registry number: 103577-45-3

Molecular formula: C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S

Molecular weight: 369.37

Structure:

**Relevant INDs/NDAs/DMFs:**

IND: 74,256 (lansoprazole delayed release capsules) / 30,159 / 58,341,

NDA: 20-406 and supplements / 21-281

DMF:

b(4)

b(4)

**Data reliance:** Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-327 are owned by Novartis Consumer Health, Inc. or are data for which Novartis Consumer Health, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-327 that Novartis Consumer Health, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Novartis Consumer Health, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-327.

**Background:**

Prevacid delayed-release capsules, 15 mg, contain the active ingredient lansoprazole in a two piece hard gelatin capsule with a black tamper-evident band for oral ingestion. The product is being proposed to treat frequent heartburn (which occurs 2 or more days a week) in adults 18 years of age and older. The recommended maximum daily dosage is 1 capsule prior to eating breakfast, and the maximum duration of dosing is 14 days. The treatment can be repeated once every 4 months.

This is an application to switch Prevacid Delayed-Release capsules dosage strength 15 mg from prescription to OTC status. Reference is made by the applicant to NDA 20-406, Prevacid® approved on May 10, 1995 and its subsequent supplements. Novartis Consumer Health, Inc. has obtained full written right of reference to the supporting information in NDA 20-406.

**Pharmacology/Toxicology Review:**

The in-depth review of nonclinical safety information can be found in NDA 20-406 and its corresponding supplements. A review of recently published pharmacology and toxicology studies (non-GLP) is provided below.

The nonclinical section in this application includes the nonclinical summaries from NDA 20-406 and supplements. New relevant published literature (as of the end of 2007) was also provided: A total of 11 publications were submitted including six clinical studies and five nonclinical publications (Blandizzi et al 2005; Ichikawa et al 2004; Kuroda et al 2006 in secondary pharmacodynamics; Youssef et al 2003 in Reproductive and developmental toxicity; and Coulson et al 2003 in testosterone-related studies). The five

nonclinical publications are summarized in this review. Clinical publications will be discussed by the clinical reviewer of this NDA.

1. Blandizzi et al. reported in 2005 that lansoprazole has anti-inflammatory properties through inhibition of neutrophil activation induced by NSAIDS in rats. Ichikawa et al. (2004) and Kuroda et al. (2006) suggested that lansoprazole at a dose of 1 mg/kg may protect against some types of mucosal injury via an anti-inflammatory effect in rats. Ichikawa reported that lansoprazole ameliorated acid-unrelated intestinal mucosal damage induced by ischemia-reperfusion in rats. Kuroda showed that lansoprazole reduced indomethacin-induced lipid peroxidation and intestinal mucosal inflammation through inhibition of cytokine-induced neutrophil chemoattractant-1 (CINC-1) production in the intestinal mucosa.

2. A lansoprazole juvenile toxicity study was conducted by Youssef et al. in 2003 in Sprague-Dawley rats from weaning through sexual maturity at doses of 0, 5, 15, 50, or 150 mg/kg/day. No unexpected signs of toxicity were observed in the preadolescent rats relative to those previously observed in adult rats based on the study report. This study revealed that the area under the curve (AUC) values in 21-day-old rats were higher than those observed in 60-day-old rats, and higher in females than male 60-day-old rats. However, the proposed NDA does not include the patient population younger than 18 year-old.

3. Coulson et al. reported in 2003 that lansoprazole induced hepatic CYP-dependent testosterone metabolism and enhanced its plasma clearance in rats at 150 mg/kg/day for 14 days. This dose provides a large safety margin of 600-fold when compared to the proposed dose of 0.25 mg/kg/day based on a dose of 15 mg/60 kg (average body weight/day as proposed in this NDA).

**Conclusions:** Based on the risk-benefit analysis of the existing nonclinical information, the recently published nonclinical information and the experience of human use, NDA 22-327 can be approved from the nonclinical perspective for adults over 18 years of age.

#### OVERALL CONCLUSIONS AND RECOMMENDATIONS

On overview of the NDA application: there are no outstanding pharmacology/ toxicology issues.

Unresolved toxicology issues (if any): None

Recommendations: NDA22-327 can be approved from the nonclinical perspective.

Reviewer Signature \_\_\_\_\_

Supervisor Signature \_\_\_\_\_ Concurrence Yes \_\_\_ No \_\_\_

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Xinguang Li  
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Please sign. Thanks!

Paul Brown  
3/24/2009 10:04:37 AM  
PHARMACOLOGIST

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 22-327    **Applicant:** Novartis Consumer Health, Inc    **Stamp Date:** July 16, 2008

**Drug Name:** Prevacid    **NDA Type:** 505(b)(1)  
Lansoprazole delayed-release capsules 15 mg

**Background:** Prevacid Lansoprazole delayed-release capsules, 15 mg, contain the active ingredient lansoprazole in a two piece hard gelatin capsule with a black tamper-evident band for oral ingestion. The product is being proposed to treat frequent heartburn (occurs 2 or more days a week) in adults 18 years of age and older. The recommended maximum daily dosage is 1 capsule, and the maximum duration of dosing is 14 days. The treatment can be repeated once every 4 months. Self-medication is recommended prior to eating breakfast.

This is an application to switch Prevacid Delayed-Release capsules dosage strength 15 mg from prescription to self medication status. Reference is made by the sponsor to NDA 20-406, Prevacid® approved May 10, 1995 and subsequent supplements.

On initial overview of the NDA application: There are no outstanding pharmacology/toxicology issues since there is no requirement for additional pharmacology/toxicology information to be submitted at this time in the section.

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	x		Yes- this is a 505(b)(1) application. The sponsor is relying on data submitted under NDA 20-406
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?			N/A-see 1
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?			N/A-see 1
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?	x		Yes-see 1
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the			N/A

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A  
NEW NDA/BLA**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
	appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route?	x		Yes-see 1
7	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	If there are any impurities – etc. issues, have these been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the sponsor addressed any abuse potential issues in the submission?			N/A
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?	x		Yes- The sponsor is relying on data submitted under NDA 20-406
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	x		

Cindy Li

Sep 12 2008

Reviewing Pharmacologist

Date

Paul Brown

Sep 12 2008

Team Leader/Supervisor

Date

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/s/

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Xinguang Li  
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Revised Doc

Paul Brown  
9/12/2008 04:30:45 PM  
PHARMACOLOGIST