CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78-730

Name: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

Sponsor: Teva Pharmaceuticals USA

Approval Date: October 15, 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-730

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-730

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 078730

Teva Pharmaceuticals USA
Attention: Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 27, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg.

Reference is also made to your amendments dated October 12, 2007; March 27, June 11, and October 5, 2009; and March 22, May 7, May 18, June 11, August 12, September 8, September 14, and September 15, 2010 (2 submissions).

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Prevacid SoluTab Delayed-release Orally Disintegrating Tablets of Takeda Pharmaceuticals North America, Inc. (Takeda).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The “interim” dissolution specifications are as follows:

> Dissolution testing should be conducted by following the FDA-recommended dissolution method and specifications:

Medium: 500 mL of 0.1N HCl for the first hour, followed by 900 mL of phosphate buffer pH 6.8, with 5 mM SDS (second hour)

Temperature: 37°C
Apparatus: USP II (paddles)
Rotation: 75 rpm

Specifications: Acid stage: NMT (b) (4) in 60 minutes
Buffer stage: NLT (b) (4) % (Q) in 30 minutes

These "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement - Changes Being Effected" when there are no revisions to be made to the "interim" specifications or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, Takeda's Prevacid Delayed-Release Orally Disintegrating Tablets, is subject to periods of patent protection. The following unexpired patents and their expiration dates (with pediatric exclusivity added) are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
5,464,632 (the '632 patent)	May 7, 2012
6,328,994 (the '994 patent)	November 17, 2019
7,399,485 (the '485 patent)	November 26, 2018
7,431,942 (the '942 patent)	November 17, 2019

With respect to the '485 and '942 patents, the agency recognizes that these patents were late listed with respect to your ANDA and no certification is required. See 21 CFR 314.94(a)(12)(vi).

With respect to the '632 and '994 patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of

an ANDA shall be made effective immediately, unless an action was brought against Teva Pharmaceuticals USA (Teva) for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. You notified the agency that Teva complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '632 and '994 patents was brought against Teva in the United States District Court for the District of Delaware [Takeda Pharmaceutical Company Limited, TAP Pharmaceutical Products, Inc., and Ethypharm, SA v. TEVA Pharmaceuticals USA and TEVA Pharmaceutical Industries Ltd., Civil Action No. 07-331]. You also notified the agency that the court decided that the '632 patent is not infringed, and the '994 patent infringement lawsuit was dismissed in an agreement with Takeda. Therefore, under section 505(j)(5)(B)(iii) your ANDA is eligible for approval.

With respect to 180-day generic drug exclusivity, the agency has concluded that Teva was the first ANDA applicant to submit a substantially complete ANDA for Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg, with paragraph IV certifications to the ‘632 and ‘994 patents. Therefore, with this approval, Teva may be eligible for 180 days of generic drug exclusivity for Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg. Generic drug exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, begins to run from the date of commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date commercial marketing begins. The agency notes that Teva failed to obtain tentative approval of this ANDA within 30 months after the date on which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the Act. However, the agency is not making a formal determination at this time of Teva’s eligibility for 180-day generic drug exclusivity. It will do so only if another applicant becomes eligible for approval within 180 days after Teva begins commercial marketing of Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U_CM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Generic Drugs
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 L WEST

10/15/2010

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-730

LABELING

NDC 0093-7448-65

LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS
15 mg

Each tablet contains:
lansoprazole as enteric-coated microgranules 15 mg

Phenylketonurics: Contains Phenylalanine 3.71 mg Per Tablet.

PACKAGE NOT CHILD-RESISTANT
This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

℞ only

30 TABLETS (3 blister cards x 10 tablets)

TEVA

NDC 0093-7448-65
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS
15 mg

333-30-100035

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-7448-65 5

NDC 0093-7448-65

LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS
15 mg

Each tablet contains:
lansoprazole as enteric-coated microgranules 15 mg

Phenylketonurics: Contains Phenylalanine 3.71 mg Per Tablet.

PACKAGE NOT CHILD-RESISTANT
This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

℞ only

30 TABLETS (3 blister cards x 10 tablets)

TEVA

Usual Dosage: See package insert for full prescribing information including Nasogastric Tube Administration.

PHARMACIST INSTRUCTIONS FOR THE PATIENT:

Please inform patients of the following instructions for product use:

Lansoprazole delayed-release orally disintegrating tablets should not be chewed. Lansoprazole delayed-release orally disintegrating tablets should be taken before eating. Place the tablet on the tongue and allow it to disintegrate, with or without water, until the particles can be swallowed.

Alternatively for children or other patients who have difficulty swallowing tablets, lansoprazole delayed-release orally disintegrating tablets can be delivered via oral syringe.

- Place a 15 mg tablet in oral syringe and draw up approximately 4 mL of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, administer the contents within 15 minutes.
- Refill the syringe with approximately 2 mL of water, shake gently, and administer any remaining contents.

Rev. A 1/2009

12345
67890

NDC 0093-7449-65

LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS
30 mg

Each tablet contains:
lansoprazole as enteric-coated microgranules 30 mg

Phenylketonurics: Contains Phenylalanine 7.41 mg Per Tablet.

PACKAGE NOT CHILD-RESISTANT
This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

℞ only

30 TABLETS (5 blister cards x 6 tablets)

TEVA

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-7449-65 2

NDC 0093-7449-65
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS
30 mg

NDC 0093-7449-65

LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS
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Each tablet contains:
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PACKAGE NOT CHILD-RESISTANT
This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

℞ only

30 TABLETS (5 blister cards x 6 tablets)

TEVA

Usual Dosage: See package insert for full prescribing information including Nasogastric Tube Administration.

PHARMACIST INSTRUCTIONS FOR THE PATIENT:

Please inform patients of the following instructions for product use:

Lansoprazole delayed-release orally disintegrating tablets should not be chewed. Lansoprazole delayed-release orally disintegrating tablets should be taken before eating. Place the tablet on the tongue and allow it to disintegrate, with or without water, until the particles can be swallowed.

Alternatively for children or other patients who have difficulty swallowing tablets, lansoprazole delayed-release orally disintegrating tablets can be delivered via oral syringe.

- Place a 30 mg tablet in oral syringe and draw up approximately 10 mL of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, administer the contents within 15 minutes.
- Refill the syringe with approximately 5 mL of water, shake gently, and administer any remaining contents.

Rev. A 1/2009

NDC 0093-**7448**-19

Lansoprazole Delayed-Release Orally Disintegrating Tablet
15 mg ℞ only

Phenylketonurics: Contains
Phenylalanine 3.71 mg per tablet
Mfd. By: Iss. 12/2008
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot: Exp:

(01)00300937448198

NDC 0093-**7448**-19

Lansoprazole Delayed-Release Orally Disintegrating Tablet
15 mg ℞ only

Phenylketonurics: Contains
Phenylalanine 3.71 mg per tablet
Mfd. By: Iss. 12/2008
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot: Exp:

(01)00300937448198

NDC 0093-**7448**-19

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15 mg ℞ only

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Phenylalanine 3.71 mg per tablet
Mfd. By: Iss. 12/2008
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot: Exp:

(01)00300937448198

NDC 0093-**7448**-19

Lansoprazole Delayed-Release Orally Disintegrating Tablet
15 mg ℞ only

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Mfd. By: Iss. 12/2008
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot: Exp:

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(01)00300937448198

NDC 0093-**7448**-19

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15 mg ℞ only

Phenylketonurics: Contains
Phenylalanine 3.71 mg per tablet
Mfd. By: Iss. 12/2008
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot: Exp:

(01)00300937448198

NDC 0093-**7449**-19

Lansoprazole Delayed-Release Orally Disintegrating Tablet

30 mg ℞ only

Phenylketonurics: Contains
Phenylalanine 7.41 mg per tablet
Mfd. By: Iss. 12/2008
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot: Exp:

(01)00300937449195

NDC 0093-**7449**-19

Lansoprazole Delayed-Release Orally Disintegrating Tablet

30 mg ℞ only

Phenylketonurics: Contains
Phenylalanine 7.41 mg per tablet
Mfd. By: Iss. 12/2008
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot: Exp:

(01)00300937449195

NDC 0093-**7449**-19

Lansoprazole Delayed-Release Orally Disintegrating Tablet

30 mg ℞ only

Phenylketonurics: Contains
Phenylalanine 7.41 mg per tablet
Mfd. By: Iss. 12/2008
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot: Exp:

(01)00300937449195

NDC 0093-**7449**-19

Lansoprazole Delayed-Release Orally Disintegrating Tablet

30 mg ℞ only

Phenylketonurics: Contains
Phenylalanine 7.41 mg per tablet
Mfd. By: Iss. 12/2008
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot: Exp:

(01)00300937449195

NDC 0093-**7449**-19

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Mfd. By: Iss. 12/2008
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Lot: Exp:

(01)00300937449195

7448
7449

LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS

℞ only

Iss. 9/2010

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use lansoprazole delayed-release orally disintegrating tablets safely and effectively. See full prescribing information for lansoprazole delayed-release orally disintegrating tablets.

LANSOPRAZOLE delayed-release orally disintegrating tablets for oral use

Initial U.S. Approval: 1995

----- RECENT MAJOR CHANGES -----

Dosage and Administration:
Important Administration Information (2.3) June 2009

Warnings and Precautions: Bone Fracture (5.2) August 2010

------ INDICATIONS AND USAGE ------

Lansoprazole is a proton pump inhibitor (PPI). Refer to **DOSAGE AND ADMINISTRATION** table (below) for indications and usage.

---- DOSAGE AND ADMINISTRATION ----

Indication	Dose	Frequency
Duodenal Ulcers (1.1, 1.3)		
Short-Term Treatment	15 mg	Once daily for 4 wks
Maintenance of Healed	15 mg	Once daily
***H. pylori* Eradication to Reduce Recurrence of Duodenal Ulcer** (1.2)		
Triple Therapy: Lansoprazole Delayed-Release Orally Disintegrating Tablets	30 mg	Twice daily for 10 or 14 days
Amoxicillin	1 gram	
Clarithromycin	500 mg	
Dual Therapy: Lansoprazole Delayed-Release Orally Disintegrating Tablets	30 mg	Three times daily for 14 days
Amoxicillin	1 gram	
Benign Gastric Ulcer (1.4)		
Short-Term Treatment	30 mg	Once daily up to 8 wks
NSAID-associated Gastric Ulcer (1.6)		
Healing	30 mg	Once daily for 8 wks
Risk Reduction	15 mg	Once daily up to 12 wks
GERD (1.7)		
Short-Term Treatment of Symptomatic GERD	15 mg	Once daily up to 8 wks
Short-Term Treatment of EE	30 mg	Once daily up to 8 wks
Pediatric (8.4)		
(1 to 11 years of age) Short-Term Treatment of Symptomatic GERD and Short-Term Treatment of EE		
≤ 30 kg	15 mg	Once daily up to 12 wks
> 30 kg	30 mg	Once daily up to 12 wks
(12 to 17 years of age) Short-Term Treatment of Symptomatic GERD		
Nonerosive GERD	15 mg	Once daily up to 8 wks
EE	30 mg	Once daily up to 8 wks
Maintenance of Healing of EE (1.8)	15 mg	Once daily
Pathological Hypersecretory Conditions (i.e., ZES) (1.9)	60 mg	Once daily

----- DOSAGE FORMS AND STRENGTHS -----

Tablets: 15 mg and 30 mg. (3)

--------- CONTRAINDICATIONS ---------

Contraindicated in patients with known severe hypersensitivity to any component of the lansoprazole delayed-release orally disintegrating tablets formulation. (4)

----- WARNINGS AND PRECAUTIONS -----

- Symptomatic response with lansoprazole does not preclude the presence of gastric malignancy. (5.1)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.2)

------- ADVERSE REACTIONS -------

Most commonly reported adverse reactions (≥ 1%): diarrhea, abdominal pain, nausea and constipation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-888-838-2872, X6351 or drug.safety@tevausa.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

------- DRUG INTERACTIONS --------

- Do not coadminister with atazanavir. (7)
- May interfere with the absorption of drugs where gastric pH is important for bioavailability. (7)
- Concomitant warfarin use may require monitoring for increases in INR and prothrombin time. (7)
- Concomitant tacrolimus use may increase tacrolimus whole blood concentrations. (7)
- Titration of theophylline dosage may be required when concomitant lansoprazole use is started or stopped. (7)

----- USE IN SPECIFIC POPULATIONS -----

- Consider dose adjustment in patients with severe liver impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling

Revised: 09/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Short-Term Treatment of Active Duodenal Ulcer

Lansoprazole delayed-release orally disintegrating tablets are indicated for short-term treatment (for 4 weeks) for healing and symptom relief of active duodenal ulcer [*see Clinical Studies (14)*].

1.2 *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy: Lansoprazole delayed-release orally disintegrating tablets/amoxicillin/clarithromycin

Lansoprazole delayed-release orally disintegrating tablets in combination with amoxicillin plus clarithromycin as triple therapy is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence [*see Clinical Studies (14)*].

Please refer to the full prescribing information for amoxicillin and clarithromycin.

Dual Therapy: Lansoprazole delayed-release orally disintegrating tablets/amoxicillin

Lansoprazole delayed-release orally disintegrating tablets in combination with amoxicillin as dual therapy is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected** (see the clarithromycin package insert, MICROBIOLOGY section). Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence [*see Clinical Studies (14)*].
Please refer to the full prescribing information for amoxicillin.

1.3 Maintenance of Healed Duodenal Ulcers

Lansoprazole delayed-release orally disintegrating tablets are indicated to maintain healing of duodenal ulcers. Controlled studies do not extend beyond 12 months [*see Clinical Studies (14)*].

1.4 Short-Term Treatment of Active Benign Gastric Ulcer

Lansoprazole delayed-release orally disintegrating tablets are indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of active benign gastric ulcer [*see Clinical Studies (14)*].

1.5 Healing of NSAID-Associated Gastric Ulcer

Lansoprazole delayed-release orally disintegrating tablets are indicated for the treatment of NSAID-associated gastric ulcer in patients who continue NSAID use. Controlled studies did not extend beyond 8 weeks [*see Clinical Studies (14)*].

1.6 Risk Reduction of NSAID-Associated Gastric Ulcer

Lansoprazole delayed-release orally disintegrating tablets are indicated for reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID. Controlled studies did not extend beyond 12 weeks [*see Clinical Studies (14)*].

1.7 Gastroesophageal Reflux Disease (GERD)

Short-Term Treatment of Symptomatic GERD

Lansoprazole delayed-release orally disintegrating tablets are indicated for the treatment of heartburn and other symptoms associated with GERD [*see Clinical Studies (14)*].

Short-Term Treatment of Erosive Esophagitis

Lansoprazole delayed-release orally disintegrating tablets are indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of erosive esophagitis. For patients who do not heal with lansoprazole delayed-release orally disintegrating tablets for 8 weeks (5 to 10%), it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of erosive esophagitis an additional 8 week course of lansoprazole delayed-release orally disintegrating tablets may be considered [*see Clinical Studies (14)*].

1.8 Maintenance of Healing of Erosive Esophagitis (EE)

Lansoprazole delayed-release orally disintegrating tablets are indicated to maintain healing of erosive esophagitis. Controlled studies did not extend beyond 12 months [*see Clinical Studies (14)*].

1.9 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome (ZES)

Lansoprazole delayed-release orally disintegrating tablets are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome [*see Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

Lansoprazole is available as a delayed-release orally disintegrating tablet in 15 mg and 30 mg strengths. Directions for use specific to the route and available methods of administration for this dosage form is presented below. Lansoprazole delayed-release orally disintegrating tablets should be taken before eating. Lansoprazole delayed-release orally disintegrating tablets SHOULD NOT BE CRUSHED OR CHEWED. In the clinical trials, antacids were used concomitantly with lansoprazole.

2.1 Recommended Dose

Indication	Recommended Dose	Frequency
Duodenal Ulcers		
Short-Term Treatment	15 mg	Once daily for 4 weeks
Maintenance of Healed	15 mg	Once daily
H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence^{a}		
Triple Therapy:		
Lansoprazole Delayed-Release Orally Disintegrating Tablets	30 mg	Twice daily (q12h) for 10 or 14 days
Amoxicillin	1 gram	Twice daily (q12h) for 10 or 14 days
Clarithromycin	500 mg	Twice daily (q12h) for 10 or 14 days
Dual Therapy:		
Lansoprazole Delayed-Release Orally Disintegrating Tablets	30 mg	Three times daily (q8h) for 14 days
Amoxicillin	1 gram	Three times daily (q8h) for 14 days
Benign Gastric Ulcer		
Short-Term Treatment	30 mg	Once daily for up to 8 weeks
NSAID-associated Gastric Ulcer		
Healing	30 mg	Once daily for 8 weeks^{b}
Risk Reduction	15 mg	Once daily for up to 12 weeks^{b}
Gastroesophageal Reflux Disease (GERD)		
Short-Term Treatment of Symptomatic GERD	15 mg	Once daily for up to 8 weeks
Short-Term Treatment of Erosive Esophagitis	30 mg	Once daily for up to 8 weeks^{c}
Pediatric		
(1 to 11 years of age) Short-Term Treatment of Symptomatic GERD and Short-Term Treatment of Erosive Esophagitis		
≤ 30 kg	15 mg	Once daily for up to 12 weeks^{d}
> 30 kg	30 mg	Once daily for up to 12 weeks^{d}
(12 to 17 years of age) Short-Term Treatment of Symptomatic GERD		
Nonerosive GERD	15 mg	Once daily for up to 8 weeks
Erosive Esophagitis	30 mg	Once daily for up to 8 weeks
Maintenance of Healing of Erosive Esophagitis	15 mg	Once daily
Pathological Hypersecretory Conditions Including Zollinger-Ellison syndrome	60 mg	Once daily^{e}

[a] Please refer to amoxicillin and clarithromycin full prescribing information for CONTRAINDICATIONS and WARNINGS, and for information regarding dosing in elderly and renally-impaired patients.

[b] Controlled studies did not extend beyond indicated duration.

[c] For patients who do not heal with lansoprazole delayed-release orally disintegrating tablets for 8 weeks (5 to 10%), it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of erosive esophagitis, an additional 8 week course of lansoprazole delayed-release orally disintegrating tablets may be considered.

[d] The lansoprazole dose was increased (up to 30 mg twice daily) in some pediatric patients after 2 or more weeks of treatment if they remained symptomatic. For pediatric patients unable to swallow an intact capsule please see Administration Options.

[e] Varies with individual patient. Recommended adult starting dose is 60 mg once daily. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Dosages up to 90 mg twice daily have been administered. Daily dose of greater than 120 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with lansoprazole for more than 4 years.

2.2 Special Populations

Renal impairment patients and geriatric patients do not require dosage adjustment. However, consider dose adjustment in patients with severe liver impairment [*see Use in Specific Populations (8.5, 8.6 and 8.7)*].

2.3 Important Administration Information

Administration Options

Lansoprazole delayed-release orally disintegrating tablets

- Lansoprazole delayed-release orally disintegrating tablets should not be broken or cut.
- Lansoprazole delayed-release orally disintegrating tablets should not be chewed.
  - Place the tablet on the tongue and allow it to disintegrate, with or without water, until the particles can be swallowed.
  - The tablet typically disintegrates in less than 1 minute.
  - Alternatively, for children or other patients who have difficulty swallowing tablets, lansoprazole delayed-release orally disintegrating tablets can be delivered in two different ways.

Lansoprazole delayed-release orally disintegrating tablets – Oral Syringe

For administration via oral syringe, lansoprazole delayed-release orally disintegrating tablets can be administered as follows:

- Place a 15 mg tablet in oral syringe and draw up 4 mL of water, or place a 30 mg tablet in oral syringe and draw up 10 mL of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, administer the contents within 15 minutes.
- Refill the syringe with approximately 2 mL (5 mL for the 30 mg tablet) of water, shake gently, and administer any remaining contents.

Lansoprazole delayed-release orally disintegrating tablets – Nasogastric Tube (≥ 8 French) Administration

For administration via a nasogastric tube, lansoprazole delayed-release orally disintegrating tablets can be administered as follows:

- Place a 15 mg tablet in a syringe and draw up 4 mL of water, or place a 30 mg tablet in a syringe and draw up 10 mL of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, inject through the nasogastric tube into the stomach within 15 minutes.
- Refill the syringe with approximately 5 mL of water, shake gently, and flush the nasogastric tube.

3 DOSAGE FORMS AND STRENGTHS

- 15 mg tablets are white to off-white, flat, beveled round, artificial strawberry flavored with white to grayish speckles, debossed with "15" on one side of the tablet and plain on the other side.
- 30 mg tablets are white to off-white, flat, beveled round, artificial strawberry flavored with white to grayish speckles, debossed with "30" on one side of the tablet and plain on the other side.

4 CONTRAINDICATIONS

Lansoprazole delayed-release orally disintegrating tablets are contraindicated in patients with known severe hypersensitivity to any component of the formulation of lansoprazole delayed-release orally disintegrating tablets. For information on contraindications for amoxicillin or clarithromycin, refer to their full prescribing information, CONTRAINDICATIONS sections.

5 WARNINGS AND PRECAUTIONS

5.1 Gastric Malignancy

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

5.2 Bone Fracture

Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines [*see Dosage and Administration (2) and Adverse Reactions (6.2)*].

For information on warnings and precautions for amoxicillin or clarithromycin, refer to their full prescribing information, WARNINGS and PRECAUTIONS sections.

6 ADVERSE REACTIONS

6.1 Clinical

Worldwide, over 10,000 patients have been treated with lansoprazole in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment. In general, lansoprazole treatment has been well-tolerated in both short-term and long-term trials.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following adverse reactions were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of lansoprazole-treated patients and occurred at a greater rate in lansoprazole-treated patients than placebo-treated patients in **Table 1**.

Table 1: Incidence of Possibly or Probably Treatment-Related Adverse Reactions in Short-Term, Placebo-Controlled Lansoprazole Studies

Body System/Adverse Event	Lansoprazole (N = 2768) %	Placebo (N = 1023) %
Body as a Whole		
Abdominal Pain	2.1	1.2
Digestive System		
Constipation	1.0	0.4
Diarrhea	3.8	2.3
Nausea	1.3	1.2

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received 15 mg and 30 mg of lansoprazole, but higher in the patients who received 60 mg of lansoprazole (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In the risk reduction study of lansoprazole for NSAID-associated gastric ulcers, the incidence of diarrhea for patients treated with lansoprazole, misoprostol, and placebo was 5%, 22%, and 3%, respectively.

Another study for the same indication, where patients took either a COX-2 inhibitor or lansoprazole and naproxen, demonstrated that the safety profile was similar to the prior study. Additional reactions from this study not previously observed in other clinical trials with lansoprazole included contusion, duodenitis, epigastric discomfort, esophageal disorder, fatigue, hunger, hiatal hernia, hoarseness, impaired gastric emptying, metaplasia, and renal impairment.

Additional adverse experiences occurring in less than 1% of patients or subjects who received lansoprazole in domestic trials are shown below:

Body as a Whole – abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain

Cardiovascular System - angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation

Digestive System – abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, gastrointestinal moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis

Endocrine System - diabetes mellitus, goiter, hypothyroidism

Hemic and Lymphatic System - anemia, hemolysis, lymphadenopathy

Metabolic and Nutritional Disorders - avitaminosis, gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss

Musculoskeletal System - arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, ptosis, synovitis

Nervous System - abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, dementia, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo

Respiratory System - asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, lung fibrosis, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor

Skin and Appendages - acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria

Special Senses - abnormal vision, amblyopia, blepharitis, blurred vision, cataract, conjunctivitis, deafness, dry eyes, ear/eye disorder, eye pain, glaucoma, otitis media, parosmia, photophobia, retinal degeneration/disorder, taste loss, taste perversion, tinnitus, visual field defect

Urogenital System - abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary retention, urinary tract infection, urinary urgency, urination impaired, vaginitis.

6.2 Postmarketing Experience

Additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole has not been established. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

Body as a Whole - anaphylactic/anaphylactoid reactions; *Digestive System* - hepatotoxicity, pancreatitis, vomiting; *Hemic and Lymphatic System* - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Musculoskeletal System* - bone fracture, myositis; *Skin and Appendages* - severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal); *Special Senses* - speech disorder; *Urogenital System* - interstitial nephritis, urinary retention.

6.3 Combination Therapy With Amoxicillin and Clarithromycin

In clinical trials using combination therapy with lansoprazole plus amoxicillin and clarithromycin, and lansoprazole plus amoxicillin, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with lansoprazole, amoxicillin, or clarithromycin.

Triple Therapy: Lansoprazole/amoxicillin/clarithromycin
The most frequently reported adverse reactions for patients who received triple therapy for 14 days were diarrhea (7%), headache (6%), and taste perversion (5%). There were no statistically significant differences in the frequency of reported adverse reactions between the 10 and 14 day triple therapy regimens. No treatment-emergent adverse reactions were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual Therapy: Lansoprazole/amoxicillin
The most frequently reported adverse reactions for patients who received lansoprazole three times daily plus amoxicillin three times daily dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse reactions were observed at significantly higher rates with lansoprazole three times daily plus amoxicillin three times daily dual therapy than with lansoprazole alone.

For information on adverse reactions with amoxicillin or clarithromycin, refer to their full prescribing information, ADVERSE REACTIONS sections.

6.4 Laboratory Values

The following changes in laboratory parameters in patients who received lansoprazole were reported as adverse reactions:

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, blood potassium increased, blood urea increased, crystal urine present, eosinophilia, hemoglobin decreased, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, increased gastrin levels and positive fecal occult blood. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) and 0.4% (11/2677) patients, who received placebo and lansoprazole, respectively, had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these patients who received lansoprazole reported jaundice at any time during the study.

In clinical trials using combination therapy with lansoprazole plus amoxicillin and clarithromycin, and lansoprazole plus amoxicillin, no increased laboratory abnormalities particular to these drug combinations were observed.

For information on laboratory value changes with amoxicillin or clarithromycin, refer to their full prescribing information, ADVERSE REACTIONS sections.

7 DRUG INTERACTIONS

Drugs With pH-Dependent Absorption Kinetics

Lansoprazole causes long-lasting inhibition of gastric acid secretion. Lansoprazole and other PPIs are likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole and other PPIs should not be coadministered with atazanavir [*see Clinical Pharmacology (12.5)*].

It is theoretically possible that lansoprazole and other PPIs may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole) [*see Clinical Pharmacology (12.5)*].

Warfarin

In a study of healthy subjects, coadministration of single or multiple 60 mg doses of lansoprazole and warfarin did not affect the pharmacokinetics of warfarin nor prothrombin time [*see Clinical Pharmacology (12.5)*]. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time [*see Clinical Pharmacology (12.5)*].

Tacrolimus

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

Theophylline

A minor increase (10%) in the clearance of theophylline was observed following the administration of lansoprazole concomitantly with theophylline. Although the magnitude of the effect on theophylline clearance is small, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels [*see Clinical Pharmacology (12.5)*].

For information on drug interactions for amoxicillin or clarithromycin, refer to their full prescribing information, DRUG INTERACTIONS sections.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy category B

Reproduction studies have been performed in pregnant rats at oral doses up to 40 times the recommended human dose and in pregnant rabbits at oral doses up to 16 times the recommended human dose and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed [*see Nonclinical Toxicology (13.2)*].

See full prescribing information for clarithromycin before using in pregnant women.

8.3 Nursing Mothers

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue lansoprazole, taking into account the importance of lansoprazole to the mother.

8.4 Pediatric Use

The safety and effectiveness of lansoprazole have been established in pediatric patients 1 to 17 years of age for short-term treatment of symptomatic GERD and erosive esophagitis.

One to 11 years of age

In an uncontrolled, open-label, U.S. multicenter study, 66 pediatric patients (1 to 11 years of age) with GERD were assigned, based on body weight, to receive an initial dose of either lansoprazole 15 mg daily if ≤ 30 kg or lansoprazole 30 mg daily if greater than 30 kg administered for 8 to 12 weeks. The lansoprazole dose was increased (up to 30 mg twice daily) in 24 of 66 pediatric patients after 2 or more weeks of treatment if they remained symptomatic. At baseline 85% of patients had mild to moderate overall GERD symptoms (assessed by investigator interview), 58% had non-erosive GERD and 42% had erosive esophagitis (assessed by endoscopy).

After 8 to 12 weeks of lansoprazole treatment, the intent-to-treat analysis demonstrated an approximate 50% reduction in frequency and severity of GERD symptoms.

Twenty-one of 27 erosive esophagitis patients were healed at 8 weeks and 100% of patients were healed at 12 weeks by endoscopy (**Table 2**).

Table 2: GERD Symptom Improvement and Erosive Esophagitis Healing Rates in Pediatric Patients Age 1 to 11

GERD	Final Visit^{a} **%** (n/N)
Symptomatic GERD	
Improvement in Overall GERD Symptoms^{b}	76% (47/62^{c})
Erosive Esophagitis	
Improvement in Overall GERD Symptoms^{b}	81% (22/27)
Healing Rate	100% (27/27)

[a] At Week 8 or Week 12

[b] Symptoms assessed by patients diary kept by caregiver.

[c] No data were available for 4 pediatric patients.

In a study of 66 pediatric patients in the age group 1 year to 11 years old after treatment with lansoprazole given orally in doses of 15 mg daily to 30 mg twice daily, increases in serum gastrin levels were similar to those observed in adult studies. Median fasting serum gastrin levels increased 89% from 51 pg/mL at baseline to 97 pg/mL [interquartile range (25th to 75th percentile) of 71 to 130 pg/mL] at the final visit.

The pediatric safety of lansoprazole delayed-release capsules has been assessed in 66 pediatric patients aged 1 to 11 years of age. Of the 66 patients with GERD 85% (56/66) took lansoprazole for 8 weeks and 15% (10/66) took it for 12 weeks.

The most frequently reported (2 or more patients) treatment-related adverse reactions in patients 1 to 11 years of age (N = 66) were constipation (5%) and headache (3%).

Twelve to 17 years of age

In an uncontrolled, open-label, U.S. multicenter study, 87 adolescent patients (12 to 17 years of age) with symptomatic GERD were treated with lansoprazole for 8 to 12 weeks. Baseline upper endoscopies classified these patients into two groups: 64 (74%) nonerosive GERD and 23 (26%) erosive esophagitis (EE). The nonerosive GERD patients received lansoprazole 15 mg daily for 8 weeks and the EE patients received lansoprazole 30 mg daily for 8 to 12 weeks. At baseline, 89% of these patients had mild to moderate overall GERD symptoms (assessed by investigator interviews). During 8 weeks of lansoprazole treatment, adolescent patients experienced a 63% reduction in frequency and a 69% reduction in severity of GERD symptoms based on diary results.

Twenty-one of 22 (95.5%) adolescent erosive esophagitis patients were healed after 8 weeks of lansoprazole treatment. One patient remained unhealed after 12 weeks of treatment (**Table 3**).

Table 3: GERD Symptom Improvement and Erosive Esophagitis Healing Rates in Pediatric Patients Age 12 to 17

GERD	Final Visit % (n/N)
Symptomatic GERD (All Patients)	
Improvement in Overall GERD Symptoms^{a}	73.2% (60/82)^{b}
Nonerosive GERD	
Improvement in Overall GERD Symptoms^{a}	71.2% (42/59)^{b}
Erosive Esophagitis	
Improvement in Overall GERD Symptoms^{a}	78.3% (18/23)
Healing Rate^{c}	95.5% (21/22)^{c}

[a] Symptoms assessed by patient diary (parents/caregivers as necessary).

[b] No data available for 5 patients.

[c] Data from one healed patient was excluded from this analysis due to timing of final endoscopy.

In these 87 adolescent patients, increases in serum gastrin levels were similar to those observed in adult studies, median fasting serum gastrin levels increased 42% from 45 pg/mL at baseline to 64 pg/mL [interquartile range (25th to 75th percentile) of 44 to 88 pg/mL] at the final visit. (Normal serum gastrin levels are 25 to 111 pg/mL.)

The safety of lansoprazole delayed-release capsules has been assessed in these 87 adolescent patients. Of the 87 adolescent patients with GERD, 6% (5/87) took lansoprazole for less than 6 weeks, 93% (81/87) for 6 to 10 weeks, and 1% (1/87) for greater than 10 weeks.

The most frequently reported (at least 3%) treatment-related adverse reactions in these patients were headache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%). Treatment-related dizziness, reported in this package insert as occurring in less than 1% of adult patients, was reported in this study by 3 adolescent patients with nonerosive GERD, who had dizziness concurrently with other reactions (such as migraine, dyspnea, and vomiting).

8.5 Geriatric Use

No dosage adjustment of lansoprazole is necessary in geriatric patients. The incidence rates of lansoprazole-associated adverse reactions and laboratory test abnormalities are similar to those seen in younger patients [*see Clinical Pharmacology (12.4)*].

8.6 Renal Impairment

No dosage adjustment of lansoprazole is necessary in patients with renal impairment. The pharmacokinetics of lansoprazole in patients with various degrees of renal impairment were not substantially different compared to those in subjects with normal renal function [*see Clinical Pharmacology (12.4)*].

8.7 Hepatic Impairment

In patients with various degrees of chronic hepatic impairment, an increase in the mean AUC of up to 500% was observed at steady state compared to healthy subjects. Consider dose reduction in patients with severe hepatic impairment [*see Clinical Pharmacology (12.4)*].

8.8 Gender

Over 4,000 women were treated with lansoprazole. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse reactions in females were similar to those seen in males [*see Clinical Pharmacology (12.4)*].

8.9 Race

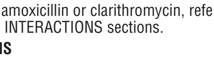
The pooled mean pharmacokinetic parameters of lansoprazole from twelve U.S. Phase 1 studies (N = 513) were compared to the mean pharmacokinetic parameters from two Asian studies (N = 20). The mean AUCs of lansoprazole in Asian subjects were approximately twice those seen in pooled U.S. data; however, the inter-individual variability was high. The C_{max} values were comparable.

10 OVERDOSAGE

Lansoprazole is not removed from the circulation by hemodialysis. In one reported overdose, a patient consumed 600 mg of lansoprazole with no adverse reaction. Oral lansoprazole doses up to 5000 mg/kg in rats [approximately 1300 times the 30 mg human dose based on body surface area (BSA)] and in mice (about 675.7 times the 30 mg human dose based on BSA) did not produce deaths or any clinical signs.

11 DESCRIPTION

The active ingredient in lansoprazole delayed-release orally disintegrating tablets is lansoprazole, a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl] sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Lansoprazole has the following structure:



$C_{16}H_{14}F_3N_3O_2S$ M.W. 369.37

Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

Lansoprazole is stable when exposed to light for up to two months. The rate of degradation of the compound in aqueous solution increases with decreasing pH. The degradation half-life of the drug substance in aqueous solution at 25°C is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.

Lansoprazole is supplied in delayed-release orally disintegrating tablets for oral administration.

Lansoprazole delayed-release orally disintegrating tablets contain the active ingredient, lansoprazole in the form of enteric-coated microgranules. The tablets are available in 15 mg and 30 mg dosage strengths. Each tablet contains lansoprazole and the following inactive ingredients: aspartame**, cis-3-hexan-1-ol, cis-3-hexen-1-yl acetate, colloidal silicon dioxide, ethyl butyrate, ethyl isovalerate, ethyl-2-methylbutyrate, ethyl valerate, gamma-decalactone cis-3-hexenyl butyrate, gum arabic, hexyl hexanoate cis-3-hexenyl hexanoate, hypromellose, lactose, magnesium carbonate, magnesium stearate, maize starch, maltodextrin, methacrylic acid copolymer type C, methyl cinnamate, sugar spheres (which contain sucrose and corn starch), talc, titanium dioxide, and triethyl citrate.

** **Phenylketonurics: Contains Phenylalanine 3.71 mg per 15 mg tablet and 7.41 mg per 30 mg tablet.**

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. Lansoprazole does not exhibit anticholinergic or histamine type-2 antagonist activity.

12.2 Pharmacodynamics

Antisecretory Activity: After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was greater than 3 and greater than 4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

The intragastric pH results of a five-day, pharmacodynamic, crossover study of 15 mg and 30 mg of once daily lansoprazole are presented in **Table 4:**

Table 4: Mean Antisecretory Effects After Single and Multiple Daily Lansoprazole Dosing

Parameter	Baseline Value	Lansoprazole			
		15 mg		30 mg	
		Day 1	Day 5	Day 1	Day 5
Mean 24 Hour pH	2.1	2.7^{a}	4.0^{a}	3.6^{b}	4.9^{b}
Mean Nighttime pH	1.9	2.4	3.0^{a}	2.6	3.8^{b}
% Time Gastric pH > 3	18	33^{a}	59^{a}	51^{b}	72^{b}
% Time Gastric pH > 4	12	22^{a}	49^{a}	41^{b}	66^{b}

[a] ($p < 0.05$) versus baseline only.

[b] ($p < 0.05$) versus baseline and lansoprazole 15 mg.

NOTE: An intragastric pH of greater than 4 reflects a reduction in gastric acid by 99%.

After the initial dose in this study, increased gastric pH was seen within 1 to 2 hours with 30 mg of lansoprazole and 2 to 3 hours with 15 mg of lansoprazole. After multiple daily dosing, increased gastric pH was seen within the first hour post-dosing with 30 mg of lansoprazole and within 1 to 2 hours post-dosing with 15 mg of lansoprazole.

Acid suppression may enhance the effect of antimicrobials in eradicating *Helicobacter pylori (H. pylori)*. The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of lansoprazole given daily, twice daily and three times daily (**Table 5**).

Table 5: Mean Antisecretory Effects After 5 Days of Twice Daily and Three Times Daily Dosing

Parameter	Lansoprazole			
	30 mg daily	15 mg twice daily	30 mg twice daily	30 mg three times daily
% Time Gastric pH > 5	43	47	59^{a}	77^{b}
% Time Gastric pH > 6	20	23	28	45^{b}

[a] ($p < 0.05$) versus lansoprazole 30 mg daily.

[b] ($p < 0.05$) versus lansoprazole 30 mg daily, 15 mg twice daily and 30 mg twice daily.

The inhibition of gastric acid secretion as measured by intragastric pH gradually returned to normal over two to four days after multiple doses. There was no indication of rebound gastric acidity.

Enterochromaffin-like (ECL) Cell Effects

During lifetime exposure of rats with up to 150 mg/kg/day of lansoprazole dosed seven days per week, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats. Gastric biopsy specimens from the body of the stomach from approximately 150 patients treated continuously with lansoprazole for at least one year did not show evidence of ECL cell effects similar to those seen in rat studies. Longer term data are needed to rule out the possibility of an increased risk of the development of gastric tumors in patients receiving long-term therapy with lansoprazole [*see Nonclinical Toxicology (13.1)*].

Other Gastric Effects in Humans

Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal physiologic effect caused by the inhibition of gastric acid secretion, a decrease of about 17% in blood flow in the antrum, pylorus, and duodenal bulb was seen. Lansoprazole significantly slowed the gastric emptying of digestible solids. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. As with other agents that elevate intragastric pH, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

Serum Gastrin Effects

In over 2100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline but remained within normal range after treatment with 15 to 60 mg of oral lansoprazole. These elevations reached a plateau within two months of therapy and returned to pretreatment levels within four weeks after discontinuation of therapy.

Endocrine Effects

Human studies for up to one year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and somatotropic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function. In 24 month carcinogenicity studies in Sprague-Dawley rats with daily lansoprazole dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rats.

Other Effects

No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory systems have been found in humans. Among 56 patients who had extensive baseline eye evaluations, no visual toxicity was observed after lansoprazole treatment (up to 180 mg/day) for up to 58 months. After lifetime lansoprazole exposure in rats, focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy were seen.

Microbiology

Lansoprazole, clarithromycin and/or amoxicillin have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section [*see Indications and Usage (1.2)*].

Helicobacter pylori Pretreatment Resistance

Clarithromycin pretreatment resistance (≥ 2.0 mcg/mL) was 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the dual and triple therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95-399).

Amoxicillin pretreatment susceptible isolates (≤ 0.25 mcg/mL) occurred in 97.8% (936/957) and 98.0% (98/100) of the patients in the dual and triple therapy clinical trials by E-test and agar dilution, respectively. Twenty-one of 957 patients (2.2%) by E-test, and 2 of 100 patients (2.0%) by agar dilution, had amoxicillin pretreatment MICs of greater than 0.25 mcg/mL. One patient on the 14 day triple therapy regimen had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of greater than 256 mcg/mL by E-test and the patient was eradicated of *H. pylori* (**Table 6**).

Table 6: Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes^{a}

Clarithromycin Pretreatment Results		Clarithromycin Post-treatment Results				
		H. pylori negative - eradicated	*H. pylori* positive – not eradicated Post-treatment susceptibility results			
			S^{b}	I^{b}	R^{b}	No MIC
Triple Therapy 14 Day (lansoprazole 30 mg twice daily/amoxicillin 1 g twice daily/clarithromycin 500 mg twice daily) (M95-399, M93-131, M95-392)						
Susceptible^{b}	112	105				7
Intermediate^{b}	3	3				
Resistant^{b}	17	6			7	4
Triple Therapy 10 Day (lansoprazole 30 mg twice daily/amoxicillin 1 g twice daily/clarithromycin 500 mg twice daily) (M95-399)						
Susceptible^{b}	42	40	1		1	
Intermediate^{b}						
Resistant^{b}	4	1			3	

[a] Includes only patients with pretreatment clarithromycin susceptibility test results

[b] Susceptible (S) MIC ≤ 0.25 mcg/mL, Intermediate (I) MIC 0.5 to 1.0 mcg/mL, Resistant (R) MIC ≥ 2 mcg/mL

Patients not eradicated of *H. pylori* following lansoprazole/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori*. Therefore, for those patients who fail therapy, clarithromycin susceptibility testing should be done when possible. Patients with clarithromycin resistant *H. pylori* should not be treated with lansoprazole/amoxicillin/clarithromycin triple therapy or with regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes: In the dual and triple therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (≤ 0.25 mcg/mL) were eradicated of *H. pylori*. Of those with pretreatment amoxicillin MICs of greater than 0.25 mcg/mL, three of six had the *H. pylori* eradicated. A total of 30% (21/70) of the patients failed lansoprazole 30 mg three times daily/amoxicillin 1 g three times daily dual therapy and a total of 12.8% (22/172) of the patients failed the 10 and 14 day triple therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine of the 11 patients with amoxicillin post-treatment MICs that failed the triple therapy regimen also had clarithromycin resistant *H. pylori* isolates.

Susceptibility Test for Helicobacter pylori: The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.[1] One to three microliters of an inoculum equivalent to a No. 2 McFarland standard (1 x 10^7 to 1 x 10^8 CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial-containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters.

After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria (**Table 7**):

Table 7

Clarithromycin MIC (mcg/mL)^{a}	Interpretation
≤ 0.25	Susceptible (S)
0.5 to 1.0	Intermediate (I)
≥ 2.0	Resistant (R)
Amoxicillin MIC (mcg/mL)^{a,b}	Interpretation
≤ 0.25	Susceptible (S)

[a] These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.

[b] There were not enough organisms with MICs greater than 0.25 mcg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values (**Table 8**):

Table 8

Microorganism	Antimicrobial Agent	MIC (mcg/mL)^{a}
H. pylori ATCC 43504	Clarithromycin	0.015 to 0.12
H. pylori ATCC 43504	Amoxicillin	0.015 to 0.12

[a] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

12.3 Pharmacokinetics

Lansoprazole delayed-release orally disintegrating tablets contain an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. After a single-dose administration of 15 mg to 60 mg of oral lansoprazole, the peak plasma concentrations (C_{max}) of lansoprazole and the area under the plasma concentration curves (AUCs) of lansoprazole were approximately proportional to the administered dose. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

Absorption: The absorption of lansoprazole is rapid, with the mean C_{max} occurring approximately 1.7 hours after oral dosing, and the absolute bioavailability is over 80%. In healthy subjects, the mean (± SD) plasma half-life was 1.5 (± 1.0) hours. Both the C_{max} and AUC are diminished by about 50% to 70% if lansoprazole is given 30 minutes after food, compared to the fasting condition. There is no significant food effect if lansoprazole is given before meals.

Distribution: Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 mcg/mL.

Metabolism: Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by blocking the proton pump [(H^+, K^+)-ATPase enzyme system] at the secretory surface of the gastric parietal cell. The two active species are not present in the systemic circulation. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. Therefore, the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.

Elimination: Following single-dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of ^{14}C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the lansoprazole metabolites.

12.4 Specific Populations

Pediatric Use

One to 17 years of age

The pharmacokinetics of lansoprazole were studied in pediatric patients with GERD aged 1 to 11 years and 12 to 17 years in two separate clinical studies. In children aged 1 to 11 years, lansoprazole was dosed 15 mg daily for subjects weighing ≤ 30 kg and 30 mg daily for subjects weighing greater than 30 kg. Mean C_{max} and AUC values observed on Day 5 of dosing were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in the study. In adolescent subjects aged 12 to 17 years, subjects were randomized to receive lansoprazole at 15 mg or 30 mg daily. Mean C_{max} and AUC values of lansoprazole were not affected by body weight or age; and nearly dose-proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, lansoprazole pharmacokinetics in pediatric patients aged 1 to 17 years were similar to those observed in healthy adult subjects.

Geriatric Use
The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once-daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly. No dosage adjustment is necessary in the elderly. *See Use in Specific Populations (8.5).*

Renal Impairment
Patients with severe renal impairment, plasma protein binding decreased by 1.0% to 1.5%, after administration of 60 mg of lansoprazole. *Patients with renal impairment had a shortened elimination half-life and decreased total AUC (free and bound). The AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment; the mean and C_{max} (free) tripled to reach the maximum concentration were not different from those C_{max} and T_{max} from subjects with normal renal function. No dosage adjustment is necessary in patients with renal impairment. *See Use in Specific Populations (8.6).*

Hepatic Impairment
In patients with serious degrees of chronic hepatic impairment, the mean plasma half-life of lansoprazole was prolonged from 1.5 hours to 3.2 to 7.2 hours, and the mean total AUC and C_{max} (free) tripled. *A dose of 30 mg is a study state in hepatically-impaired patients compared to healthy subjects. Consider dose reduction in patients with severe hepatic impairment. [see Use in Specific Populations (8.7)].*

Gender
In a study comparing 12 male and 6 female subjects who received lansoprazole, no gender related differences were observed in lansoprazole and stereogenic pharmacokinetics. *See Use in Specific Populations (8.5).*

12.3 Drug Interactions
It is theoretically possible that lansoprazole may interfere with the absorption of other drugs when given at the same time, or in important dosage adjustments (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

Lansoprazole is metabolized through the cytochrome P450 system, specifically, through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P_{450} system, such as warfarin, antipyrine, indomethacin, ibuprofen, piroxicam, propranolol, diazepam, phenytoin, and or clarithromycin in healthy subjects. These compounds are metabolized by various enzymes in the cytochrome P450 system: CYP1A2, CYP2C9, CYP2D6, CYP2C19, and CYP3A.

Atazanavir- Lansoprazole causes long-lasting inhibition of gastric acid secretion. Lansoprazole significantly decreases the systemic concentration of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect and viral resistance. *Do not coadminister atazanavir and the development of HIV resistance. Therefore, lansoprazole, or other proton pump inhibitors, should not be coadministered with atazanavir.*

Theophylline: When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is coadministered with other clinically effective blood levels.

Warfarin: In a study of healthy subjects neither the pharmacokinetics or warfarin enantiomers nor prothrombin time were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratios (INR) and prothrombin time in patients receiving proton pump inhibitors, including lansoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Therefore, patients treated with prothrombin and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Methotrexate and 7-hydroxymethotrexate: In an open-label, single-arm, eight-day, pharmacokinetic study of high-dose methotrexate administered to patients required the chronic use of 7.5 to 15 mg of methotrexate given weekly, lansoprazole 30 mg daily, administered 5 days prior to the methotrexate administration, 30 mg daily had no effect on the pharmacokinetics of methotrexate and 7-hydroxymethotrexate. While this study was not designed to assess the safety of this combination of drugs, no major adverse reactions were noted.

Amoxicillin: Lansoprazole has also been shown to have no clinically significant interactions with amoxicillin.

Sucralfate: In a single-dose crossover study examining lansoprazole 30 mg and sucralfate 1 gm and sucralfate administered alone and concomitantly, sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 37% and 16%, respectively when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with lansoprazole and there was no evidence of a change in the efficacy of lansoprazole.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 2-year carcinogenicity study, Sprague-Dawley rats were treated with oral lansoprazole doses of 5 to 150 mg/kg/day, about 1 to 40 times the exposure on a body surface area (BSA) given the recommended human dose of 30 mg/day, and female mice were treated with oral lansoprazole or omeprazole (0.2), (1), and (5) mg/kg/day, about 0.1 to 3 times the recommended human dose based on BSA, also increased the incidence of intestinal metaplasia of the gastric epithelium in both species. In male rats, lansoprazole produced a dose-dependent increase in rectal/anal intestinal cell adenomas. The incidence of these adenomas in rats treated with doses of 15 to 150 mg/kg/day (1 to 40 times the recommended human dose based on BSA) exceeded the low background incidence (range = 0 to 1.9%) for this type of tumor in rats.

In a 24 month carcinogenicity study, CD-1 mice were treated with oral omeprazole doses of 0.2 (1) and (5) mg/kg/day, 0.1 to 3 times the recommended human dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The incidence of tumors in male mice treated with 150 and 600 mg/kg/day (40 to 160 times the recommended human dose based on BSA) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on BSA) exceeded the ranges of background incidences in control groups. The incidence of hepatocellular carcinomas in female mice adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on BSA).

In 26 week p53 (+/-) transgenic mouse carcinogenicity study was not carcinogenic.

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis test, the *in vivo* mouse micronucleus test, or the rat bone marrow cell chromosomal aberration test. It was positive in one human lymphoblast chromosomal aberration assay.

Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology
Reproductive Toxicology Studies
Reproductive studies have been performed in pregnant rats at oral exposures to lansoprazole of 15 mg/kg/day (40 times the recommended human dose (100 mg/day) based on body surface area (BSA)) and pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (195 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

14 CLINICAL STUDIES

14.1 Duodenal Ulcer
In a U.S. multicenter, double-blind, placebo-controlled, dose-response study, 30 and 60 mg of lansoprazole (once daily) study of 284 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after two and four weeks was significantly higher with all three lansoprazole than with placebo. There was no evidence of a greater or earlier response with the two higher doses compared to 30 mg lansoprazole. The data, based on this study and the second study described below, the recommended dose of lansoprazole for duodenal ulcer is 15 mg daily for 4 weeks.

Table 9: Duodenal Ulcer Healing Rates

	Lansoprazole				Placebo
Week	15 mg daily (N = 48)	30 mg daily (N = 47)	60 mg daily (N = 46)		(N = 72)
2	42.4%[a]	35.6%[a]	39.1%[a]		11.3%
4	89.4%[a]	91.7%[a]	89.9%[a]		46.1%

[a] = (p 0.001) versus placebo.

Lansoprazole 15 mg was significantly more effective than placebo in relieving day and nighttime abdominal pain and in decreasing the amount of antacid taken per day.

In a second U.S. multicenter study, also double-blind, placebo-controlled, dose-comparison (15 and 30 mg of lansoprazole once daily), and including a comparison with ranitidine, in 260 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after four weeks was significantly higher with both doses of lansoprazole than with ranitidine. There was no evidence of a greater or earlier response with the higher dose of lansoprazole. The 15 mg dose of lansoprazole healed at four and eight weeks was significantly higher with lansoprazole 15 mg and 30 mg than with ranitidine. *See Table 10 and Graph (14.1).*

Table 10: Duodenal Ulcer Healing Rates

	Lansoprazole		Ranitidine	Placebo
Week	15 mg daily (N = 66)	30 mg daily (N = 64)	150 mg bid (N = 67)	(N = 63)
4	64.6%[a]	56.1%[a]	53.3%[a]	37.5%
8	92.2%[a]	96.8%[a]	93.2%[a]	76.7%

[a] = (p 0.05) versus placebo.

Patients treated with lansoprazole dose reported significantly less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets used per day than those taking placebo.

Independent substratification of the effectiveness of lansoprazole 30 mg was obtained by a meta-analysis of published and unpublished studies.

Table 12: *H. pylori* Eradication Rates - 14 Day Dual Therapy

	(lansoprazole/amoxicillin)	
Study	Dual Therapy Evaluable Analysis[a]	Dual Therapy Intent-to-Treat Analysis[b]
	Percent of Patients Cured (Number of patients)	
M93-131	79% [62.5 to 87.2] (N = 51)	79% [56.8 to 81.2] (N = 65)
M93-135	86% [51.9 to 77.5] (N = 61)	74% [48.5 to 72.9] (N = 67)

[a] Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least one of three positive endoscopic tests from CLOtest, histology and/or culture. Patients were included in the analysis if they completed the study, received the assigned treatment and had a documented *H. pylori* status.

[b] Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least one of three positive endoscopic tests from CLOtest, histology and/or culture. Patients were included in the analysis if they completed the study, received the assigned treatment and had a documented *H. pylori* status. Patients were included in the analysis if they had documented *H. pylori* status after the treatment. All dropouts were included as failures of therapy.

[c] = (p 0.05) versus lansoprazole alone.

[d] = (p < 0.05) versus lansoprazole alone or amoxicillin alone.

14.2 Gastroesophageal Reflux Disease (GERD)
Lansoprazole has been shown to prevent the recurrence of duodenal ulcers. In a randomized, double-blind, placebo-controlled study of recurrence of duodenal ulcers in patients with endoscopically confirmed healed duodenal ulcers. Patients randomized to lansoprazole 15 mg had significantly fewer recurrences of duodenal ulcers was significantly less in patients treated with lansoprazole than in patients treated with placebo over a 12 month period (**Table 13**) *(see Indications and Usage (1.3)).*

Table 13: Endoscopic Remission Rates

		Percent in Endoscopic Remission		
Trial	Drug	No. of pts.	0 to 3 mos.	9 to 12 mos.
M93-112	Lansoprazole 15 mg daily	86	90%[a]	87%[a]
	Placebo	83	49%	41%
M92-127	Lansoprazole 30 mg daily	94	94%[a]	85%[a]
	Placebo	15	87%[a]	79%[a]
M93-131	Lansoprazole 15 mg daily	14	79%[a]	70%[a]
	Placebo	15	33%	0%

[a] = (p 0.01) versus placebo.
% = Life Table Estimate

In trial #2, no significant difference was noted between lansoprazole 15 mg and 30 mg in maintaining remission.

14.3 Healing
In a U.S. multicenter, double-blind, placebo-controlled study of 253 patients with endoscopically confirmed erosive esophagitis, lansoprazole 15 mg healed at four and eight weeks was significantly higher with lansoprazole 15 mg and 30 mg than with placebo (**Table 14**) *(see Indications and Usage (1.4)).*

Table 14: Gastric Ulcer Healing Rates

	Lansoprazole		Placebo
Week	15 mg daily (N = 65)	30 mg daily (N = 63)	(N = 61) (N = 64)
4	64.6%[a]	58.1%[a]	33.3%[a] 37.5%
8	92.2%[a]	96.8%[a]	93.2%[a] 76.7%

[a] = (p 0.05) versus placebo.

Patients treated with lansoprazole dose reported significantly less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets used per day than those taking placebo.

Independent substratification of the effectiveness of lansoprazole 30 mg was obtained by a meta-analysis of published and unpublished studies.

Table 15: NSAID-Associated Gastric Ulcer Healing Rates

	Study #1		
Week	Lansoprazole 30 mg daily (N = 66)	Active Control[a] (N = 68)	
4	79% (62/79)[c]	55% (41/74)	
8	77% (47/61)[c]	50% (33/66)	
	Study #2		
Week	Lansoprazole 30 mg daily (N = 135)	Active Control[b] (N = 137)	
4	77% (47/61)[c]	50% (33/66)	
8	85% (84/99)[c]	63% (62/98)	

[a] Active control (diclofenac sodium 75 mg bid).
[b] Active control (misoprostol 200 mcg qid).
[c] = (p 0.05) versus the active control

14.4 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
In open studies of 57 patients with pathological hypersecretory conditions, such as Zollinger-Ellison syndrome, including 24 patients with gastrinomas, adenomas, lansoprazole significantly inhibited gastric acid secretion and controlled associated symptoms for periods of dosing up to 24 months. Doses ranging from 15 mg every other day to 180 mg per day maintained basal acid secretion (BAO) to less than 10 mEq/hr in 33 patients and maintained BAO to 5 mEq/hr in patients with prior gastric surgery.

Dose titration to achieve this stated endpoint patient need, and adjustments were necessary with time in some patients (*see Dosage and Administration (2.7)*). Lansoprazole was generally well tolerated in these long-term treatment periods (greater than four years in some patients). In most 225 patients, serum gastrin rose to fasting levels greater than pretreatment levels. However, in some patients, serum gastrin increased to levels greater than those present prior to therapy with lansoprazole (*see Indications and Usage (1.5)*).

15 REFERENCES

1. Recommendations for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Susceptibility Testing, January 11-13, 1994.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lansoprazole delayed-release orally disintegrating tablets are available as follows:

• 15 mg white to off-white, flat, beveled round, artificial strawberry flavored tablet, with white to grayish speckles, debossed with "15" on one side of the tablet and plain on the other side in bottles of 30 tablets (30 bottles per carton) and 30 tablets.

• 30 mg white to off-white, flat, beveled round, artificial strawberry flavored tablet, with white to grayish speckles, debossed with "30" on one side of the tablet and plain on the other side in bottles of 30 tablets (30 bottles per carton) and 30 tablets.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Patient should be advised to read the FDA-approved
Information for Patients
Lansoprazole is available as an orally disintegrating tablet and is available in 15 mg and 30 mg strengths. Directions for use specific to the route and available methods of administration are provided in the Dosage and Administration *(see Dosage and Administration (2.3)).*

Lansoprazole delayed-release orally disintegrating tablets should be taken before eating.

Lansoprazole delayed-release orally disintegrating tablets SHOULD NOT BE CHEWED OR CRUSHED.

• **Phenylketonuria: Contains Phenylalanine 3.71 mg per 15 mg tablet and 7.41 mg per 30 mg tablet.**

Administration Options
Lansoprazole delayed-release orally disintegrating tablets
Lansoprazole delayed-release orally disintegrating tablets should not be broken or crushed.
• Lansoprazole delayed-release orally disintegrating tablets should not be chewed.
  ○ Place the tablet on the tongue and allow it to disintegrate, with or without water, until the particles can be swallowed.
  ○ The tablet typically disintegrates in less than 1 minute.
  ○ Alternatively, for children or other patients who have difficulty swallowing tablets, lansoprazole delayed-release orally disintegrating tablets can be delivered in two different ways.

Lansoprazole delayed-release orally disintegrating tablets – Oral Syringe
For administration using an oral syringe, lansoprazole delayed-release orally disintegrating tablets can be administered as follows:
• Place the tablet in a small amount of water, or a mixture of water, or a mixture of 30 mg tablet in oral syringe and draw up 10 mL of water.
• Shake gently and allow tablet to disintegrate.
• After the tablet has dispersed, administer the contents within 15 minutes.
• Refill the syringe with approximately 2 mL (5 ml, for the 30 mg tablet) of water, shake gently, and administer any remaining contents.

Lansoprazole delayed-release orally disintegrating tablets – Nasogastric Tube (n = 8 French) Administration
For administration of nasogastric tube, lansoprazole delayed-release orally disintegrating tablets can be administered as follows:
• Place a 15 mg tablet in a syringe and draw up 4 mL of water, or place a 30 mg tablet in a syringe and draw up 10 mL of water.
• Shake gently to allow for a quick dispersal.
• After the tablet has dispersed, inject through the nasogastric tube into the stomach in 1-3 mL increments.
• Refill the syringe with approximately 5 mL of water, shake gently, and flush the nasogastric tube.

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FDA-Approved Patient Leaflet

Patient Information

Lansoprazole Delayed-Release Orally Disintegrating Tablets

Read the information that comes with lansoprazole delayed-release orally disintegrating tablets carefully before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What are lansoprazole delayed-release orally disintegrating tablets?
Lansoprazole delayed-release orally disintegrating tablets are a prescription medicine called a proton pump inhibitor (PPI). Lansoprazole delayed-release orally disintegrating tablets reduce the amount of acid in your stomach.

Lansoprazole delayed-release orally disintegrating tablets are used in adults to:

• for 4 weeks to heal ulcers in the first part of the small bowel (duodenal ulcers).
• for up to 12 months to stop healed duodenal ulcers from coming back.
• for up to 8 weeks to heal stomach ulcers.
• for up to 8 weeks to heal stomach ulcers in some people taking medicines called non-steroidal anti-inflammatory drugs (NSAIDs).
• for reducing the risk of stomach ulcers in some people taking NSAIDs.
• for reducing the risk of stomach infections (Helicobacter pylori), along with antibiotics amoxicillin and clarithromycin.
• for up to 8 weeks for the relief of heartburn and other symptoms of gastroesophageal reflux disease (GERD). GERD happens when acid from your stomach enters the tube (esophagus) that connects your mouth to your stomach. This may cause a burning feeling in your chest or throat, sour taste or burping. In some cases, acid can damage the lining of your esophagus. This damage is called erosive esophagitis.
• for 8 weeks to heal the acid-related damage to the lining of the esophagus (called erosive esophagitis) and to relieve symptoms of heartburn and other pain. If needed, your doctor may prescribe an additional 8 weeks of lansoprazole delayed-release orally disintegrating tablets.
• to stop erosive esophagitis from coming back (studies lasted 12 months).
• for the long-term treatment of conditions where your stomach makes too much acid. This includes a condition called Zollinger-Ellison syndrome.

Lansoprazole delayed-release orally disintegrating tablets are used in children and adolescents (ages 1 to 17):
• for up to 12 weeks to treat GERD and erosive esophagitis, in children 1 to 11 years old.
• for up to 8 weeks to treat GERD and erosive esophagitis, in adolescents 12 to 17 years old.

Lansoprazole delayed-release orally disintegrating tablets are not recommended for children under the age of 1 year.

Lansoprazole delayed-release orally disintegrating tablets may help you in the long-term, but you may still have a serious stomach problems. Talk with your doctor.

Who should not take lansoprazole delayed-release orally disintegrating tablets?
Do not take lansoprazole delayed-release orally disintegrating tablets if you are allergic to lansoprazole delayed-release orally disintegrating tablets or any of its ingredients. See the end of this leaflet for a complete list of ingredients in lansoprazole delayed-release orally disintegrating tablets.

What should I tell my doctor before taking lansoprazole delayed-release orally disintegrating tablets?
Before you take lansoprazole delayed-release orally disintegrating tablets, tell your doctor if you:
• have liver problems
• have Phenylketonuria. Lansoprazole delayed-release orally disintegrating tablets contain aspartame.
• have any other medical conditions
• are pregnant or plan to become pregnant. It is not known if lansoprazole delayed-release orally disintegrating tablets will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
• are breastfeeding or planning to breast-feed. You and your doctor should decide if you will take lansoprazole delayed-release orally disintegrating tablets or breast-feed. You should not do both at the same time.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Lansoprazole delayed-release orally disintegrating tablets may affect how other medicines work, and other medicines may affect how lansoprazole delayed-release orally disintegrating tablets work. Especially tell your doctor if you take:
• ampicillin sodium (Unasyn®) or ampicillin trihydrate (Principen®)
• atazanavir (Reyataz®)
• digoxin (Lanoxicaps, Lanoxin®)
• a product that contains iron
• ketoconazole (Nizoral®)
• warfarin (Coumadin®, Jantoven®)
• tacrolimus (Prograf®)
• theophylline (Theo-24, Theolair)
• a drug for your mood or anxiety, if you are not sure if your medicine is listed above.

How should I take lansoprazole delayed-release orally disintegrating tablets?
Take lansoprazole delayed-release orally disintegrating tablets exactly as prescribed by your doctor.
• Do not change your dose or stop taking lansoprazole delayed-release orally disintegrating tablets without talking to your doctor first.
• You should take lansoprazole delayed-release orally disintegrating tablets before eating.
• Lansoprazole delayed-release orally disintegrating tablets is a tablet that melts in your mouth. Do not swallow the tablet whole, break, cut or chew the tablets. See **"Patient Instructions for Use"** at the end of this leaflet for instructions on how to mix the tablet with water and how to take lansoprazole delayed-release orally disintegrating tablets through a syringe and nasogastric tube.
• If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time. Do not take 2 doses at the same time. If you are not sure what to do, call your doctor.
• If you take too many lansoprazole delayed-release orally disintegrating tablets, call your doctor right away.

What are the possible side effects of lansoprazole delayed-release orally disintegrating tablets?
Serious allergic reactions. Tell your doctor if you get any of the following symptoms with lansoprazole delayed-release orally disintegrating tablets.
• rash
• face swelling
• hives
• difficulty breathing

Your doctor may stop lansoprazole delayed-release orally disintegrating tablets if these symptoms happen.

The most common side effects of lansoprazole delayed-release orally disintegrating tablets in adults and children include:
• diarrhea
• stomach pain
• headache
• constipation
• nausea
• dizziness

People who are taking multiple daily doses of proton pump inhibitors for more than a long period of time may have an increased risk of fractures of the hip, wrist or spine.

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of lansoprazole delayed-release orally disintegrating tablets. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store lansoprazole delayed-release orally disintegrating tablets?
• Store lansoprazole delayed-release orally disintegrating tablets at room temperature between 20° to 25°C (68° to 77°F).
• **Keep lansoprazole delayed-release orally disintegrating tablets and all medicines out of the reach of children.**

General information about lansoprazole delayed-release orally disintegrating tablets.
Medicines are sometimes prescribed for conditions other than those listed in a Patient Information Leaflet. Do not use lansoprazole delayed-release orally disintegrating tablets for conditions for which they were not prescribed. Do not give lansoprazole delayed-release orally disintegrating tablets to other people, even if they have the same symptoms you have. They may harm them.

This Patient Information Leaflet provides a summary of the most important information about lansoprazole delayed-release orally disintegrating tablets. For more information, talk with your doctor. You can ask your doctor or pharmacist for information that is written for healthcare professionals. For more information, call 1-888-838-2872, MEDICAL AFFAIRS.

Patients Instructions for Use

Lansoprazole Delayed-Release Orally Disintegrating Tablets
• Do not chew, crush, cut or break tablets.
• Place the tablet in your mouth and let it dissolve, with or without water. Swallow after the tablet dissolves.
  ○ The tablet typically dissolves in less than 1 minute.

For administration using an oral syringe, lansoprazole delayed-release orally disintegrating tablets can be given lansoprazole delayed-release orally disintegrating tablets with an oral syringe or through a nasogastric tube (NG tube) ≥ 8 French, as prescribed by your doctor.

For giving Lansoprazole Delayed-Release Orally Disintegrating Tablets with an oral syringe:
• Put a 15 mg tablet in oral syringe and add 4 mL of water, or put a 30 mg tablet in oral syringe and add 10 mL of water.
  ○ Shake the syringe gently to let the tablet dissolve quickly.
  ○ After the tablet has dissolved, give the medicine in the syringe through the NG tube into the stomach within 15 minutes.
  ○ Refill the syringe with about 5 mL of water, shake gently, and flush the NG tube.

What is in lansoprazole delayed-release orally disintegrating tablets?
Active ingredient: lansoprazole.
Inactive ingredients in lansoprazole delayed-release orally disintegrating tablets:
aspartame*****, cis-3-hexen-1-ol, cis-3-hexen-1-yl acetate, colloidal silicon dioxide, ethyl butyrate, ethyl isovalerate, ethyl-2-methylbutyrate, ethyl valerate, gamma-decalactone cis-3-hexenyl butyrate, gum arabic, hexyl hexanoate cis-3-hexenyl hexanoate, hypromellose, lactose, magnesium carbonate, magnesium stearate, maize starch, maltodextrin, mannitol (E421), methacrylic acid, methyl cinnamate, methyl cinnamate spheres (which contain sucrose and corn starch), talc, titanium dioxide, and triethyl citrate.

*** Aspartame: Contains Phenylalanine 3.71 mg per 15 mg tablet and 7.41 mg per 30 mg tablet.**

Manufactured in Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 9/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-730

LABELING REVIEWS

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-730

Date of Submission: December 27, 2006 (Original) and June 11, 2009 (Amendment)

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

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TENTATIVE APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

All labeling pieces submitted electronically in DRAFT.

		Submission Dates	Recommendation
Blister	15 mg: 10 (2 x 5)	June 11, 2009	Acceptable for Tentative Approval
	30 mg: 6 (2 x 3)	June 11, 2009	Acceptable for Tentative Approval
Carton	15 mg: 30's (3 x 10)	June 11, 2009	Acceptable for Tentative Approval
	30 mg: 30's (5 x 6)	June 11, 2009	Acceptable for Tentative Approval
INSERT		June 11, 2009	Acceptable for Tentative Approval

Revisions needed PRE-approval: YES

1. GENERAL COMMENT:

   The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). We believe the container of 30s to be unit-of-use packaging. Please comment.

2. INSERT:

   a. CONTENTS, 1.9 – Add "(ZES)" following "Syndrome".

   b. CLINICAL STUDIES, Table 16 – Delete the table heading which reads (b) (4) (b) (4), .

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:
(Part of this review came from Chemistry Review #3)

1. MODEL LABELING: Prevacid SoluTab Delayed-Release Orally Disintegrating Tablets, 21-428/S-017, approved October 28, 2008

   NOTE: This is the first generic for this dosage form.

2. INACTIVE INGREDIENTS: Consistent with application. Insert and carton contains aspartame statement (Phenylketonurics: Contains Phenylalanine 3.71 mg per 15 mg tablet and 7.41 mg per 30 mg tablet.)

3. PATENTS/EXCLUSIVITIES

   Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Certification	Labeling Impact	Patent Use Code
021428	002	4628098	May 10, 2009	IV		
021428	002	4628098*PED	Nov 10, 2009	IV		
021428	002	5013743	Feb 12, 2010	IV	**Carved out**	U-452
021428	002	5013743*PED	Aug 12, 2010	IV		
021428	002	5026560*PED	Dec 25, 2008	IV - Expired		
021428	002	5045321	Sep 3, 2008	IV - Expired		
021428	002	5045321*PED	Mar 3, 2009	IV - Expired		
021428	002	5093132	Sep 3, 2008	IV - Expired		
021428	002	5093132*PED	Mar 3, 2009	IV - Expired		
021428	002	5433959	Sep 3, 2008	IV - Expired		
021428	002	5433959*PED	Mar 3, 2009	IV - Expired		
021428	002	5464632	Nov 7, 2012	IV		
021428	002	5464632*PED	May 7, 2013	IV		
021428	002	6328994	May 17, 2019	IV		
021428	002	6328994*PED	Nov 17, 2019	IV		
021428	002	7399485	May 26, 2018	Late-listed		
021428	002	7399485*PED	Nov 26, 2018	Late-listed		
021428	002	7431942	May 17, 2019	Late-listed		
021428	002	7431942*PED	Nov 17, 2019	Late-listed		

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
021428	002	**M-85**	Oct 28, 2011	**Carved out**
021428	002	**PED**	Apr 28, 2012	**Carved out**

Code	Definition
U-452	USE OF LANSOPRAZOLE FOR COMBATTING DISEASES CAUSED BY THE GENUS CAMPYLOBACTER (C.PYLORI=H.PYLORI)
M-85	INFORMATION ADDED TO LABELING REGARDING USE OF PREVACID IN PATIENTS LESS THAN 1 YEAR WITH SYMPTOMATIC GERD

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - USP: No
   - NDA: Store at 25°C (77°F); excursions permitted to 15-30° C (59-86°F) [See USP Controlled Room Temperature]
   - ANDA: Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature].
   - Stability conducted at 40°C/75% RH and 25°C/60% RH

5. DISPENSING STATEMENT COMPARISON
   - NDA: "PACKAGE NOT CHILD-RESISTANT Dispense in a child-resistant container-closure package"
   - ANDA: "PACKAGE NOT CHILD-RESISTANT This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized."

6. PACKAGE CONFIGURATION
   - NDA: Unit dose packages of 100
   - ANDA: 15 mg: unit dose cartons of 30 tablets (3 blister cards x 10 tablets)
     30 mg: unit dose cartons of 30 tablets (5 blister cards x 6 tablets)

7. CONTAINER/CLOSURE
   blister packed in aluminum foil with (b) (4) aluminum foil on one side and aluminum foil with (b) (4) on the other

8. FINISHED DOSAGE FORM
   - NDA: 15 mg: white to yellowish white uncoated tablets with orange to dark brown speckles, with "15" debossed on one side of the tablet. 30 mg: white to yellowish white uncoated tablets with orange to dark brown speckles, with "30" debossed on one side of the tablet.
   - ANDA: 15 mg: white to off-white, flat, beveled tablet, with white to grayish speckles, debossed with "15" on one side of the tablet and plain on the other side. 30 mg: white to off-white, flat, beveled tablet, with white to grayish speckles, debossed with "30" on one side of the tablet and plain on the other side

10. MANUFACTURER
    First manufacturer: TEVA Pharmaceutical Industries, Ltd.
    Hashikma Street, Industrial Area, P.O. Box 353, Kfar-Saba 44102 Israel

    Additional manufacturer proposed in amendment dated September 15, 2008:
    TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

11. The disintegration time is NMT 60 seconds for both 15 mg and 30 mg strengths. (See Chemistry Review #3 and September 10, 2008 Amendment)

12. Dissolution per the Bioequivalence Review (signed on 6/24/09) states:

```
The dissolution testing should be conducted in 500 mL of
0.1 N HCl for the first hour followed by 900 mL phosphate
buffer pH 6.8 with 5 mM SDS (second hour) at 37ºC + 0.5ºC
using USP apparatus 2 at 75 rpm. The test product should
meet the following specifications:

   Acid stage: NMT (b) (4) in 60 minutes
   Buffer stage: NLT (b) (4) (Q) in 30 minutes
```

Primary Reviewer: Sarah Park

Team Leader: Koung Lee

TA Summary

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

/s/

Soojung Sarah Park
6/25/2009 02:11:01 PM
LABELING REVIEWER

Koung Lee
6/26/2009 11:38:21 AM
LABELING REVIEWER
For Wm Peter Rickman

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-730

Date of Submission: October 5, 2009 (Amendment)

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

---

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

All labeling pieces submitted electronically in final print.

		Submission Dates	Recommendation
Blister	15 mg: 10 (2 x 5)	October 5, 2009	Acceptable for Approval
	30 mg: 6 (2 x 3)	October 5, 2009	Acceptable for Approval
Carton	15 mg: 30's (3 x 10)	October 5, 2009	Acceptable for Approval
	30 mg: 30's (5 x 6)	October 5, 2009	Acceptable for Approval
INSERT		October 5, 2009	Acceptable for Approval

Revisions needed post-approval: yes

INSERT

a. HIGHLIGHT OF PRESCRIBING INFORMATION – Add "For oral administration" above "Initial U.S. Approval…"

b. Please delete the use of the terminal zero (e.g. "5 mcg/mL" instead of "5.0 mcg/mL").

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:
(Part of this review came from Chemistry Review #3)

1. MODEL LABELING: Prevacid SoluTab Delayed-Release Orally Disintegrating Tablets, 21-428/S-019, approved July 31, 2009

   NOTE: This is the first generic for this dosage form.

2. INACTIVE INGREDIENTS: Consistent with application. Insert and carton contains aspartame statement (Phenylketonurics: Contains Phenylalanine 3.71 mg per 15 mg tablet and 7.41 mg per 30 mg tablet.)

3. PATENTS/EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Certification	Labeling Impact	Patent Use Code
021428	002	4628098	May 10, 2009	IV		
021428	002	4628098*PED	Nov 10, 2009	IV		
021428	002	5013743	Feb 12, 2010	viii	**MOU - Carved out**	U-452
021428	002	5013743*PED	Aug 12, 2010	viii		
021428	002	5026560*PED	Dec 25, 2008	IV - Expired		
021428	002	5045321	Sep 3, 2008	IV - Expired		
021428	002	5045321*PED	Mar 3, 2009	IV - Expired		
021428	002	5093132	Sep 3, 2008	IV - Expired		
021428	002	5093132*PED	Mar 3, 2009	IV - Expired		
021428	002	5433959	Sep 3, 2008	IV - Expired		
021428	002	5433959*PED	Mar 3, 2009	IV - Expired		
021428	002	5464632	Nov 7, 2012	IV		
021428	002	5464632*PED	May 7, 2013	IV		
021428	002	6328994	May 17, 2019	IV		
021428	002	6328994*PED	Nov 17, 2019	IV		
021428	002	7399485	May 26, 2018	Late-listed		
021428	002	7399485*PED	Nov 26, 2018	Late-listed		
021428	002	7431942	May 17, 2019	Late-listed		
021428	002	7431942*PED	Nov 17, 2019	Late-listed		

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
021428	002	M-85 *	Oct 28, 2011	**Carved out**
021428	002	PED	Apr 28, 2012	**Carved out**

Code	Definition
U-452	USE OF LANSOPRAZOLE FOR COMBATTING DISEASES CAUSED BY THE GENUS CAMPYLOBACTER (C.PYLORI=H.PYLORI)
M-85	INFORMATION ADDED TO LABELING REGARDING USE OF PREVACID IN PATIENTS LESS THAN 1 YEAR WITH SYMPTOMATIC GERD

*** The new pediatric information is regarding a pediatric study which showed that lansoprazole was not effective in pediatric patients 1 month to less than 12 months of age. An NPP (method of use) was not granted for this age group. No safety information was added as a result of the failed clinical studies. Previous pediatric exclusivities for ages 1 to 11 years and 12 to 17 years have both expired.**

In a meeting on June 5, 2009 with Peter Rickman, Koung Lee, and Sarah Park, it was decided that the information protected by M-85 can be a straight carve out, and a BPCA consult would not be initiated.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - USP: No
   - NDA: Store at 25°C (77°F); excursions permitted to 15-30° C (59-86°F) [See USP Controlled Room Temperature]
   - ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
   - Stability conducted at 40°C/75% RH and 25°C/60% RH

5. DISPENSING STATEMENT COMPARISON
   - NDA: "PACKAGE NOT CHILD-RESISTANT Dispense in a child-resistant container-closure package"
   - ANDA: "PACKAGE NOT CHILD-RESISTANT This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized."

6. PACKAGE CONFIGURATION
   - NDA: Unit dose packages of 100
   - ANDA: 15 mg: unit dose cartons of 30 tablets (3 blister cards x 10 tablets)
     30 mg: unit dose cartons of 30 tablets (5 blister cards x 6 tablets)

7. CONTAINER/CLOSURE
   blister packed in aluminum foil with (b) (4) aluminum foil on one side and aluminum foil with (b) (4) on the other

8. FINISHED DOSAGE FORM
   - NDA: 15 mg: white to yellowish white uncoated tablets with orange to dark brown speckles, with "15" debossed on one side of the tablet. 30 mg: white to yellowish white uncoated tablets with orange to dark brown speckles, with "30" debossed on one side of the tablet.
   - ANDA: 15 mg: white to off-white, flat, beveled tablet, with white to grayish speckles, debossed with "15" on one side of the tablet and plain on the other side. 30 mg: white to off-white, flat, beveled tablet, with white to grayish speckles, debossed with "30" on one side of the tablet and plain on the other side

10. MANUFACTURER
    First manufacturer: TEVA Pharmaceutical Industries, Ltd.
    Hashikma Street, Industrial Area, P.O. Box 353, Kfar-Saba 44102 Israel

    Additional manufacturer proposed in amendment dated September 15, 2008:
    TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

11. The disintegration time is NMT 60 seconds for both 15 mg and 30 mg strengths. (See Chemistry Review #3 and September 10, 2008 Amendment) This is consistent with the approved labeling "The tablet typically disintegrates in less than 1 minute."

12. Dissolution per the Bioequivalence Review (signed on 6/24/09) states:

```
The dissolution testing should be conducted in 500 mL of
0.1 N HCl for the first hour followed by 900 mL phosphate
buffer pH 6.8 with 5 mM SDS (second hour) at 37ºC + 0.5ºC
using USP apparatus 2 at 75 rpm. The test product should
meet the following specifications:

   Acid stage: NMT (b) (4) in 60 minutes
   Buffer stage: NLT (b) (4) (Q) in 30 minutes
```

Primary Reviewer: Sarah Park

Team Leader: Koung Lee

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

SOOJUNG S PARK
10/30/2009

KOUNG U LEE
10/30/2009
For Wm Peter Rickman

****This AP Summary review supersedes review dated October 30, 2009.****

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 078730

Date of Submission: May 18, 2010, August 12, 2010, and September 14, 2010 (Amendments)

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Lansoprazole Delayed-release Orally Disintegrating Tablets, 15 mg and 30 mg

Proprietary Name: None proposed

REMS required?
☐ Yes ☒No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? E-Submission.

	Date Submitted	Recommendation
BLISTER [Blister card of 10 (2 x 5) and 6 (2 x3)]	October 5, 2009	Acceptable for Approval
CARTON [Unit dose tablets of 30 (3 x 10) and (5 x 6)]	October 5, 2009	Acceptable for Approval
INSERT	September 14, 2010	Acceptable for Approval

REVISIONS NEEDED POST-APPROVAL: No

NOTES/QUESTIONS TO THE CHEMIST: No

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of Prevacid SoluTab Delayed-release Orally Disintegrating Tablets, NDA 021428/S-021; approved September 3, 2010 (Shares the insert with Prevacid Delayed-release Capsules). NDA 021428/S-022 is pending review with OND.

2. USP MONOGRAPH (checked on 10/12/10)
   This drug product is not the subject of a USP Monograph.
   PF: no new information.

3. PATENTS AND EXCLUSIVITIES (checked on 10/12/10)
   Patent Data NDA

Patent #	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5,464,632	May 7, 2013	None		pIV	None
6,328,994	November 17, 2019	None		pIV	None
7,399,485	November 26, 2018	None		Late Listed	None
7,431,942	November 17, 2019	None		Late Listed	None

Exclusivity Data NDA

Code/Sup	Expiration	Description	How Filed	Labeling Impact
PED	April 28, 2012	Pediatric Exclusivity		Carved Out
M-85	October 28, 2011	Use in patients less than 1 year with symptomatic GERD		Carved Out

Per AP Summary review dated October 30, 2009, “in a meeting on June 5, 2009 with Peter Rickman, Koung Lee and Sarah Park, it was decided that the information protected by M-85 can be a straight carve out, and a BPCA consult would not be initiated.”

4. INACTIVE INGREDIENTS:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert **IS** consistent with the listing of inactive ingredients found in the statement of components and composition.

   Insert and carton contains aspartame statement: Phenylketonurics: Contains Phenylalanine 3.71 mg per 15 mg tablet and 7.41 mg per 30 mg tablet.

5. MANUFACTURING FACILITY
   Manufactured by:
   TEVA Pharmaceutical Ind. Ltd.
   Jerusalem, 91010
   Isreal

   Manufactured for:
   TEVA Pharmaceuticals USA
   Sellersville, PA

6. PRODUCT DESCRIPTION:
   RLD: 15 mg: white to yellowish white uncoated tablets with orange to dark brown speckles, with “15” debossed on one side of the tablet.
   30 mg: white to yellowish white uncoated tablets with orange to dark brown speckles, with “30” debossed on one side of the tablet.
   ANDA: 15 mg: white to off-white, flat, beveled round, artificial strawberry flavored tablet, with white to grayish speckles, debossed with “15” on one side of the tablet.
   30 mg: white to off-white, flat, beveled round, artificial strawberry flavored tablet, with white to

grayish speckles, debossed with “30” on one side of the tablet.

None of the tablets are scored.

7. CONTAINER/CLOSURE SYSTEM:
   Blister packed in aluminum foil with (b) (4) *aluminum foil on one side and aluminum foil with* (b) (4) *on the other side.*

8. PRODUCT LINE:
   RLD: Unit dose packages of 100
   ANDA: 15 mg: unit dose cartons of 30 tablets (3 blister cards x 10 tablets)
   30 mg: unit dose cartons of 30 tablets (5 blister cards x 6 tablets)

9. STORAGE CONDITIONS:
   RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
   ANDA: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

   Stability studies of exhibit are conducted at 25 ± 2°C and 60 ± 5% RH and 40 ± 2°C and 75 ± 5% RH.

10. DISPENSING RECOMMENDATIONS:
    RLD: “PACKAGE NOT CHILD-RESISTANT Dispense in a child-resistant container-closure package.”
    ANDA: “PACKAGE NOT CHILD-RESISTANT This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.”

11. SPL DATA ELEMENTS: (checked 10/12/10)
    Not submitted.

12. MEDWATCH: (checked 10/12/10)
    No new alerts or labeling changes.

13. REMS: (checked 10/12/10)
    No approved REMS.

14. MEDICATION GUIDE: None

15. TALL MAN LETTERS: N/A

16. CITIZEN'S PETITION/SUITABILITY PETITION/PROPRIETARY NAME: None

---

Date of Review: October 12, 2010

Primary Reviewer: Theresa Liu

Team Leader: Koung Lee

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

/s/

THERESA C LIU
10/14/2010

KOUNG U LEE
10/14/2010
For Wm Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-730

CHEMISTRY REVIEWS

ANDA 78-730

Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

TEVA Pharmaceuticals USA

Shahnaz Read
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 78-730

2. REVIEW #: 1

3. REVIEW DATE: May 16, 2007

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS: NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	December 27, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative	Philip Erikson, R.Ph., Senior Director, Regulatory Affairs
Telephone:	215-591-3141
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Lansoprazole Delayed-Release Orally Disintegrating Tablets

9. LEGAL BASIS FOR SUBMISSION:
The basis for this ANDA submission is the RLD Prevacid® (NDA 21-428) manufactured by Tap Pharmaceuticals. The applicant has filed paragraph III certification for U.S. Patent Nos. 6,123,962 and 6,749,864 which expire on February 13, 2007. The applicant has filed paragraph IV certification for U.S. Patent Nos. 5013743 (February 12, 2010), 5026560 (June 25, 2008), 5045321 (September 3, 2008), 5093132 (September 3, 2008) and 5433959 (September 3, 2008)5464632 (November 7, 2012) and 6328994 (May 17, 2007). The applicant also certifies there is a marketing exclusivity for New Patient Population listed for this product in the Orange Book and that they do not plan to market the product prior to its expiration on June 17, 2007.

10. PHARMACOLOGICAL CATEGORY: Anti-ulcer.

11. DOSAGE FORM: Delayed-Release Capsules

12. STRENGTH/POTENCY: 15 mg and 30 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

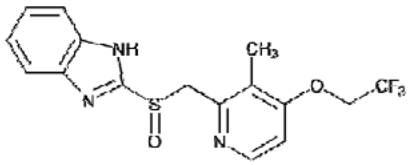
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl] sulfinyl]-1H-Benzimidazole.
2-(2-Benzimidazolylsulfinylmethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine.

Chemical Structure:



Molecular Formula: $C_{16}H_{14}F_3N_3O_2S$
Molecular Weight: 369.37

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
17551	II	Assia (Teva)	Lansoprazole	1	Adequate	1/26/07	
(b) (4)	III	(b) (4)		4	NA		

[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 NA (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	4/18/07	S. Adams
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Pending		
EA	Categorical Exclusion		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for ANDA # 78-730

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable for CMC.

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 substance is compendial. It is a white to brownish, odorless crystalline powder that is freely soluble in dimethylformamide and soluble in methanol. It exists in two polymorphic forms and the applicant has used the form that they (b) (4) (b) (4)

The drug product is not compendial. It is manufactured by (b) (4) to produce two strengths, 15 mg and 30 mg. These are then packaged into unit dose aluminum blister packs.

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

It is used as an oral drug for treatment in healing and symptomatic relief of active duodenal ulcers.

C. Basis for Approvability or Not-Approval Recommendation

The firm needs to resolve issues relating to

Following this page, 16 pages withheld in full - (b)(4)

34. BIOEQUIVALENCE

Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

A categorical exclusion from the requirement of an Environmental Assessment or Environmental Impact Statement is requested in accordance with 21 CFR 25.31(a).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-730 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

9.

B. Comments:

1. The labeling and bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

2. Please provide updated stability data for the exhibit batch.

3. Please provide representative packaged samples of the RLD and your own drug product to assist in our evaluation of the ANDA. The samples should be sent separately to:

   Theresa Liu, Project Manager, Team 7
   Division of Chemistry II
   Office of Generic Drugs
   7500 Standish Place
   Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-730
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/5/16/07

HFD-645/SFurness/05/31/07

HFD-617/TLiu/05/31/07

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

/s/

Shanaz Read
6/6/2007 09:26:23 AM
CHEMIST

Theresa Liu
6/6/2007 11:03:24 AM
CSO

Michael S Furness
6/7/2007 02:09:11 PM
CHEMIST

ANDA 78-730

Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

TEVA Pharmaceuticals USA

Shahnaz Read
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 78-730

2. REVIEW #: 2

3. REVIEW DATE: January 12, 2009

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS: NA

Submission(s) Reviewed	Document Date
Original	December 27, 2006
Review #1	May 16, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Major Amendment	September 10, 2008
Minor Amendment	September 15, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative	Philip Erikson, R.Ph., Senior Director, Regulatory Affairs
Telephone:	215-591-3141
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Lansoprazole Delayed-Release Orally Disintegrating Tablets

9. LEGAL BASIS FOR SUBMISSION:
The basis for this ANDA submission is the RLD Prevacid® (NDA 21-428) manufactured by Tap Pharmaceuticals. The applicant has filed paragraph III certification for U.S. Patent Nos. 6,123,962 and 6,749,864 which expire on February 13, 2007. The applicant has filed paragraph IV certification for U.S. Patent Nos. 5013743 (February 12, 2010), 5026560 (June 25, 2008), 5045321 (September 3, 2008), 5093132 (September 3, 2008) and 5433959 (September 3, 2008)5464632 (November 7, 2012) and 6328994 (May 17, 2007). The applicant also certifies there is a marketing exclusivity for New Patient Population listed for this product in the Orange Book and that they do not plan to market the product prior to its expiration on June 17, 2007.

10. PHARMACOLOGICAL CATEGORY: Anti-ulcer.

11. DOSAGE FORM: Delayed-Release Capsules

12. STRENGTH/POTENCY: 15 mg and 30 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

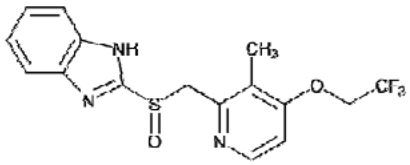
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl] sulfinyl]-1H-Benzimidazole.
2-(2-Benzimidazolylsulfinylmethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine.

Chemical Structure:



Molecular Formula: $C_{16}H_{14}F_3N_3O_2S$
Molecular Weight: 369.37

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
17551	II	Assia (Teva)	Lansoprazole	1	Adequate	1/26/07	
(b) (4)	III	(b) (4)		4	NA		

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4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

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

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for ANDA # 78-730

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable for CMC.

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 substance is compendial. It is a white to brownish, odorless crystalline powder that is freely soluble in dimethylformamide and soluble in methanol. It exists in two polymorphic forms and the applicant has used the form that they (b) (4) (b) (4)

The drug product is not compendial. It is manufactured by (b) (4) to produce two strengths, 15 mg and 30 mg. These are then packaged into unit dose aluminum blister packs.

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

It is used as an oral drug for treatment in healing and symptomatic relief of active duodenal ulcers.

C. Basis for Approvability or Not-Approval Recommendation

The firm needs to resolve issues noted in the deficiency letter.

Following this page, 20 pages withheld in full - (b)(4)

Comment from Review #2: Please explain the (b) (4) ***of batches 2621-014 and 2621-015.***

30. MICROBIOLOGY

NA

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

NA

32. LABELING

Pending

33. ESTABLISHMENT INSPECTION

Pending

34. BIOEQUIVALENCE

Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

A categorical exclusion from the requirement of an Environmental Assessment or Environmental Impact Statement is requested in accordance with 21 CFR 25.31(a).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-730 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

1.

2.

3.

4.

5. (b) (4)

6.

B. Comments:

1. Please provide updated stability data for the exhibit batches.

2. Please provide representative packaged samples (about 20 tablets each) of the drug product batches made with the revised formulation K-39662 (15 mg) and K-39663 (30 mg) and the batches manufactured at the alternate site 2621-014 (15 mg) and 2621-015 (30 mg) to assist in our evaluation of the ANDA. The samples should be sent separately to:

   Theresa Liu, Project Manager, Team 7
   Division of Chemistry II
   Office of Generic Drugs
   7500 Standish Place
   Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-730
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/1/12/09

HFD-645/2/18/09

HFD-617/TLiu/2/19/09

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

/s/

Shanaz Read
2/20/2009 08:35:47 AM
CHEMIST

Theresa Liu
2/20/2009 10:06:14 AM
CSO

Damaris Maldonado
2/20/2009 10:30:11 AM
CHEMIST

ANDA 78-730

Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

TEVA Pharmaceuticals USA

Shahnaz Read
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 78-730

2. REVIEW #: 4

3. REVIEW DATE: June 16, 2009; July 29, 2009

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS: NA

Submission(s) Reviewed	Document Date
Original	December 27, 2006
Review #1	May 16, 2007
Major Amendment	September 10, 2008
Minor Amendment	September 15, 2008
Review #2	January 12, 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendments	March 27 and 31, 2009
Telephone Amendment	June 16 and 23, 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative	Philip Erikson, R.Ph., Senior Director, Regulatory Affairs
Telephone:	215-591-3141
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Lansoprazole Delayed-Release Orally Disintegrating Tablets

9. LEGAL BASIS FOR SUBMISSION:
The basis for this ANDA submission is the RLD Prevacid® (NDA 21-428) manufactured by Tap Pharmaceuticals. The applicant has filed paragraph III certification for U.S. Patent Nos. 6,123,962 and 6,749,864 which expire on February 13, 2007. The applicant has filed paragraph IV certification for U.S. Patent Nos. 5013743 (February 12, 2010), 5026560 (June 25, 2008), 5045321 (September 3, 2008), 5093132 (September 3, 2008) and 5433959 (September 3, 2008)5464632 (November 7, 2012) and 6328994 (May 17, 2007). The applicant also certifies there is a marketing exclusivity for New Patient Population listed for this product in the Orange Book and that they do not plan to market the product prior to its expiration on June 17, 2007.

10. PHARMACOLOGICAL CATEGORY: Anti-ulcer.

11. DOSAGE FORM: Delayed-Release Capsules

12. STRENGTH/POTENCY: 15 mg and 30 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

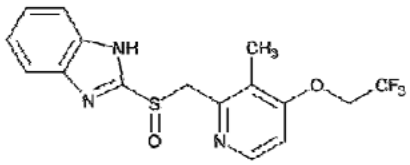
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl] sulfinyl]-1H-Benzimidazole.
2-(2-Benzimidazolylsulfinylmethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine.

Chemical Structure:



Molecular Formula: $C_{16}H_{14}F_3N_3O_2S$
Molecular Weight: 369.37

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
17551	II	Assia (Teva)	Lansoprazole	1	Adequate	1/26/07	
(b) (4)	III	(b) (4)		4	NA		

[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 NA (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	6/24/09	
Methods Validation	NA		
Labeling	Acceptable	6/26/09	
Bioequivalence	Acceptable	6/24/09	
EA	Categorical Exclusion		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for ANDA # 78-730

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 substance is compendial. It is a white to brownish, odorless crystalline powder that is freely soluble in dimethylformamide and soluble in methanol. It exists in two polymorphic forms and the applicant has used the form that they (b) (4) (b) (4).

The drug product is not compendial. It is manufactured by (b) (4) to produce two strengths, 15 mg and 30 mg. These are then packaged into unit dose aluminum blister packs.

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

It is used as an oral drug for treatment in healing and symptomatic relief of active duodenal ulcers.

C. Basis for Approvability or Not-Approval Recommendation

The firm needs to address manufacturing issues as detailed in the letter.

Following this page, 23 pages withheld in full - (b)(4)

32. LABELING

Acceptable 6/26/09

33. ESTABLISHMENT INSPECTION

Acceptable 6/24/09

34. BIOEQUIVALENCE

Acceptable 6/24/09

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

A categorical exclusion from the requirement of an Environmental Assessment or Environmental Impact Statement is requested in accordance with 21 CFR 25.31(a).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-730 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

A. The deficiencies presented below represent Minor deficiencies.

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

9.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-730
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/6/16/09

HFD-645/DMaldonado/6/16/09; 7/29/09

HFD-617/TLiu/7/30/09

Minor

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
ANDA 78730	ORIG 1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

SHAHNAZ T READ
07/30/2009

THERESA C LIU
07/30/2009

DAMARIS C MALDONADO
07/30/2009

ANDA 78-730

Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

TEVA Pharmaceuticals USA

Shahnaz Read
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 78-730

2. REVIEW #: 4

3. REVIEW DATE: September 25, 2009, revised November 1, 2009

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS: NA

Submission(s) Reviewed	Document Date
Original	December 27, 2006
Review #1	May 16, 2007
Major Amendment	September 10, 2008
Minor Amendment	September 15, 2008
Review #2	January 12, 2009
Minor Amendments	March 27 and 31, 2009
Telephone Amendment	June 16 and 23, 2009
Review #3	July 29, 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendments	August 27, 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative	Philip Erikson, R.Ph., Senior Director, Regulatory Affairs
Telephone:	215-591-3141
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA

b) Non-Proprietary Name (USAN): Lansoprazole Delayed-Release Orally Disintegrating Tablets

9. LEGAL BASIS FOR SUBMISSION:
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10. PHARMACOLOGICAL CATEGORY: Anti-ulcer.

11. DOSAGE FORM: Delayed-Release Capsules

12. STRENGTH/POTENCY: 15 mg and 30 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

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

__X__ Not a SPOTS product

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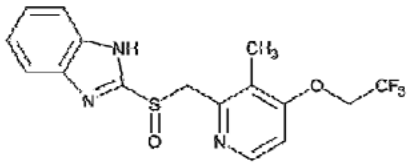
2-(2-Benzimidazolylsulfinylmethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine.

Chemical Structure:



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6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	6/24/09	
Methods Validation	NA		
Labeling	Acceptable	10/30/09	
Bioequivalence	Acceptable	6/24/09	
EA	Categorical Exclusion		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for ANDA # 78-730

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Minor Deficiency.

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 substance is compendial. It is a white to brownish, odorless crystalline powder that is freely soluble in dimethylformamide and soluble in methanol. It exists in two polymorphic forms and the applicant has used the form that they (b) (4) (b) (4)

The drug product is not compendial. It is manufactured by (b) (4) to produce two strengths, 15 mg and 30 mg. These are then packaged into unit dose aluminum blister packs.

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

It is used as an oral drug for treatment in healing and symptomatic relief of active duodenal ulcers.

C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been addressed.

Following this page, 24 pages withheld in full - (b)(4)

(b) (4)

[redacted]

30. MICROBIOLOGY

NA

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

NA

32. LABELING

Acceptable 10/30/09

33. ESTABLISHMENT INSPECTION

Acceptable 6/24/09

34. BIOEQUIVALENCE

Acceptable 6/24/09

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

A categorical exclusion from the requirement of an Environmental Assessment or Environmental Impact Statement is requested in accordance with 21 CFR 25.31(a).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-730 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

3.

4.

5.

c. (b) (4)

d.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-730
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/9/25/09, revised 11/1/09

HFD-645/DMaldonado/11/2/09

HFD-617/TLiu/11/2/09

Minor

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

SHAHNAZ T READ
11/02/2009

THERESA C LIU
11/02/2009

DAMARIS C MALDONADO
11/02/2009

ANDA 78-730

Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

TEVA Pharmaceuticals USA

Shahnaz Read
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 78-730

2. REVIEW #: 5

3. REVIEW DATE: January 10, 2010

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS: NA

Submission(s) Reviewed	Document Date
Original	December 27, 2006
Review #1	May 16, 2007
Major Amendment	September 10, 2008
Minor Amendment	September 15, 2008
Review #2	January 12, 2009
Minor Amendments	March 27 and 31, 2009
Telephone Amendment	June 16 and 23, 2009
Review #3	July 29, 2009
Minor Amendments	August 27, 2009
Review #4	November 1, 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendments	November 12, 2009, November 25, 2009, December 28, 2009 and January 8, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative	Philip Erikson, R.Ph., Senior Director, Regulatory Affairs
Telephone:	215-591-3141
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Lansoprazole Delayed-Release Orally Disintegrating Tablets

9. LEGAL BASIS FOR SUBMISSION:
The basis for this ANDA submission is the RLD Prevacid® (NDA 21-428) manufactured by Tap Pharmaceuticals. The applicant has filed paragraph III certification for U.S. Patent Nos. 6,123,962 and 6,749,864 which expire on February 13, 2007. The applicant has filed paragraph IV certification for U.S. Patent Nos. 5013743 (February 12, 2010), 5026560 (June 25, 2008), 5045321 (September 3, 2008), 5093132 (September 3, 2008) and 5433959 (September 3, 2008)5464632 (November 7, 2012) and 6328994 (May 17, 2007). The applicant also certifies there is a marketing exclusivity for New Patient Population listed for this product in the Orange Book and that they do not plan to market the product prior to its expiration on June 17, 2007.

10. PHARMACOLOGICAL CATEGORY: Anti-ulcer.

11. DOSAGE FORM: Delayed-Release Capsules

12. STRENGTH/POTENCY: 15 mg and 30 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

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

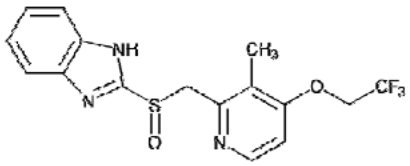
__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl] sulfinyl]-1H-Benzimidazole.
2-(2-Benzimidazolylsulfinylmethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine.

Chemical Structure:

Chemistry Review Data Sheet



Molecular Formula: $C_{16}H_{14}F_3N_3O_2S$
Molecular Weight: 369.37

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
17551	II	Assia (Teva)	Lansoprazole	1	Adequate	10/1/09	
(b) (4)	III	(b) (4)		4	NA		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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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 NA (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	6/24/09	
Methods Validation	NA		
Labeling	Acceptable	6/26/09	
Bioequivalence	Acceptable	6/24/09	
EA	Categorical Exclusion		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for ANDA # 78-730

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)

The drug substance is compendial. It is a white to brownish, odorless crystalline powder that is freely soluble in dimethylformamide and soluble in methanol. It exists in two polymorphic forms and the applicant has used the form that they (b) (4) (b) (4)

The drug product is not compendial. It is manufactured by (b) (4) to produce two strengths, 15 mg and 30 mg. These are then packaged into unit dose aluminum blister packs.

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

It is used as an oral drug for treatment in healing and symptomatic relief of active duodenal ulcers.

C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been addressed.

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35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

A categorical exclusion from the requirement of an Environmental Assessment or Environmental Impact Statement is requested in accordance with 21 CFR 25.31(a).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

None

cc: ANDA 78-730
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/1/10/10

HFD-645/DMaldonado/01/11/10

HFD-617/TLiu/1/14/10

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

SHAHNAZ T READ
01/15/2010

DAMARIS C MALDONADO
01/19/2010

THERESA C LIU
01/19/2010

ANDA 78730

Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

TEVA Pharmaceuticals USA

Shahnaz Read
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 78730

2. REVIEW #: 5

3. REVIEW DATE: January 10, 2010, amended March 19, 2010

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS: NA

Submission(s) Reviewed	Document Date
Original	December 27, 2006
Review #1	May 16, 2007
Major Amendment	September 10, 2008
Minor Amendment	September 15, 2008
Review #2	January 12, 2009
Minor Amendments	March 27 and 31, 2009
Telephone Amendment	June 16 and 23, 2009
Review #3	July 29, 2009
Minor Amendments	August 27, 2009
Review #4	November 1, 2009

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Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative	Philip Erikson, R.Ph., Senior Director, Regulatory Affairs
Telephone:	215-591-3141
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Lansoprazole Delayed-Release Orally Disintegrating Tablets

9. LEGAL BASIS FOR SUBMISSION:
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11. DOSAGE FORM: Delayed-Release Capsules

12. STRENGTH/POTENCY: 15 mg and 30 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

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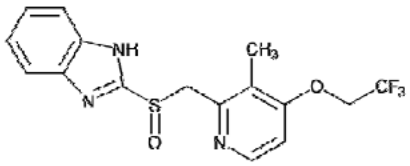
Chemical Name(s): 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl] sulfinyl]-1H-Benzimidazole.
2-(2-Benzimidazolylsulfinylmethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine.

Chemical Structure:

Chemistry Review Data Sheet



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Molecular Weight: 369.37

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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(b) (4)	III	(b) (4)		4	NA		

[1] Action codes for DMF Table:
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3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
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7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	6/24/09	
Methods Validation	NA		
Labeling	Acceptable	6/26/09	
Bioequivalence	Acceptable	6/24/09	
EA	Categorical Exclusion		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for ANDA # 78730

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 substance is compendial. It is a white to brownish, odorless crystalline powder that is freely soluble in dimethylformamide and soluble in methanol. It exists in two polymorphic forms and the applicant has used the form that they (b) (4) (b) (4)

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

It is used as an oral drug for treatment in healing and symptomatic relief of active duodenal ulcers.

C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have not been resolved.

Following this page, 34 pages withheld in full - (b)(4)

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
A categorical exclusion from the requirement of an Environmental Assessment or Environmental Impact Statement is requested in accordance with 21 CFR 25.31(a).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-730 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

A. The deficiencies presented below represent Minor deficiencies.

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

9.

10.

11. [redacted] (b) (4)

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-730
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/3/19/10

HFD-645/RRajagopalan/3/19/09

HFD-617/TLiu/3/19/09

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

SHAHNAZ T READ
03/19/2010

THERESA C LIU
03/19/2010

RADHIKA RAJAGOPALAN
03/19/2010

ANDA 78730

Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

TEVA Pharmaceuticals USA

Shahnaz Read
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 78730

2. REVIEW #: 6

3. REVIEW DATE: March 25, 2010, revised September 23, 2010

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS: NA

Submission(s) Reviewed	Document Date
Original	December 27, 2006
Review #1	May 16, 2007
Major Amendment	September 10, 2008
Minor Amendment	September 15, 2008
Review #2	January 12, 2009
Minor Amendments	March 27 and 31, 2009
Telephone Amendment	June 16 and 23, 2009
Review #3	July 29, 2009
Minor Amendments	August 27, 2009
Review #4	November 1, 2009
Minor Amendments	November 12, 2009, November 25, 2009, December 28, 2009 and January 8, 2010
Review #5	March 19, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	March 23, 2010
Minor Amendments	June 11, 2010, September 8 and 15, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	TEVA Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454

Representative	Philip Erikson, R.Ph., Senior Director, Regulatory Affairs
Telephone:	215-591-3141
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Lansoprazole Delayed-Release Orally Disintegrating Tablets

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12. STRENGTH/POTENCY: 15 mg and 30 mg.

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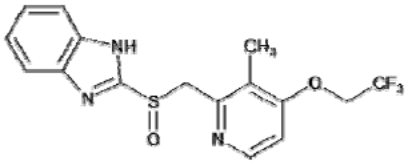
Chemical Name(s): 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl] sulfinyl]-1H-Benzimidazole.
2-(2-Benzimidazolylsulfinylmethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine.

Chemical Structure:



Molecular Formula: $C_{16}H_{14}F_3N_3O_2S$
Molecular Weight: 369.37

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
17551	II	Assia (Teva)	Lansoprazole	1	Adequate	10/1/09	S. Read
(b) (4)	III	(b) (4)		4	NA		

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	6/24/09	
Methods Validation	NA		
Labeling	Pending		See Final Approval Routing summary
Bioequivalence	Acceptable	9/22/10	P. Kaur
EA	Categorical Exclusion		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for ANDA # 78730

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)

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The drug product is not compendial. It is manufactured by (b) (4) to produce two strengths, 15 mg and 30 mg. These are then packaged into unit dose aluminum blister packs.

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

It is used as an oral drug for treatment in healing and symptomatic relief of active duodenal ulcers. Maximum daily dose for this drug product is 30 mg (or 15 mg).

C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been resolved. For labeling see Final Approval Routing Summary.

Following this page, 51 pages withheld in full - (b)(4)

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
A categorical exclusion from the requirement of an Environmental Assessment or Environmental Impact Statement is requested in accordance with 21 CFR 25.31(a).

cc: ANDA 78-730
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/3/25/10, revised 9/23/10

HFD-645/RRajagopalan/4/22/10; 6/4/10 (T-con With Teva during meeting with Bio, and OGD Science staff); 9/23/10 (joint T-con by Bio and CMC staff with Teva's personnel regarding dissolution testing procedure); 9/23/10 (CMC review finalized)

HFD-617/FNice/9/24/10

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

/s/

SHAHNAZ T READ
09/24/2010

RADHIKA RAJAGOPALAN
09/24/2010

FRANK J NICE
09/24/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-730

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION CHECKLIST

ANDA No.	78-730		
Drug Product Name	Lansoprazole Delayed Release Orally Disintegrating Tablets		
Strength (s)	15 mg and 30 mg		
Applicant Name	Teva		
Address	1090 Horsham Road PO Box 1090 North Wales, PA 19454		
Applicant's Point of Contact	Philip Erickson		
Contact's Phone Number	215-591-3141		
Contact's Fax Number	215-591-8812		
Submission Date(s)	12-27-06		
First Generic	no		
Reviewer	Ethan M. Stier, R.Ph., Ph.D.		
Study Number (s)	**2006-1270**	**2006-1287**	-
Study Type (s)	**fed**	**fasting**	-
Strength(s)	**30 mg**	**30 mg**	-
Clinical Site	Pharma Medica Research		
Clinical Site Address	1410 Warden Ave Toronto, Ontario		
Analytical Site	Pharma Medica Research		
Analytical Address	966 Pantera Mississauga, Ontario		

Table 1. Submission Content Checklist

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☒	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒*	☐	☐
Is FDA method in the public dissolution database (on the web)			☐	☒	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are all eight electronic summary biotables present			☒	☐	☐
Are electronic summary biotables in pdf format			☒	☐	☐

If the answer to either of the last two questions is no, indicate which summary biotables are not submitted. – Not Applicable.

Firm's method: Acid Stage: 500 mL of 0.1 N HCl at 75 rpm using USP Apparatus II (paddle); Buffer Stage 900 mL of phosphate buffer 6.8.

The current FDA dissolution method is from [redacted] (b) (4) 's Control Document # 03-315

Recommendations

1. Please conduct and submit dissolution testing on all strengths of the test and reference products (12 units each) using the following FDA-recommended method:

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Sampling Times:	60 minutes for acid stage and 5, 10, 15, 20, 30, and 45 minutes, and until at least 80% of the labeled content is dissolved for buffer stage

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data summary, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. Please submit the data both in MSWord and in *.pdf format. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

BIOEQUIVALENCE DEFICIENCY

ANDA:78-730 APPLICANT: Teva

DRUG PRODUCT: Lansoprazole Delayed Release Orally Disintegrating Tablets 15 mg and 30 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiency has been identified:

Please conduct and submit dissolution testing on all strengths of the test and reference products (12 units each) using the following FDA-recommended method:

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Sampling Times:	60 minutes for acid stage and 5, 10, 15, 20, 30, and 45 minutes, and until at least 80% of the labeled content is dissolved for buffer stage

The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in the ANDA submission.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: 78-730

BIOEQUIVALENCE – DISSOLUTION INCOMPLETE Submission date: 12-27-06

[NOTE: The in vitro testing is incomplete. The fasting and fed BE studies and waiver request are pending review]

1. DISSOLUTION (Dissolution Data)	Strength:	15 mg and 30 mg
	Outcome:	**IC**

Outcome Decisions: IC - Incomplete

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

/s/

Ethan Stier
6/22/2007 12:15:19 PM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
6/22/2007 12:55:06 PM
BIOPHARMACEUTICS

Barbara Davit
6/22/2007 05:45:17 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78730	
Drug Product Name	LANSOPRAZOLE Delayed-Release Orally Disintegrating Tablets	
Strength(s)	15 and 30 mg	
Applicant Name	Teva Pharmaceuticals USA	
Address	1090 Horsham Road P.O. Box 1090 North Wales, PA 19454-1090	
Applicant's Point of Contact	Philip Erickson R.Ph.	
Contact's Telephone Number	(215) 591-3000	
Contact's Fax Number	(215) 591-8600	
Original Submission Date(s)	December 27, 2006	
Submission Date(s) of Amendment(s) Under Review	October 12, 2007	
Reviewer	Svetlana Cherstniakova, Ph.D.	
Study Number (s)	2006-1287	2006-1270
Study Type (s)	Fasting	Fed
Strength (s)	30 mg	30 mg
Clinical Site	Pharma Medica Research Inc.	
Clinical Site Address	1410 Warden Avenue, Toronto, Ontario, Canada,M1R 5A3	
Analytical Site	Pharma Medica Research Inc.	
Analytical Site Address	966 Pantera Drive, Unit 31, Mississauga, Ontario Canada, L4W 2S1	
OUTCOME DECISION	**INCOMPLETE**	

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product Lansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg to the corresponding reference product Prevacid® SoluTab™ (Lansoprazole) Delayed-Release Orally Desintegrating Tablets 30 mg. The fasting BE study was designed as a single-dose, two-way crossover study in healthy subjects. The fed BE study was designed as a single-dose, three-period, six-sequence, three-treatment crossover study in healthy subjects. The fed study compared two different formulations of the test product, Lansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg, lot #K36295 and lot #K36986, concluding that only formulation used for lot #K36986 is bioequivalent to the RLD. As indicated in the Table below, lot #K36295 failed the 90% confidence interval criterian for the Cmax. It is further noted that the firm used lot #K36986 for the fasting study. The results are summarized in the tables below.

Parent Drug, Dose Lansoprazole, 30 mg Fasting Bioequivalence Study No. 2006-1287, N=87 (Male=41 and Female=46) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	**Test Teva lot K36986**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng·hr/mL)	2166.79	2218.08	0.98	93.25 – 102.33
AUC∞ (ng·hr/mL)	2204.75	2256.84	0.98	93.32 – 102.27
Cmax (ng/mL)	876.55	955.10	0.92	85.13 – 98.94

Parent Drug, Dose Lansoprazole, 30 mg Fed Bioequivalence Study No. 2006-1270, N=80 (Male=41 and Female=39) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
Test: lot K36295				
AUC0-t (ng·hr/mL)	1682.81	1561.35	1.08	100.11 – 116.03
AUC∞ (ng·hr/mL)	1715.59	1587.38	1.08	100.33 – 116.42
Cmax (ng/mL)	421.73	369.64	1.14	103.25 – 126.07*
Test: lot K36986				
AUC0-t (ng·hr/mL)	1655.25	1561.35	1.06	98.48 – 114.13
AUC∞ (ng·hr/mL)	1689.20	1587.38	1.06	98.75 – 114.67
Cmax (ng/mL)	415.51	369.64	1.12	101.73 – 124.21

*ouside the acceptable range

The firm has conducted dissolution testing using its own proposed method (DFS N 078730 N 000 27-Dec-2006), and, was requested to conduct the dissolution testing using the FDA-recommended method. The firm submitted a bioequivalence amendment on

October 12, 2007 generating new dissolution profiles for 15 mg and 30 mg strengths of its test product using the FDA-recommended method. Based on the submitted data, the DBE recommends the following dissolution method and specification:

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Sampling Times:	60 minutes for acid stage and 5, 10, 15, 20, 30, and 45 minutes, and until at least 80% of the labeled content is dissolved for buffer stage

Specification in the buffer stage: NLT (b) (4) (Q) in 30 minutes

The firm's dissolution method on the 30 mg and 15 mg strengths is acceptable, however, the application is incomplete pending firm's acknowledgement of its acceptance of the DBE-recommended method and specification.

The formulation for the 15 mg strength is proportionally similar to the 30 mg strength of the test product which underwent bioequivalence testing. The waiver of in vivo bioequivalence study requirements for 15 mg tablets of the test product will be granted upon receipt of the firm's acceptance and acknowledgement of the DBE-recommended dissolution method and specification.

The BE studies are acceptable, however, the application is incomplete due to the dissolution deficiency.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Lansoprazole Delayed-Release Orally Desintegrating Tablets, 15 mg and 30 mg
Reference Product	Prevacid® SoluTab™ (Lansoprazole) Delayed-Release Orally Desintegrating Tablets, 15 mg and 30 mg
RLD Manufacturer	Tap Pharmaceuticals Inc
NDA No.	21428
RLD Approval Date	August 30, 2002
Indication	Duodenal ulcer, benign gastric ulcer, NSAID-associated gastric ulcer, heartburn and other symptoms associated with GERD, erosive esophagitis, pathological hypersecretory conditions, including Zollinger-Ellison syndrome

3.2 PK/PD Information

Bioavailability	The absolute bioavailability is over 80%
Food Effect	When the drug is taken 30 minutes after food, both C max and AUC are reduced by about 50% to 70%. There is no significant food effect if the drug is taken before meals
Tmax	1.7 hrs
Metabolism	Extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity
Excretion	No unchanged lansoprazole was excreted in the urine after a single oral dose
Half-life	1.5 hrs
Drug Specific Issues (if any)	

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	30 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo

Strength:	30 mg
Subjects:	Normal healthy males and females, general population
Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Lansoprazole
Bioequivalence based on:	(90% CI)
Waiver request of in-vivo testing:	15 mg
Source of most recent recommendations:	OGD #07-0254 (b) (4) .)
Summary of OGD or DBE History (for details, see Appendix 4.4):	OGD provides the following recommendations regarding Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg: 1. a. A single-dose, two-way crossover fasting in-vivo bioequivalence study comparing Lansoprazole Delayed-release Orally Disintegrating Tablets, 30 mg, to the reference listed drug (RLD), Prevacid® (Lansoprazole) Delayed-Release Orally Disintegrating Tablets, 30 mg. b. A single-dose, non-replicate fed in-vivo bioequivalence study comparing Lansoprazole Delayed-release Orally Disintegrating Tablets, 30 mg, to the RLD. 2. Please measure the parent drug, lansoprazole, in plasma. 3. Lansoprazole Delayed-release Orally Disintegrating Tablets, 15 mg, may be considered for a waiver of in-vivo bioequivalence testing based on (1) an acceptable bioequivalence study on the 30 mg strength, (2) acceptable dissolution testing of the 15 mg, and 30 mg strengths, and (3) proportional similarity in the formulations of the 15 mg, and 30 mg strengths. 4. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following FDA method: Apparatus: USP Apparatus II (Paddle) Speed: 75 rpm Medium: 500 mL 0.1N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour) Sampling times: 5, 10, 15, 20, 30 and 45 minutes and until at least 80% of the labeled content is dissolved.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	0
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Volume 10, page 445-508
Analyte	Lansoprazole
Internal standard (IS)	(b) (4)
Method description	(b) (4); LC-MS/MS
Limit of quantitation	2.00 ng/mL
Average recovery of drug (%)	85.3 % to 101.7 %
Average recovery of IS (%)	94.2 %
Standard curve concentrations (units/mL)	2.00 ng/mL – 2000 ng/mL
QC concentrations (units/mL)	6.00 ng/mL, 300 ng/mL and 1600 ng/mL
QC Intraday precision range (%)	0.7 % - 5.9 %
QC Intraday accuracy range (%)	90.3 % to 104.8 %
QC Interday precision range (%)	2.5 % - 5.6 %
QC Interday accuracy range (%)	101.3 % to 102.4 %
Bench-top stability (hrs)	4.50 hours @ room temperature
Stock stability (days)	48 days @ -20° C
Processed stability (hrs)	122.75 hours @ approximately 5° C
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	55 days @ -20° C
Dilution integrity	Concentration* diluted 5-fold and 2-fold
Selectivity	No significant interfering peaks noted in blank plasma samples

*4000 ng/mL

SOPs submitted	SOP # LAB300.04: Calibration Standards, Quality Control Samples and Analytical Run Acceptance Criteria	SOP # LAB105.04: Repeat Sample Analysis Procedure and Acceptance Criteria
Bioanalytical method is acceptable	Yes (May 05, 2006) Sample analysis: October 19 – October 26, 2006	

Comments on the Pre-Study Method Validation:

Acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (CV%)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng*h/mL)	AUC∞ (ng*h/mL)	T½ (hr)	Kel (hr-1)	
2006-1270	A Single-Dose, Comparative Bioavailability Study of Three Formulations of Lansoprazole 30 mg Delayed-Release Orally Disintegrating Tablets Under Fed Conditions	Randomized, single-dose, crossover	LANSOPRAZOLE DR OD, 30 mg Tab., p.o. [Batch # K-36295] LANSOPRAZOLE DR OD, 30 mg Tab., p.o. [Batch # K-36986] PREVACID® SoluTab™ DR OD, 30 mg, Tab., p.o. [Lot # 140089P22]	80 completing (41M/39F) Healthy subjects Age (yrs): 36 (18-55)	563.92 (74) 549.41 (71) 454.71 (65)	4.60 (45) 4.44 (42) 3.80 (43)	2733.06 (109) 2687.05 (109) 2413.89 (108)	2858.73 (113) 2845.15 (113) 2542.85 (112)	2.04 (85) 2.05 (81) 2.10 (80)	0.4973 (48) 0.4957 (46) 0.4791 (48)	Synopsis p. 1 008
2006-1287	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Lansoprazole 30 mg Delayed-Release Orally Disintegrating Tablets Under Fasting Conditions	Randomized, single-dose, crossover	LANSOPRAZOLE DR OD, 30 mg Tab., p.o. [Batch # K-36986] PREVACID® SoluTab™ DR OD, 30 mg, Tab., p.o. [Lot # 330269P22]	87 completing (41M/46F) Healthy subjects Age (yrs): 37 (19-60)	937.86 (34) 1012.84 (33)	2.21 (33) 1.89 (50)	2488.11 (59) 2502.37 (51)	2593.70 (70) 2589.50 (57)	1.43 (57) 1.42 (54)	0.5616 (31) 0.5680 (33)	Synopsis p. 1 008

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Drug Lansoprazole Dose (1 x 30 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. 2006-1287), N=87 (Male=41 and Female=46)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	2166.79	2218.08	0.98	93.25	102.33
AUC∞ (ng·hr/mL)	2204.75	2256.84	0.98	93.32	102.27
Cmax (ng/mL)	876.55	955.10	0.92	85.13	98.94

Drug Lansoprazole Dose (1 x 30 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. 2006-1270), N=80 (Male=41 and Female=39)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
Test A: lot # K-36295					
AUC0-t (ng·hr/mL)	1682.81	1561.35	1.08	100.11	116.03
AUC∞ (ng·hr/mL)	1715.59	1587.38	1.08	100.33	116.42
Cmax (ng/mL)	421.73	369.64	1.14	103.25	126.07
Test B: lot # K-36986					
AUC0-t (ng·hr/mL)	1655.25	1561.35	1.06	98.48	114.13
AUC∞ (ng·hr/mL)	1689.20	1587.38	1.06	98.75	114.67
Cmax (ng/mL)	415.51	369.64	1.12	101.73	124.21

Table 3. Reanalysis of Study Samples

Fasting Study No. 2006-1287 Additional information in volume 8, Pages 022-024								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Analytical	**32**	**34**	**1.75**	**1.86**	**32**	**34**	**1.75**	**1.86**
Reason IE[1]	1	0	0.05	0	1	0	0.05	0
Reason UISR[2]	31	34	1.70	1.86	31	34	1.70	1.86
Total	**32**	**34**	**1.75**	**1.86**	**32**	**34**	**1.75**	**1.86**

Fed Study No. 2006-1270 Additional information in volume 9, Pages 026-039												
Reason why assay was repeated	**Number of samples reanalyzed**						**Number of recalculated values used after reanalysis**					
	Actual number			**% of total assays**			**Actual number**			**% of total assays**		
	T1	**T2**	**R**	**T1**	**T2**	**R**	**T1**	**T2**	**R**	**T1**	**T2**	**R**
Pharmacokinetic[1]	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Analytical	**132**	**83**	**126**	**7.50**	**4.72**	**7 16**	**132**	**83**	**126**	**7.50**	**4.72**	**7.16**
Reason UISR	132	83	126	7.50	4.72	7 16	132	83	126	7.50	4.72	7.16
Total	**132**	**83**	**126**	**7.50**	**4.72**	**7 16**	**132**	**83**	**126**	**7.50**	**4.72**	**7.16**

[1]IE: Injection Error
[2]UISR: Unacceptable internal standard response

Did use of recalculated plasma concentration data change study outcome? No. All reassays were performed for analytical reasons; there were no pharmacokinetic repeats and no recalculations were performed.

Comments from the Reviewer: The reanalysis of the study samples included a total of 1.75-7.5% reassay repeats, all the repeats were conducted according to the firm's SOP. The SOP was approved on 09/05/2005 and the date of first sample analyzed was on 09/11/06. The repeated samples did not compromise the integrity of both fasting and fed BE studies.

3.7 Formulation

Location in appendix	Section 4.2, Page 41
If a tablet, is the RLD scored?	**No**
If a tablet, is the test product biobatch scored	**No**
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	Section 4.3, Page 46
Source of Method (FDA)	FDA
Medium	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Volume (mL)	900 mL
USP Apparatus type	2 (Paddle)
Rotation (rpm)	75
DBE-recommended specifications	NLT (b) (4) (Q) is dissolved in 30 min in the Buffer Stage
If a modified-release tablet, was testing done on ½ tablets?	No
F2 metric calculated?	No
If no, reason why F2 not calculated	ODT
Is method acceptable?	**Acceptable**
If not then why?	

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**

3.9 Waiver Request(s)

Strengths for which waivers are requested	15 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No
Waivers granted?	**WAIVER PENDING**
If not then why?	Pending the firm's response to the dissolution deficiency

3.10 Deficiency Comments

The firm's dissolution method on the 30 mg and 15 mg strengths is acceptable,. Based on the submitted data, the DBE recommends a specification of NLT (b) (4)% in 30 mintues in the buffer stage. The firm's in vitro dissolution testing is incomplete pending its acceptance and acknowledgment of the FDA method and specification. The dissolution testing should be conducted in 500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH6.8 with 5 mM SDS (second hour) at 37ºC ± 0.5ºC using USP apparatus 2 at 75 rpm. The test product should meet the following specification in the buffer stage:

Specifications:
Acid Stage: NMT (b) (4)% in 60 minutes
Buffer Stage: NLT in 30 minutes

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study No. 2006-1287 incomplete due to the deficiency mentioned above. The Teva Pharmaceuticals conducted the fasting BE study on its Lansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg, lot # K36986 comparing it to Tap Pharmaceuticals' Prevacid® SoluTab™ (Lansoprazole) Delayed-Release Orally Desintegrating Tablets 30 mg, lot # 330269P22.

2. The Division of Bioequivalence finds the fed BE study No. 2006-1270 incomplete due to the deficiency mentioned above. The Teva Pharmaceuticals conducted the fed BE study on its Lansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg, lot # K36986 and lot K36295 comparing it to Tap Pharmaceuticals' Prevacid® SoluTab™ (Lansoprazole) Delayed-Release Orally Desintegrating Tablets 30 mg, lot # 330269P22.

Dissolution recommendations:

The firm's in vitro dissolution testing is incomplete pending its acceptance and acknowledgment of the FDA method and specification. The dissolution testing should be conducted in 500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH6.8 with 5 mM SDS (second hour) at 37ºC ± 0.5ºC using USP apparatus 2 at 75 rpm. The test product should meet the following specification in the buffer stage:

NLT (b)(4)% of Lansoprazole dissolved in 30 min

Waiver Request for Solid Oral Dosage Forms

The dissolution testing conducted by TEVA Pharmaceuticals USA on its Lansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg, lot # K36986 and Lansoprazole Delayed-Release Orally Disintegrating Tablets 15 mg, lot # K36985 is acceptable. The firm has conducted acceptable in vivo bioequivalence testing (submission date December 27, 2006) comparing 30 mg Tablets of the test product with 30 mg Tablets of the reference product Prevacid® SoluTab™ manufactured by Tap Pharmaceuticals. The formulation for the 15 mg strength is proportionally similar to the 30 mg strength of the test product which underwent bioequivalence testing. The waiver of in vivo bioequivalence study requirements for 15 mg tablets of the test product will be granted upon receipt of the firm's acceptance and acknowledgement of the DBE-recommended dissolution method and specification.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
None	

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	2006-1287
Study Title	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Lansoprazole 30 mg Delayed-Release Orally Disintegrating Tablets Under Fasting Conditions
Clinical Site (Name, Address, Phone #)	Pharma Medica Research Inc. 1410 Warden Avenue, Toronto, Ontario, Canada,M1R 5A3
Principal Investigator	Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)
Dosing Dates	October 10, 2006 October 17, 2006
Analytical Site (Name, Address, Phone #)	Pharma Medica Research Inc. 966 Pantera Drive, Unit 31, Mississauga, Ontario Canada, L4W 2S1
Analysis Dates	October 19, 2006 – October 26, 2006
Analytical Director	(b) (6) B.Sc., MBA
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	16

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	LANSOPRAZOLE, DR, ODT	PREVACID® SoluTab™
Manufacturer	Teva Pharmaceuticals, USA	TAP Pharmaceuticals Inc., USA
Batch/Lot No.	K-36986	330269P22
Manufacture Date	June 26, 2006	N/A
Expiration Date	N/A	APRIL 2008
Strength	30 mg	30 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4) ablets	N/A
Production Batch Size	tablets	N/A
Potency	99.8	97.6%
Content Uniformity (mean, %CV)	99.1%, 2.1%	96.2%, 2.1%
Dose Administered	30 mg	30 mg
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	89 dosed 87 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB:2,4,6,8,9,10,14,16,17,19,23,24,27,28,29,30,33,36,39,40,42,44, 47,48,50,52,54,56,57,59,61,63,67,68,70,72,73,76,77,79,82,84,85, 88,89,92,93,96 BA:1,3,5,7,11,12,13,15,18,20,21,22,25,26,31,32,34,35,37,38,41,43, 45,46,49,51,53,55,58,60,62,64,65,66,69,71,74,75,78,80,81,83,86, 87,90,91,94,95
Blood Sampling Times	Pre-dose, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12
Blood Volume Collected/Sample	6 mL
Blood Sample Processing/Storage	-20 $\pm$ 5°C
IRB Approval	September 28, 2006
Informed Consent	September 28, 2006
Length of Fasting	10 hours
Length of Confinement	At least 10 hours prior to drug administration until 12 hours post-dose
Safety Monitoring	Subjects were questioned regarding their health status throughout the study. An exit physical examination is conducted at the end of the study or after termination of a subject from the study.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. 2006-1287			
		Treatment Groups	
		Test Product N = 87	Reference Product N = 87
Age (years)	Mean ± SD	37 ± 10	37 ± 10
	Range	19 – 60	19 – 60
Age Groups	< 18	0(0%)	0(0%)
	18 – 40	49(56%)	49(56%)
	41 – 64	38(44%)	38(44%)
	65 – 75	0(0%)	0(0%)
	> 75	0(0%)	0(0%)
Sex	Male	41(47%)	41(47%)
	Female	46(53%)	46(53%)
Race	Asian	4(5%)	4(5%)
	Black	18(21%)	18(21%)
	Caucasian	65(75%)	65(75%)
	Hispanic	0(0%)	0(0%)
	Other	0(0%)	0(0%)
BMI	Mean ± SD	25.2 ± 3.1	25.2 ± 3.1
	Range	19.0 – 30.0	19.0 – 30.0
Other Factors		N/A	N/A

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. 2006-1287				
Subject No	Reason for dropout/replacement*	Period	Replaced?	Replaced with
52	Dropped out between October 10, 2006 and October 17, 2006, Test	1	No	N/A
88	Dropped out between October 10, 2006 and October 17, 2006, Test	1	No	N/A

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. 2006-1287	
	Test (N=89)	Reference (N=87)
Body as a whole		
Headache	4 (4.5%)	4 (4.6%)
Pain abdo	0 (0%)	1 (1.1%)
Pain	0 (0%)	1 (1.1%)
Cardiovascular System		
Hypertens	3 (3.4%)	0 (0%)
Tachycardia	1 (1.1%)	1 (1.1%)
Metabolic and Nutritional Disorders		
Hyperkalem	0 (0%)	1 (1.1%)
Creatinine Inc	5 (5.6%)	6 (6.9%)
Hyperglycem	2 (2.2%)	3 (3.4%)
BUN INC	0 (0%)	1 (1.1%)
Nervous System		
Dizziness	3 (3.4%)	0 (0%)
Respiratory System		
Cough Inc	1 (1.1%)	0 (0%)
Pharyngitis	0 (0%)	1 (1.1%)
Rhinitis	1 (1.1%)	1 (1.1%)
Urogenital System		
Urin Abnorm	2 (2.2%)	4 (4.6%)
Total	22 (24.7%)	24 (27.6%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. 2006-1287		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Protocol required that 96 subjects be enrolled, while only 89 subjects were dosed in the study.	01-89	01-51,53-87,89
The absence of full documentation does not allow the duration of pre-dose fasting to be verified.	52,54	N/A
An error in documentation does not allow the duration of centrifugation for Draw 11 (time point 2.75 hour) to be verified.	N/A	89

Comments on Dropouts/Adverse Events/Protocol Deviations: A total of 89 subjects were dosed in Period 1, and 87 subjects completed both study periods. Subjects 52 and 88 voluntarily withdrew from the study after completing Period 1 but prior to dosing in Period 2 for personal reasons. The data from these subjects were not included in the firm's pharmacokinetic and statistical analyses. There were 60 adverse events (AE) involving 36 subjects in this study. There were 29 AE associated with the Test product. There were 31 AE associated with the Reference product. No serious AE were reported during the study. The protocol deviations reported for the subjects included in the analysis were judged to have no significant impact on determination of bioequivalence.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. 2006-1287 Lansoprazole								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	2.00	4.00	12.0	30.0	100	400	1200	2000
Inter day Precision (%CV)	6.2	4.5	3.6	5.0	5.3	2.4	1.9	0.8
Inter day Accuracy (%Actual)	99.5	100.3	100.8	100.0	100.0	99.8	100.3	100.0
Linearity	0.9995 – 1.0000							
Linearity Range (ng/mL)	2.00 – 2000							
Sensitivity/LOQ (ng/mL)	2.00							
Bioequivalence Study No. 2006-1287 Lansoprazole								
Parameter	**Quality Control Samples**							
Concentration (ng/mL)	6.00	301	1600	-				
Inter day Precision (%CV)	5.6	4.1	4.0	-				
Inter day Accuracy (%Actual)	99.3	100.3	99.5	-				

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
LAB 105.04	Sep. 05, 2005	Repeat Sample Analysis Procedure and Acceptance Criteria.

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	NA
Does the reviewer agree with the outcome of the repeat assays?	NA
If no, reason for disagreement	

Summary/Conclusions, Study Assays: Acceptable. The analysis of samples is complete. The firm submitted the SOPs for analytical run acceptance and repeat analysis.

All sample re-assays were for analytical reasons only. The long-term stability data (55 days) cover the entire duration of the study sample storage.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Fasting Bioequivalence Study, Study No. 2006-1287, N=87									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	2487.71	59.31	659.26	8080.43	2502.34	50.77	791.50	7333.36	0.99
AUC∞ (hr *ng/ml)	2593.31	69.96	684.33	11512.00	2589.48	57.22	798.37	8967.17	1.00
Cmax (ng/ml)	937.86	34.09	135.00	1810.00	1012.84	32.82	365.00	1730.00	0.93
Tmax* (hr)	2.00	.	1.25	4.50	1.75	.	0.75	5.00	1.14
Kel (hr^{-1})	0.56	30.58	0.11	0.95	0.57	32.52	0.13	0.99	0.99
T1/2 (hr)	1.43	56.94	0.73	6.49	1.42	54.26	0.70	5.45	1.00

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Drug name Lansoprazole Dose 30 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 2006-1287, N=87				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	2167.17	2218.12	97.70	93.27 - 102.35
AUC∞ (hr *ng/ml)	2205.13	2256.89	97.71	93.33 - 102.28
Cmax (ng/ml)	876.55	955.10	91.77	85.13 - 98.94

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Drug name Lansoprazole Dose 30 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 2006-1287, N=87					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	2166.79	2218.08	0.98	93.25	102.33

AUC∞ (hr *ng/ml)	2204.75	2256.84	0.98	93.32	102.27
Cmax (ng/ml)	876.55	955.10	0.92	85.13	98.94

Table 17. Additional Study Information, Fasting Study No. 2006-1287

Root mean square error, AUC0-t	0.1842	
Root mean square error, AUC∞	0.1816	
Root mean square error, Cmax	0.2981	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	87	87
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	87	0.98	0.68	1.00
Reference	87	0.98	0.72	1.00

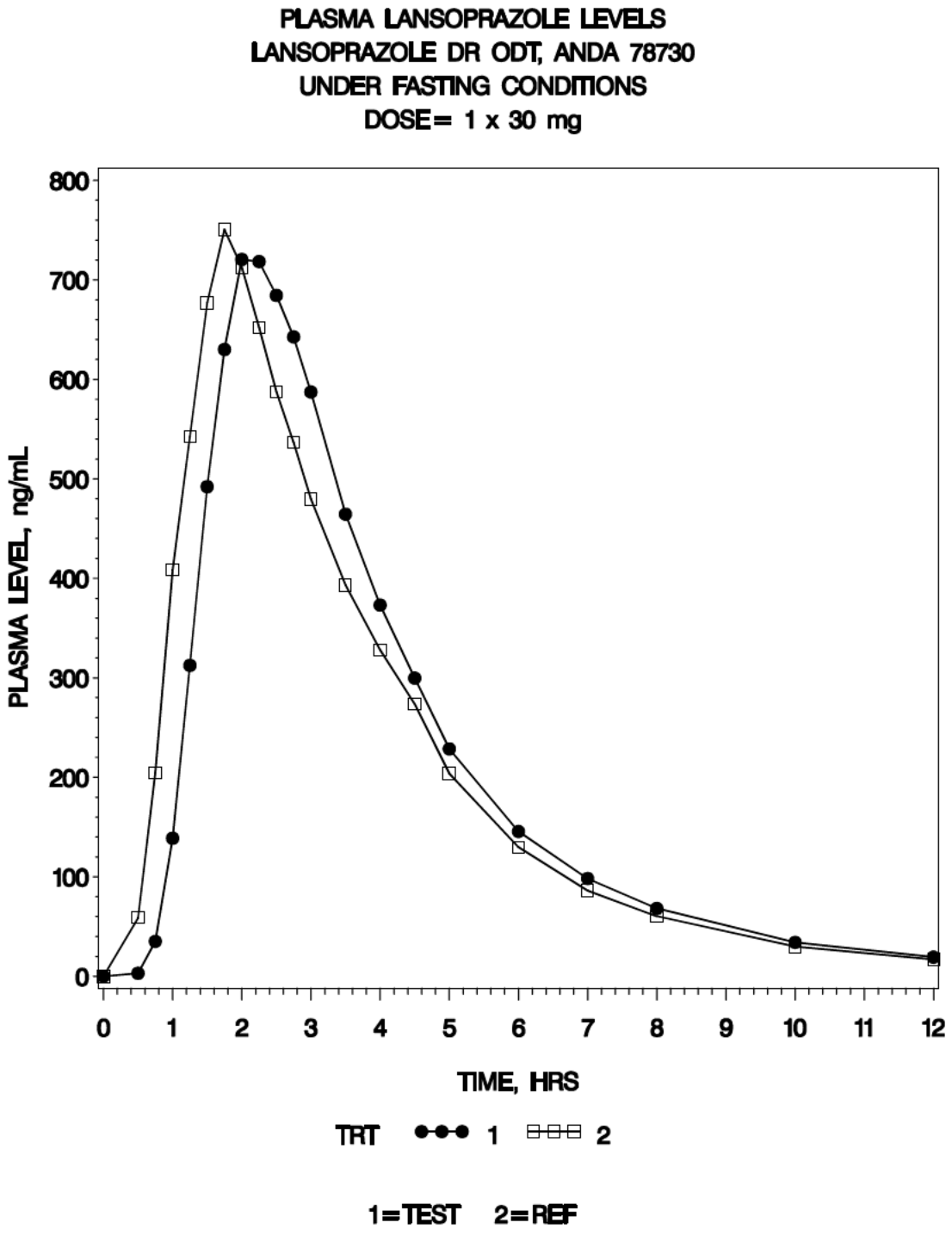
Comments on Pharmacokinetic and Statistical Analysis: A total of 89 subjects were dosed in Period 1, and 87 subjects completed both study periods. Subjects 52 and 88 voluntarily withdrew from the study after completing Period 1 but prior to dosing in Period 2 for personal reasons. The data from these subjects were not included in the firm's pharmacokinetic and statistical analyses. The reviewer calculated 90% confidence intervals for the T/R ratios for LAUCT, LAUCI and LC_{max} of lansoprazole and the results are within the acceptable limits (80%-125%) and similar to those reported by the firm.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The single-dose fasted bioequivalence study is acceptable

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=87)		Reference (n=87)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	3.12	303.42	58.83	171.11	0.05
0.75	35.23	164.90	204.77	136.64	0.17
1.00	138.86	130.34	408.33	105.80	0.34
1.25	312.50	106.17	542.43	83.68	0.58
1.50	492.16	86.06	676.93	66.96	0.73
1.75	630.05	66.11	750.49	58.03	0.84
2.00	720.52	57.52	712.72	55.28	1.01
2.25	718.36	52.90	651.87	52.40	1.10
2.50	684.43	48.45	587.27	51.28	1.17
2.75	642.66	47.44	536.74	49.59	1.20
3.00	587.25	50.47	479.77	50.01	1.22
3.50	464.55	57.33	393.17	54.12	1.18
4.00	373.14	62.62	328.14	61.94	1.14
4.50	299.77	70.26	273.65	72.01	1.10
5.00	228.64	78.93	203.91	79.91	1.12
6.00	145.67	98.02	129.81	99.31	1.12
7.00	98.31	122.87	86.22	124.40	1.14
8.00	68.32	148.32	60.39	152.31	1.13
10.00	34.16	212.40	29.97	213.27	1.14
12.00	19.36	291.28	17.10	280.99	1.13

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	2006-1270
Study Title	A Single-Dose, Comparative Bioavailability Study of Three Formulations (two test lots # K36295 and K36986 (Teva) and RLD lot #140089P22) of Lansoprazole 30 mg Delayed-Release Orally Disintegrating Tablets Under Fed Conditions
Clinical Site (Name, Address, Phone #)	Pharma Medica Research Inc. 1410 Warden Avenue, Toronto, Ontario, Canada,M1R 5A3
Principal Investigator	Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C)
Dosing Dates	August 23, 2006 August 30, 2006 September 06, 2006
Analytical Site (Name, Address, Phone #)	Pharma Medica Research Inc. 966 Pantera Drive, Unit 31, Mississauga, Ontario Canada, L4W 2S1
Analysis Dates	September 11, 2006 – October 03, 2006
Analytical Director	(b) (6) B.Sc., MBA
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	41

Table 20. Product Information

Product	**Test 1**	**Test 2**	**Reference**
Treatment ID	A	B	C
Product Name	LANSOPRAZOLE DR, ODT	LANSOPRAZOLE, DR, ODT	PREVACID® SoluTab™
Manufacturer	Teva Pharmaceuticals, USA	Teva Pharmaceuticals, USA	TAP Pharmaceuticals Inc., USA
Batch/Lot No.	K-36295	K-36986	140089P22
Manufacture Date	January 9, 2006	June 26, 2006	N/A
Expiration Date	N/A	N/A	SEP2006
Strength	30 mg	30 mg	30 mg
Dosage Form	Tablet	Tablet	Tablet
Bio-batch Size	N/A	(b) (4) ablets	N/A
Production Batch Size	N/A	tablets	N/A
Potency	103.0%	99.8%	100.0%
Content Uniformity (mean, %CV)	102.2%, 2.8%	99.1%, 2.1%	95.5%, 2.2%
Dose Administered	30 mg	30 mg	30 mg
Route of Administration	Oral	Oral	Oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	88 enrolled 80 completed
No. of Sequences	6
No. of Periods	3
No. of Treatments	3
No. of Groups	1
Washout Period	7 days
Randomization Scheme	ABC:1,10,14,22,28,35,40,44,54,55,65,72,75,82,90 CAB:2,9,16,20,25,34,41,48,51,57,66,71,73,81,89 BCA:3,8,18,21,27,31,38,43,50,56,64,67,74,80,86 ACB:4,7,15,24,26,33,39,46,53,59,63,68,78,83,85 CBA:5,11,17,23,29,32,37,47,49,60,61,70,77,84,88 BAC:6,12,13,19,30,36,42,45,52,58,62,69,76,79,87
Blood Sampling Times	0,0.33,0.67,1,1.5,2,2.5,3,3.5,4,4.5,5,5.5,6,7,8,9,10,12,14,16,24
Blood Volume Collected/Sample	6 mL
Blood Sample Processing/Storage	-20±5°C
IRB Approval	August 3, 2006
Informed Consent	Yes
Length of Fasting Before Meal	10 hr
Length of Confinement	34.5 hr
Safety Monitoring	Subjects were questioned regarding their health status throughout the study. An exit physical examination is conducted at the end of the study or after termination of a subject from the study.

Standard FDA Meal Used?	Yes	
If No, then meal components and composition is listed in the tables below		
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**
Fat		
Carbohydrate		
Protein		
Total		

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. 2006-1270			
		Treatment Groups	
		Test Products N = 80	Reference Product N = 80
Age (years)	Mean ± SD	36 ± 10	36 ± 10
	Range	18 – 55	18 – 55
Age Groups	< 18	0(0%)	0(0%)
	18 – 40	50(62%)	50(62%)
	41 – 64	30(38%)	30(38%)
	65 – 75	0(0%)	0(0%)
	> 75	0(0%)	0(0%)
Sex	Male	41(51%)	41(51%)
	Female	39(49%)	39(49%)
Race	Asian	9(11%)	9(11%)
	Black	22(28%)	22(28%)
	Caucasian	49(61%)	49(61%)
	Hispanic	0(0%)	0(0%)
	Other	0(0%)	0(0%)
BMI	Mean ± SD	25.0 ± 2.8	25.0 ± 2.8
	Range	19.2 – 29.8	19.2 – 29.8
Other Factors		N/A	N/A

Table 23. Dropout Information, Fed Bioequivalence Study

Study No. 2006-1270				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
26	Dropped out at 21:30 on August 23, 2006, Test 1*	1	No	N/A
28	Dropped out at 14:57 on August 25, 2006, Test 1	1	No	N/A
30	Adverse events (constipation, diarrhea), dropped out at 13:30 on August 29, 2006, Test 2*	1	No	N/A
41	Noncompliance (positive for marijuana), dropped out at 20:02 on August 29, 2006, Reference	1	No	N/A
47	Noncompliance (positive for cocaine), dropped out at 20:02 on August 29, 2006, Reference	1	No	N/A
56	Adverse events (cough, difficulty breathing), dropped out at 14:50 on August 29, 2006, Test 2	1	No	N/A
57	Dropped out at 14:13 on August 29, 2006, Reference	1	No	N/A
67	Noncompliance (positive for marijuana), dropped out at 20:43 on August 29, 2006, Test 2	1	No	N/A

***Test 1: lot K36295, Test 2: lot K36986**

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups		
	Fed Bioequivalence Study Study No. 2006-1270		
	Test 1 (N=82) lot # K36295	Test 2 (N=83) lot # K36986	Reference (N=83)
Body as a whole			
Headache	1 (1.2%)	4 (4.8%)	3 (3.6%)
Pain abdo	0 (0%)	0 (0%)	1 (1.2%)
Pain	0 (0%)	1 (1.2%)	0 (0%)
Cardiovascular System			
Hypertens	1 (1.2%)	1 (1.2%)	0 (0%)
Palpitat	0 (0%)	1 (1.2%)	0 (0%)
Digestive System			
Constip	0 (0%)	2 (2.4%)	1 (1.2%)
Nausea	1 (1.2%)	1 (1.2%)	0 (0%)
Diarrhea	0 (0%)	1 (1.2%)	2 (2.4%)
Hemic and Lymphatic System			
Anemia Hypochrom	0 (0%)	1 (1.2%)	1 (1.2%)
Anemia	0 (0%)	1 (1.2%)	1 (1.2%)
Ecchymosis	2 (2.4%)	0 (0%)	0 (0%)
Metabolic and Nutritional Disorders			
Hyperkalem	0 (0%)	1 (1.2%)	0 (0%)
SGPT INC	1 (1.2%)	0 (0%)	0 (0%)
SGOT INC	1 (1.2%)	1 (1.2%)	0 (0%)
LDH INC	0 (0%)	0 (0%)	1 (1.2%)
Creatinine Inc	0 (0%)	0 (0%)	1 (1.2%)
Nervous System			
Somnolence	0 (0%)	0 (0%)	1 (1.2%)
Respiratory System			
Cough Inc	0 (0%)	1 (1.2%)	0 (0%)
Dyspnea	0 (0%)	1 (1.2%)	0 (0%)
Pharyngitis	0 (0%)	0 (0%)	1 (1.2%)
Skin and Appendages			
Rash	1 (1.2%)	0 (0%)	1 (1.2%)
Urogenital System			
Urin Abnorm	3 (3.7%)	1 (1.2%)	1 (1.2%)
Urin Frequency	1 (1.2%)	0 (0%)	0 (0%)
Total	12 (14.6%)	18 (21.7%)	15 (18.1%)

Table 25. Protocol Deviations, Fed Bioequivalence Study

Study No. 2006-1270		
Type	Subject #s (Test)	Subject #s (Ref.)
Protocol required that 90 subjects be enrolled, while only 88 subjects were dosed in the study.	01-40,42-46,48-56,58-88	01-25,27,29,31-55,57-66,68-88
The subject was confined in-house for 10.27 hours prior to drug administration and not 10.5 hours prior to drug administration.	N/A	31
The subject was administered the study drug 31 minutes after the start of high-fat, high-calorie breakfast and not	45	N/A

30 minutes after the start of the breakfast.		
The washout period between drug administration in Periods 2 and 3 was I minute less than 7 days.	45,48	45
Water was not restricted for 1 hour following drug administration.	87,88	86
The time of collection of twelve blood samples was not accurately documented. Compliance with the time interval of not more than 30 minutes between sample collection and centrifugation cannot be verified.	14,53,59,68,82, 84,87,88	55,83,85,86
It cannot be verified that the samples for Draw 8 (3 hour time point) were centrifuged for 10 minutes.	71-73,75-77, 79,81,82,84,87,88	74,78,80,83,85,86

Comments on Adverse Events/Protocol Deviations: A total of 88 subjects were dosed in Period 1. Eight (8) subjects did not complete the study (see Table 23). Eighty (80) subjects were dosed in Period 2 on August 30, 2006 and in Period 3 on September 6, 2006 and completed both study periods. There were 58 adverse events (AEs): 15 AE associated with the Test product (treatment A, lot #K-36295), 23 AE associated with the Test product (treatment B, lot #K-36986), and 20 AE associated with the Reference product (treatment C, lot #140089P22). No serious AEs were reported during the study. The protocol deviations reported for the subjects included in the analysis were judged to have no significant impact on determination of bioequivalence.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. 2006-1270 Lansoprazole								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	2.00	4.00	12.0	30.0	100	400	1200	2000
Inter day Precision (%CV)	7.5	4.5	4.6	5.2	5.0	3.8	2.9	1.3
Inter day Accuracy (%Actual)	95.0	98.0	102.5	102.3	103.0	100.3	98.8	100.6
Linearity	0.9989 – 1.0000							
Linearity Range (ng/mL)	2.00 – 2000							
Sensitivity/LOQ (ng/mL)	2.00							
Bioequivalence Study No. 2006-1270 Lansoprazole								
Parameter	**Quality Control Samples**							
Concentration (ng,/mL)	6.00	300	1600	-				
Inter day Precision (%CV)	6.7	5.7	5.8	-				
Inter day Accuracy (%Actual)	97.0	100.0	98.6	-				

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
LAB 105.04	Sep. 05, 2005	Repeat Sample Analysis Procedure and Acceptance Criteria.

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	NA
Does the reviewer agree with the outcome of the repeat assays?	NA
If no, reason for disagreement	

Summary/Conclusions, Study Assays: Acceptable. The analysis of samples is complete. The firm submitted the SOPs for analytical run acceptance and repeat analysis.

All sample re-assays were for analytical reasons only. The long-term stability data (55 days) cover the entire duration of the study sample storage.

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

	MEAN1	CV1	MEAN2	CV2	MEAN3	CV3	RMEAN12
PARAMETER							
AUCT	2763.48	108.77	2726.13	108.46	2443.38	107.91	1.01
AUCI	2892.26	112.87	2888.67	112.30	2563.02	112.04	1.00
CMAX	563.05	75.42	552.09	70.87	454.42	66.15	1.02
TMAX	4.65	45.00	4.46	41.70	3.83	42.87	1.04
KE	0.50	48.28	0.49	46.95	0.48	48.07	1.01
THALF	2.06	84.52	2.08	80.94	2.11	80.20	0.99
LAUCT	1682.81	0.06	1655.25	0.06	1561.35	0.06	1.01
LAUCI	1715.59	0.06	1689.20	0.06	1587.38	0.06	0.99
LCMAX	421.73	0.19	415.51	0.19	369.64	0.18	1.01

	RMEAN13	RMEAN23
PARAMETER		
AUCT	1.13	1.12
AUCI	1.13	1.13
CMAX	1.24	1.21
TMAX	1.21	1.16
KE	1.04	1.03
THALF	0.98	0.99
LAUCT	1.08	1.06
LAUCI	1.08	1.06
LCMAX	1.14	1.12

1- Test A (lot # K36295)
2- Test B (lot # K36986)
3- Reference

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Drug name Lansoprazole Dose 30 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. 2006-1270, N=80				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
A vs. C*				
AUC0-t (hr *ng/ml)	1682.81	1561.35	107.78	100.11 - 116.03
AUC∞ (hr *ng/ml)	1715.59	1587.38	108.08	100.33 - 116.42
Cmax (ng/ml)	421.73	369.64	114.09	103.25 - 126.07
B vs. C*				
AUC0-t (hr *ng/ml)	1655.25	1561.35	106.01	98.47 - 114.13
AUC∞ (hr *ng/ml)	1689.20	1587.38	106.41	98.75 - 114.67
Cmax (ng/ml)	415.51	369.64	112.41	101.73 - 124.21

* A= Teva lot K36295, B = Teva lot K36986, C = Prevacid lot 140089P22

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Drug Lansoprazole Dose 30 mg Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. 2006-1270, N=80				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
Test: lot K36295				
AUC0-t (ng·hr/mL)	1682.81	1561.35	1.08	100.11 – 116.03
AUC∞ (ng·hr/mL)	1715.59	1587.38	1.08	100.33 – 116.42
Cmax (ng/mL)	421.73	369.64	1.14	103.25 – 126.07
Test: lot K36986				
AUC0-t (ng·hr/mL)	1655.25	1561.35	1.06	98.48 – 114.13
AUC∞ (ng·hr/mL)	1689.20	1587.38	1.06	98.75 – 114.67
Cmax (ng/mL)	415.51	369.64	1.12	101.73 – 124.21

Table 32. Additional Study Information

Root mean square error, AUC0-t	0.2848		
Root mean square error, AUC∞	0.2835		
Root mean square error, Cmax	0.3846		
	Test A	**Test B**	**Reference**
Kel and AUC∞ determined for how many subjects?	80	79	78
Do you agree or disagree with firm's decision?	Yes	Yes	Yes
Indicate the number of subjects with the following:			
measurable drug concentrations at 0 hr	0	0	0
first measurable drug concentration as Cmax	0	0	0
Were the subjects dosed as more than one group?	No	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test A	80	0.98	0.73	1.0
Test B	79	0.98	0.85	1.0
Reference	78	0.98	0.84	1.0

Comments on Pharmacokinetic and Statistical Analysis: The fed study compares two different formulations of the Test product, lot #K-36295 and lot #K-36986 to the Reference product PREVACID® SoluTab™ (lot #140089P22). The reviewer calculated 90% confidence intervals for the T/R ratios for LAUCT, LAUCI and LC_{max} of lansoprazole. For Treatment B (Test product, lot #K-36986) versus Treatment C (Reference product, lot #140089P22) the results are within the acceptable limits (80%-125%), while for Treatment A (Test product, lot #K-36295) versus Treatment C (Reference product, lot #140089P22) are not. The data calculated by the reviewer are similar to those reported by the firm. It is also noted that TEVA's lot #K-36986 was further studied under fasting conditions, and exhibited acceptable BE results.

The RMSE values for PK parameters obtained in the fasting and fed studies are approaching or higher (in case of Cmax) than 30%, suggesting the high intra-subject variability. There are no other ANDAs to provide references regarding this matter for Lansoprazole Delayed-Release Orally Disintegrated Tablets. However, in the ANDA #77255 (see V:\firmsnz\Teva\ltrs&rev\ 77255N0804) the same trend of higher than 30% RMSE values is observed for Lansoprazole Delayed-Release Capsules. Furthermore, considering that the the drug substance is acid labile by nature, and that the drug is exetensively metabolized in the liver, it is difficult to predict the factor(s) that might be contributing to the the high within subject variability in the BE study. Nevertheless, based on the information – although limited at this point - obtained in ANDA #77255, in the opinion of this reviewer, the withins subject high variability of the test product

appears to be associated with the drug substance, rather than with the test product formulation subject of this study.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study: The single-dose fed bioequivalence study is acceptable

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	MEAN1	CV1	MEAN2	CV2	MEAN3	CV3	RMEAN12
TIME HR							
0	0.00	.	0.00	.	0.00	.	.
0.33	0.15	539.86	0.05	883.18	13.67	458.00	2.83
0.67	3.83	377.39	2.08	348.93	36.06	276.14	1.84
1	18.17	287.48	15.37	359.21	91.65	149.57	1.18
1.5	53.80	172.75	45.90	215.19	187.15	127.23	1.17
2	139.78	167.52	119.90	146.77	243.56	111.89	1.17
2.5	242.69	130.44	230.19	128.33	285.39	96.50	1.05
3	339.97	116.07	356.87	109.14	295.38	91.56	0.95
3.5	387.34	114.25	390.19	101.35	303.04	90.72	0.99
4	379.54	107.19	376.68	97.62	300.94	89.26	1.01
4.5	385.69	97.26	365.81	93.25	321.46	86.50	1.05
5	319.48	101.72	320.94	93.31	272.90	89.85	1.00
5.5	284.63	105.66	286.79	99.74	246.41	93.53	0.99
6	264.01	104.23	263.64	106.39	220.38	101.43	1.00
7	232.93	102.47	230.65	105.75	176.46	114.78	1.01
8	188.84	113.35	192.93	117.12	144.40	126.81	0.98
9	159.34	126.88	158.94	130.08	120.67	137.63	1.00
10	126.13	137.02	122.89	143.08	95.87	149.01	1.03
12	81.86	164.07	78.94	174.10	62.37	178.55	1.04
14	56.57	178.93	53.12	196.18	43.90	203.30	1.07
16	39.31	198.37	39.13	216.90	31.92	226.20	1.00
24	13.54	256.51	14.44	253.46	11.33	260.03	0.94

Continued:

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.33	0.01	0.00
0.67	0.11	0.06

1	0.20	0.17
1.5	0.29	0.25
2	0.57	0.49
2.5	0.85	0.81
3	1.15	1.21
3.5	1.28	1.29
4	1.26	1.25
4.5	1.20	1.14
5	1.17	1.18
5.5	1.16	1.16
6	1.20	1.20
7	1.32	1.31
8	1.31	1.34
9	1.32	1.32
10	1.32	1.28
12	1.31	1.27
14	1.29	1.21
16	1.23	1.23
24	1.19	1.27

Note: Mean 1 – mean plasma concentration (ng/ml) for Test A (lot # K36295, n=80);
Mean 2 – mean plasma concentration (ng/ml) for Test B (lot # K36986, n=80);
Mean 3- mean plasma concentration (ng/ml) for Referenfce (n=80).

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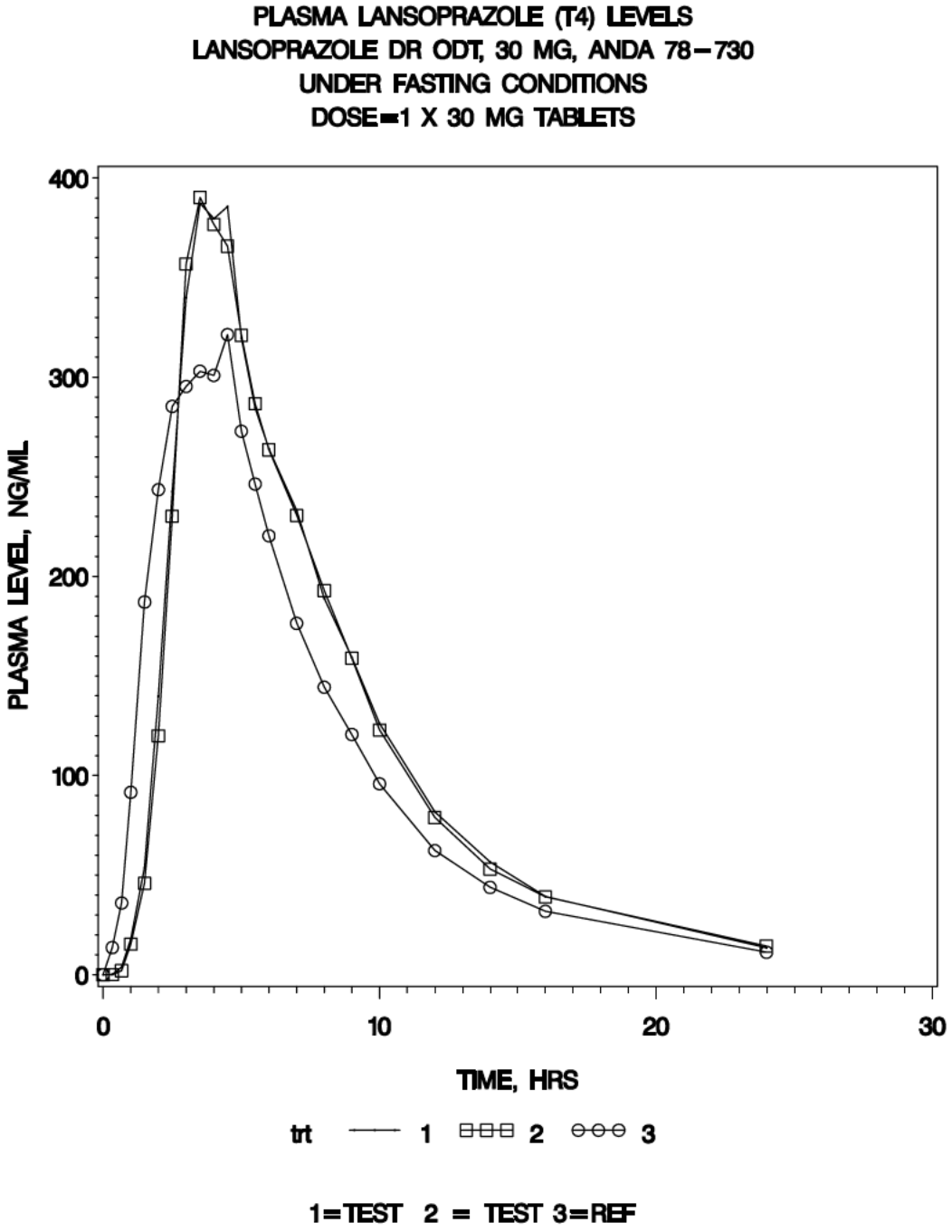
Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data (lot #K-36986)

Ingredient	Amount (mg) / Tablet		Amount (%) / Tablet	
	15 mg strength	30 mg strength	15 mg strength	30 mg strength
(b) (4)				

(b) (4)			
Total	(b) (4)	**100.0**	**100.0**

(b) (4)

Formulation Data (Continued)

Strawberry Flavour (b) (4)

Ingredient	**Amount (mg) / Tablet**		**Amount (%) / Tablet**	
	15 mg strength	**30 mg strength**	**15 mg strength**	**30 mg strength**
(b) (4)	(b) (4)			

Flavoring ingredients*: (b) (4)	(b) (4)
Total	(b) (4)

* Each of the listed flavoring components is (b) (4) of the flavoring formulation, which is (b) (4) % of the total tablet weight, therefore, their quantities are negligible and do not present safety issue.

Reviewer's comment: Based on CMC review (see DFS N 078730 N 000 27-Dec-2006), "the firm has provided the IIG limits for each ingredient except the flavoring ingredients to show that they have been previously approved at higher concentrations than present in the formulation". The firm states that quantities of the flavoring components are negligible (less than (b) (4) % of the total tablet weight) and do not present safety issue. According to the IIG database the same flavoring ingredient Strawberry Flavour (b) (4) was used in the orally disintegrated tablet (NDA N (b) (4)) in similar quantity: (b) (4) (N (b) (4)) versus (b) (4) (30 mg strength of the proposed formulation).

The fed study compares two different formulations of the test product, Lansoprazole DR ODT 30 mg, lot #K-36295 (Treatment A) and lot #K-36986 (Treatment B) to the RLD Prevacid SoluTab DR ODT 30 mg, lot #140089P22. The fasting study compares formulation used to manufacture lot #K-36986 (Treatment B) with RLDs lot #140089P22.

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	Formulations are from (b) (4). The inactive ingredients are within the acceptable IIG limits. The formulations are acceptable

4.3 Dissolution Data

Dissolution Review Path	*DFS N 078730 N 000 27-Dec-2006

*The dissolution data were reviewed previously and found deficient due to the fact that firm did not use the FDA-recommended method (the deficiency letter was sent on June 27, 2007). The firm submitted the bioequivalence amendment on October 12, 2007 generating new dissolution profiles for 15 mg and 30 mg strengths of its test products using the FDA-recommended method. The dissolution data are presented in the Tables below:

Table 34. Dissolution Data

The firm proposed the following dissolution method:

Dissolution Conditions	**Apparatus:**	Apparatus 2 (Paddle)
	Speed of Rotation:	75rpm
	Medium:	Acid Stage: 0.1N HCl Volume: 500mL Buffer Stage: Medium: Phosphate Buffer, pH 6.8
	Volume:	Acid Stage: 500mL Buffer Stage: 900mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	**Acid stage:** NMT (b) (4) dissolved in 60 minutes **Buffer stage:** NL % (Q) dissolved in 45 minutes.	
Dissolution Testing Site (Name, Address)	Teva Pharmaceutical Industries, Ltd., Hashikma Street, Industrial Area, Kfar-Saba 44102, ISRAEL	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)							Study Report Location
						Acid Stage	Buffer Stage						
						60 min	5 min	10 min	15 min	20 min	30 min	45 min	
CDP-1531/01	Aug. 3, 2006	Lansoprazole D.R. ODT K-36985	15 mg D.R Orally Disintegrating Tablets	12	Mean	0	19	59	70	74	78	80	Original ANDA pages
					Range	0-0	(b) (4)						
					%CV	0	30.2	17.5	13.2	12.7	12.3	11.1	

		Mfg.: 6/06			%CV	0	30.2	17.5	13.2	12.7	12.3	11.1	136-139
	Sept. 26, 2005	Prevacid® SoluTab™ # 130169P22 Exp.: 9/06	15 mg D.R Orally Disintegrating Tablets	12	Mean	0	86	87	87	86	85	83	
					Range	0-0	[redacted] (b) (4)						
					%CV	0	2.6	3.5	3.1	3.0	2.9	4.5	
CDP-1477/01	Aug. 6, 2006	Lansoprazole D.R. ODT K-36986 Mfg.: 6/06	30 mg D.R Orally Disintegrating Tablets	12	Mean	0	9	43	67	73	77	81	Original ANDA pages 140-143
					Range	[redacted] (b) (4)							
					%CV	*NM	64.3	29.0	9.5	8.8	8.8	7.8	
	Sept. 18, 2005	Prevacid® SoluTab™ #140089P22 Exp.: 9/06	30 mg D.R Orally Disintegrating Tablets	12	Mean	0	81	82	80	81	80	78	
					Range	0-0	[redacted] (b) (4)						
					%CV	0	3.9	4.7	3.7	4.2	4.8	2.8	

*NM - Value for %CV not meaningful due to range of 0-1%

The dissolution results of individual units for the test and reference products using FDA-method are summarized in the Table below:

Dissolution Conditions	**Apparatus:**	Apparatus 2 (Paddle)
	Speed of Rotation:	75rpm
	Medium:	Acid Stage: 0.1N HCl Volume: 500mL Buffer Stage: Medium: Phosphate Buffer, pH 6.8, with 5mM SDS
	Volume:	Acid Stage: 500mL Buffer Stage: 900mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	**Not Applicable**	
Dissolution Testing Site (Name, Address)	Teva Pharmaceutical Industries, Ltd., Hashikma Street, Industrial Area, Kfar-Saba 44102, ISRAEL	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						Acid Stage	**Buffer Stage**						
						60 min	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	

CDP-1702/01	July 26, 2007	Lansoprazole D.R. ODT K-36985 Mfg.: 6/06	15 mg D.R Orally Disintegrating Tablets	12	Mean	0	10	66	80	83	85	85	Attachment 2
					Range	0-0	[redacted] (b) (4)						
					%CV	0	51.5	13.4	10.7	8.2	7.5	6.6	
	Aug. 7, 2007	Prevacid® SoluTab™ #525552E80 Exp.: 5/09	15 mg D.R Orally Disintegrating Tablets	12	Mean	0	80	84	85	85	84	82	
					Range	0-0	[redacted] (b) (4)						
					%CV	0	12.7	7.2	3.6	2.8	2.5	2.4	
CDP-1703/01	July 26, 2007	Lansoprazole D.R. ODT K-36986 Mfg.: 6/06	30 mg D.R Orally Disintegrating Tablets	12	Mean	0	6	69	83	85	86	84	Attachment 2
					Range	0-0	[redacted] (b) (4)						
					%CV	0	41.2	10.4	6.2	5.2	4.7	6.0	
	July 26, 2007	Prevacid® SoluTab™ #330269P22 Exp.: 4/08	30 mg D.R Orally Disintegrating Tablets	12	Mean	0	85	91	91	90	88	86	
					Range	0-0	[redacted] (b) (4)						
					%CV	0	11.1	3.4	2.8	2.8	2.8	2.6	

TAB. #	% OF LABELED AMOUNT DISSOLVED					
	BUFFER STAGE					
	20 MINUTES		30 MINUTES		45 MINUTES	
	TEVA K-36985	PREVACID® SoluTab™ 525552E80	TEVA K-36985	PREVACID® SoluTab™ 525552E80	TEVA K-36985	PREVACID® SoluTab™ 525552E80
1	[redacted]					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	83	85	85	84	85	82
RSD (%)	8.2	2.8	7.5	2.5	6.6	2.4

(b) (4)

Product Name: LANSOPRAZOLE D.R. ORALLY DISINTEGRATING TABLETS 30mg

Analysis No: CDP-1703/01

TAB. #	% OF LABELED AMOUNT DISSOLVED							
	ACID STAGE		BUFFER STAGE					
	60 MINUTES 0.1N HCl		5 MINUTES		10 MINUTES		15 MINUTES	
	TEVA K-36986	PREVACID® SoluTab™ 330269P22	TEVA K-36986	PREVACID® SoluTab™ 330269P22	TEVA K-36986	PREVACID® SoluTab™ 330269P22	TEVA K-36986	PREVACID® SoluTab™ 330269P22
1	0	0	[redacted]					
2	0	0						
3	0	0						
4	0	0						
5	0	0						
6	0	0						
7	0	0						
8	0	0						
9	0	0						
10	0	0						
11	0	0						
12	0	0						
Mean	0	0	6	85	69	91	83	91
RSD (%)	0	0	41.2	11.1	10.4	3.4	6.2	2.8

(b) (4)

TAB. #	% OF LABELED AMOUNT DISSOLVED					
	BUFFER STAGE					
	20 MINUTES		30 MINUTES		45 MINUTES	
	TEVA K-36986	PREVACID® SoluTab™ 330269P22	TEVA K-36986	PREVACID® SoluTab™ 330269P22	TEVA K-36986	PREVACID® SoluTab™ 330269P22
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	85	90	86	88	84	86
RSD (%)	5.2	2.8	4.7	2.8	6.0	2.6

(b) (4)

Comments: In the NDA 21428 the innovator proposed the following specifications for Prevacid Solutab, 15 mg and 30 mg strengths:

Acid resistance: NMT (b) (4) in 60 minutes
Buffer Stage: NLT (b) (4) (Q) in 30 minutes

In the dissolution amendment dated October 12, 2007, the firm conducted dissolution testing using the FDA-recommended method. However, the firm has not proposed any dissolution specification. Based on the submitted data, lansoprazole meets a specification of NLT (b) (4) (Q) in 30 minutes at the S1 level. The firm's in vitro dissolution testing is incomplete pending its acceptance and acknowledgment of the FDA method and specification. The DBE recommends the following dissolution method and specification:

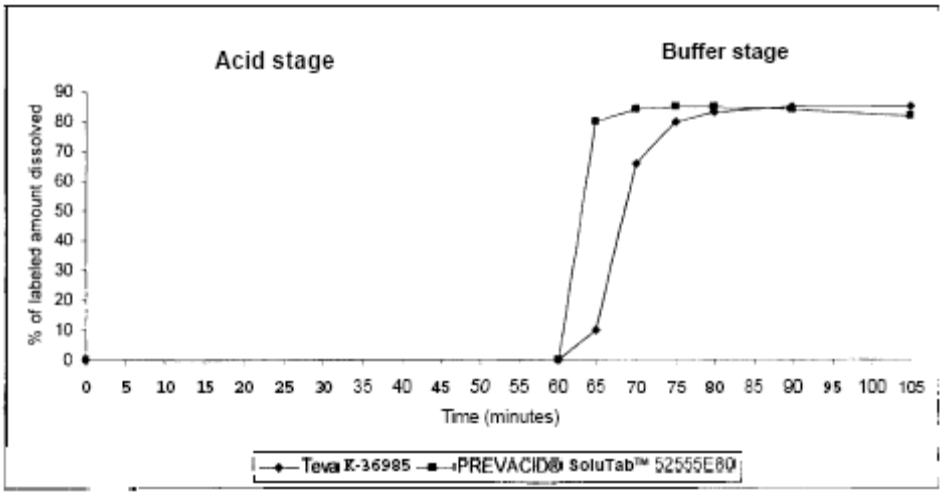
Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Sampling Times:	60 minutes for acid stage and 5, 10, 15, 20, 30, and 45 minutes, and until at least 80% of the labeled content is dissolved for buffer stage
Specifications:	
Acid Stage:	NMT (b) (4) in 60 minutes
Buffer Stage:	NLT (b) (4) in 30 minutes

Figure 3. Dissolution Profiles

Product Name: LANSOPRAZOLE D.R. ORALLY DISINTEGRATING TABLETS 15mg

Analysis No: CDP-1702101

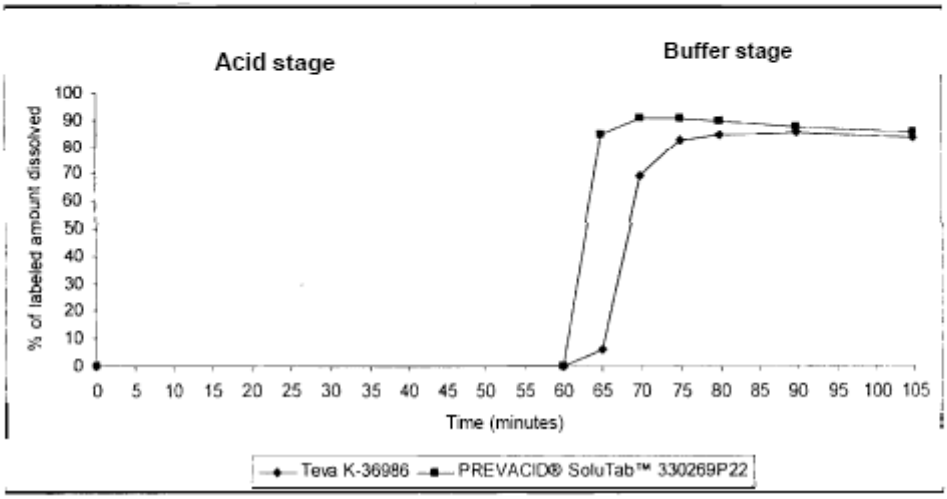
COMPARATIVE DISSOLUTION PROFILE OF LANSOPRAZOLE D.R. ORALLY DISINTEGRATING TABLETS 15mg
TEVA K-36985 vs. PREVACID® SOLUTAB™ LOT 525552E80



Product Name: LANSOPRAZOLE D.R. ORALLY DISINTEGRATING TABLETS 30mg

Analysis No: CDP-1703101

COMPARATIVE DISSOLUTION PROFILE OF LANSOPRAZOLE D.R. ORALLY DISINTEGRATING TABLETS 15mg
TEVA K-36986 vs. PREVACID® SOLUTAB™ LOT 330269P22



4.4 Detailed Regulatory History (If Applicable)

4.5 Consult Reviews

Following this page, 126 pages withheld in full - (b)(4) SAS Data

4.7 Additional Attachments

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DEFICIENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78730

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Your in vitro dissolution testing is incomplete. Please acknowledge your acceptance of the following dissolution method and specifications:

The dissolution testing should be conducted in 500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH6.8 with 5 mM SDS (second hour) at 37°C ± 0.5°C using USP apparatus 2 at 75 rpm. The test product should meet the following specification in the buffer stage:

Specifications:

Acid Stage:	NMT	(b) (4)	in 60 minutes
Buffer Stage:	NLT		in 30 minutes

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

ANDA: 78730

5 *COMPLETED ASSIGNMENT FOR 78730 ID: 911*

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
911	12/27/2006	Bioequivalence Study	Fasting Study	1	1
911	12/27/2006	Bioequivalence Study	Fed Study	1	1
911	12/27/2006	Other	Dissolution Waiver	1	1
911	10/12/2007	Other	Dissolution Amendment STA	1	1
				Bean Total:	4

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

/s/

Svetlana Cherstniakova
12/21/2007 01:55:56 PM
BIOPHARMACEUTICS

Chandra S. Chaurasia
12/21/2007 02:08:59 PM
BIOPHARMACEUTICS

Barbara Davit
12/21/2007 02:43:10 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78730
Drug Product Name	Lansoprazole Delayed Release Orally Disintegrating Tablet
Strength(s)	15 mg and 30 mg
Applicant Name	Teva Pharmaceuticals USA
Address	1090 Horsham Road, North Wales, PA 19454
Applicant's Point of Contact	Philip Erickson, R.Ph. Senior Director, Regulatory Affairs
Contact's Telephone Number	215-591-3141
Contact's Fax Number	215-591-8812
Original Submission Date(s)	December 27, 2006
Submission Date(s) of Amendment(s) Under Review	September 15, 2008 March 27, 2009 June 23, 2009
Reviewer	Paramjeet Kaur, Ph.D.
Study Number (s)	S08-0114
Study Type (s)	Fasting
Strength (s)	30 mg
Clinical Site	Gateway Medical Research, Inc. – Cetero Research
Clinical Site Address	400 Fountain Lakes Blvd. St. Charles, MO 63301 Deryk L. McDowell, M.D.
Analytical Site	(b) (4)
Analytical Site Address	(b) (4)
OUTCOME DECISION	**Acceptable**

1 EXECUTIVE SUMMARY

The original application submitted by the firm on December 27, 2006 contained the results of both dissolution testing and single dose fasting and fed bioequivalence studies comparing its test product Lansoprazole Delayed Release Orally Disintegrating Tablets, 30 mg to the corresponding reference product Prevacid® SoluTab™ (Lansoprazole), 30 mg, manufactured by Tap Pharmaceuticals. The firm conducted dissolution testing using its own proposed method (DFS N 078730 N 000 27-Dec-2006), and, was requested to conduct the dissolution testing using the FDA-recommended method. The firm submitted a bioequivalence amendment on October 12, 2007 generating new dissolution profiles for 15 mg and 30 mg strengths of its test product using the FDA-recommended method. Based on the submitted data the Division of Bioequivalence (DBE) recommended the following specifications:

Acid stage: NMT (b) (4) in 60 minutes
Buffer stage: NLT % (Q) in 30 minutes

The bioequivalence (fasting and fed) studies and dissolution method was found acceptable; however, the application was found to be incomplete due to dissolution deficiency (dissolution specifications). The firm was asked to accept and acknowledge the DBE recommended dissolution method and specifications (DFS N 078730 N 000 AB 12-Oct-2007). The firm has not acknowledged DBE-recommended dissolution method and specifications (supplemental application submitted on March 27, 2009).

On March 27, 2009 the firm submitted a supplemental application for Lansoprazole Delayed Release Orally Disintegrating Tablets, 30 mg. This supplement provides for an alternative site (Teva Pharmaceuticals, Sellersville, PA) for the manufacture, analytical testing and packaging from its approved site at Kfar-Saba, Israel; and change in the concentration of (b) (4) and (b) (4) in the formulation.

This is a Level 3 Site Change and Level 2 Change for (b) (4) excipient, (b) (4). As per the CDER Guidance for Industry, SUPAC-MR: *Modified Release Solid Oral Dosage Forms – Scale-up and Postapproval Changes: Chemistry, Manufacturing and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (1997)*, under these circumstances, the FDA requests both dissolution testing including a multipoint dissolution profile and a single-dose bioequivalence study.

The firm has submitted multipoint dissolution profile and a single-dose fasting bioequivalence (BE) study comparing the relative bioavailability (rate and extent of absorption) of Lansoprazole Delayed Release Orally Disintegrating Tablets, 30 mg, Batch # RX 2621-015 manufactured at Sellersville, PA site to that of Prevacid® SoluTab™ (Lansoprazole) Delayed Release Orally Disintegrating Tablets, 30 mg, Lot#: 578352E22. Bioequivalence study was designed as a single-dose, two-way crossover study in healthy male and female subjects. Results of the PK statistical analysis of the fasting BE study are summarized in the table below:

Lansoprazole Dose (1 x 30 mg) Fasting Bioequivalence Study No. (S08-0114), N=104 (Male=51 and Female=53) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. S08-0114				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (hr *ng/ml)	1741.59	1758.89	0.99	94.35-103.91
AUC_{∞} (hr *ng/ml)	1759.37	1773.38	0.99	94.52-104.13
C_{max} (ng/ml)	770.76	791.79	0.97	89.63-105.72

The firm has submitted dissolution profiles for the 15 mg and 30 mg strengths of its test product using the FDA-recommended method. Based on the submitted data, the DBE recommended the following dissolution method and specifications:

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Sampling Times:	60 minutes for acid stage and 5, 10, 15, 20, 30, and 45 minutes.
Specifications:	Acid stage: NMT (b) (4) in 60 minutes Buffer stage: NL % (Q) in 30 minutes

The firm's dissolution testing on the 30 mg and 15 mg strengths is acceptable. On June 23, 2009 firm has acknowledged the FDA-recommended dissolution method and specifications.

The formulation for the 15 mg strength is proportionally similar to the 30 mg strength of the test product which underwent bioequivalence testing. The 15 mg strength of the test product is deemed bioequivalent to Tap Pharmaceuticals' Prevacid® SoluTab™ (Lansoprazole) Delayed Release Orally Disintegrating Tablets, 15 mg based on the criteria set forth in 21 CFR § 320.24 (b) (6).

No Division of Scientific Investigations (DSI) inspection is pending.

The application is acceptable with no deficiencies.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg
Reference Product	Prevacid® (Lansoprazole) Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg (RLD)
RLD Manufacturer	TAKEDA PHARMS
NDA No.	021428
RLD Approval Date	Aug 30, 2002
Indication	Prevacid® is indicated for short-term treatment (for 4 weeks) for healing and symptom relief of active duodenal ulcer; H. pylori eradication to reduce the risk of duodenal ulcer recurrence; maintenance of healed duodenal ulcers; short-term treatment of active benign gastric ulcer; healing of NSAID-associated gastric ulcer; risk reduction of NSAID-associated gastric ulcer; gastroesophageal reflux disease; maintenance of healing of erosive esophagitis; and long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

3.2 PK/PD Information[1]

Bioavailability	The absolute bioavailability is over 80%.
Food Effect	Both the C_{max} and AUC are diminished by about 50% to 70% if lansoprazole is given 30 minutes after food, compared to the fasting condition. There is no significant food effect if lansoprazole is given before meals.
Tmax	1.7 hrs
Distribution	Plasma protein binding 97%; V_d = 0.5 L/kg[2]
Metabolism	Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by blocking the proton pump at the secretory surface of the gastric parietal cell. The two active species are not present in the systemic circulation. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. Therefore, the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.
Excretion	No unchanged lansoprazole was excreted in the urine after a single oral dose
Half-life	1.5 ± 1.0 hr
Drug Specific Issues (if any)	

[1] SOURCE: Most recent Prevacid® labeling revised 10/28/2008 from Drugs@fda.gov.
[2] SOURCE: Micromedex® entry for Prevacid®

3.3 OGD Recommendations for Drug Product[3]

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	30 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	Available data indicate that this product may be highly variable in the bioequivalence parameters AUC and/or C_{max}. You may consider conducting bioequivalence studies using a replicate design approach. These replicate design studies may be analyzed using the reference scaled approach. The reference-scaled approach adjusts the bioequivalence limits of highly variable drugs by scaling to the within-subject variability of the reference product in the study, and imposes a limit of 0.8 to 1.25 on the geometric mean ratio. The within-subject variability of the reference product is determined in a 3-way modified replicate-design study in which the reference product is given twice and the test product is given once. For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).
2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	30 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	See comment above
Analytes to measure		Lansoprazole in plasma
Bioequivalence based on (90% CI)		Lansoprazole
Waiver request of in-vivo testing:		15 mg based on (i) acceptable bioequivalence studies on the 30 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
Source of most recent recommendations:		http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/ucm086284.pdf

[3] SOURCE:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086284.pdf

Summary of OGD or DBE History for ANDA 78730	The original application submitted by the firm on December 27, 2006 contained the results of both dissolution testing and single dose fasting and fed bioequivalence studies comparing its test product Lansoprazole Delayed Release Orally Disintegrating Tablets, 30 mg to the corresponding reference product Prevacid® SoluTab™ (Lansoprazole), 30 mg. The firm conducted dissolution testing using its own proposed method (DFS N 078730 N 000 27-Dec-2006), and, was requested to conduct the dissolution testing using the FDA-recommended method. The firm submitted a bioequivalence amendment on October 12, 2007 generating new dissolution profiles for 15 mg and 30 mg strengths of its test product using the FDA-recommended method. Based on the submitted data Division of Bioequivalence (DBE) recommended the following specifications: Acid stage: NMT (b) (4) in 60 minutes Buffer stage: NLT % (Q) in 30 minutes The bioequivalence (fasting and fed) studies and dissolution method was found acceptable; however, the application was found to be incomplete due to dissolution deficiency (dissolution specifications). The firm was asked to accept and acknowledge the DBE recommended dissolution method and specifications (DFS N 078730 N 000 AB 12-Oct-2007). So far the firm has not acknowledged DBE-recommended dissolution method and specifications (supplemental application submitted on March 27, 2009) On March 27, 2009 firm submitted a supplemental application for Lansoprazole Delayed Release Orally Disintegrating Tablets, 30 mg. This supplement provides for an alternative site (Teva Pharmaceuticals, Sellersville, PA) for the manufacture, analytical testing and packaging from its approved site at Kfar-Saba, Israel; and change in the concentration of (b) (4) and (b) (4) in the formulation.
Summary of OGD or DBE History (for details, see Appendix 4.4):	The Division File contains the review of several relevant documents. For details please refer to appendix 4.4

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	No	0

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Analyte 1
Bioanalytical method validation report location	Module 5\clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\PMRI-879-06
Study Report Number	PMRI-879-06
Analyte	Lansoprazole
Internal standard (IS)	(b) (4)
Method description	(b) (4); LC-MS/MS
Limit of quantitation	2 ng/mL
Average recovery of drug (%)	85.3 % to 101.7 %
Average recovery of IS (%)	94.2 %
Standard curve concentrations (units/mL)	2, 4, 12, 30, 100, 400, 1200 and 2000 ng/mL
QC concentrations (units/mL)	6.00 ng/mL, 300 ng/mL and 1600 ng/mL
QC Intraday precision range (%)	0.7 % - 5.9 %
QC Intraday accuracy range (%)	90.3 % to 104.8 %
QC Interday precision range (%)	2.5%-5.6 %
QC Interday accuracy range (%)	101.3 % to 102.4 %
Bench-top stability (hrs)	4.5 hours @ room temperature
Stock stability (days)	48 days @ -20° C
Processed stability (hrs)	122.75 hours @ approximately 5 °C
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	163 days @ -20° C
Dilution integrity	Concentrations of 1600 ng/mL and 4000 ng/mL were diluted 2 fold and 5 fold, respectively.
Selectivity	No interfering peaks noted in blank plasma samples

SOPs submitted	Yes
Bioanalytical method is acceptable	Yes

Comments on the Pre-Study Method Validation:

The pre-study bioanalytical method (Report No: PMRI-879-06) was validated on March 2006 and then revalidated (Report No: PMRI-879-06-01) on February, 2007. Additional stability report for long term stability of lansoprazole in plasma (Addendum No. 1, PMR-879-06-01, March 2007) and long term stock solution stability (Addendum No. 1, PMR-879-06) has also been submitted in this submission (EDR, ANDA 078730, 15-Sep-08, Module 5\clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\PMRI-879-06). The results of pre-study method validation are acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (units/mL)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	T½ (hr)	K_{el} (hr-1)	
S08-0114	To assess the relative bioavailability of lansoprazole 30 mg DR orally disintegrating tablet (TEVA Pharmaceuticals USA, Lot No. 2621-015) compared to that of Prevacid® SoluTab™ DR orally disintegrating tablet (TAP Pharmaceuticals Inc., Lot No. 578352E22) following a single oral dose (1 x 30 mg tablet) in healthy adult subjects when administered under fasted conditions.	Randomized, open-label, single-dose, two-way crossover	Lansoprazole Delayed-Release Orally Disintegrating Tablet [Lot # 2621-015] Prevacid® SoluTab™ DR Orally Disintegrating Tablet [Lot#: 578352E22]	104 (51/ 53) Healthy volunteers 31.1 (18-70)	770.76-849.71(42) 791.79-900.65(47)	2.25(1.5-5.0) 1.75(0.97-5.0)	1741.59-2025.14 (62) 1758.89-2030.31(59)	1759.37-2066.01(68) 1773.38-2078.26(63)	1 20 (30) 1 20 (37)	0.6397(30) 0.638(29)	M5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\S08-0114/study-s08-0114-csr.pdf

[1]Subjects used in final statistical report

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Parent Drug Lansoprazole Delayed-Release Orally Disintegrating Tablets Dose (1 x 30 mg)					
	Least Squares Geometric Means		Ratio of Means	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	1741.59	1758.89	0.99	94.35	103.91
LAUCI	1759.37	1773.38	0.99	94.52	104.13
LCMAX	770.76	791.79	0.97	89.63	105.72

Table 3. Reanalysis of Study Samples

Fast Study, Study No. S08-0114								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis[4]			
	Actual number		% of total assays		Actual Number		% of total assays	
	Test N[1]	Reference N[1]	Test N[1]	Reference N[1]	Test N[1]	Reference N[1]	Test N[1]	Reference N[1]
	n[2]	n[2]	%[3]	%[3]	n[2]	n[2]	%[3]	%[3]
Pharmacokinetic	0	4	0.00	0.19	0	2	0	0.10
Unacceptable IS	11	5	0.51	0.23	11	5	0.51	0.23
IS Error	0	2	0.00	0.10	0	2	0.00	0.10
Injection Error	0	1	0.00	0.05	0	1	0.00	0.05
Greater than ULOQ	3	1	0.14	0.05	3	1	0.14	0.05
Total	14	12	0.65	0.56	14	12	0.65	0.56

[1] N = Number of samples analyzed for each treatment =2140
[2] n = Number of samples repeated
[3] % = Percentage of assays repeated (i.e. 100*(n/N) %)
[4] Reported values those are different from the original value

Did use of recalculated plasma concentration data change study outcome? No

Comments: There were no subjects repeated in their entirety due to failed runs.

Four samples (0.1%) were repeated for pharmacokinetic (PK) reasons and 22 samples were repeated for analytical reasons. Batches 1698-CR03 and 1698-CR16 were re-injected due to instrument problems. Batch 1698-CR26 was re-extracted due to inconsistent internal standard.
The reanalysis of the study samples included a total of 0.56-0.65% reassay repeats, all the repeats were conducted according to the firm's SOPs.

0.1% of reassay repeats were due to PK reasons. To calculate the PK parameters, SAS program was run after substituting both the original values and repeated PK values. The

90% CIs for $LAUC_{0-t}$, $LAUC_{0-\infty}$ and LC_{max} were within the acceptable limits of 80% - 125% using the original values or the repeated values.

To evaluate assay reproducibility, 208 incurred samples were selected randomly and reassayed by firm as specified in bioanalytical study report (EDR, ANDA 78730, letter date: 15-Sep-08; Module 5\clin-stud-rep\531-rep-biopharm-stud/ study no. S08-0114 - appendix 16.5; page 11). Statistical analysis of the reassayed data revealed that the data is reproducible. However, the firm did not submit any SOPs for incurred sample reanalysis.

3.7 Formulation

Location in appendix	Section 4.2, Page 25
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**Yes**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	Section 4.3, Page 31
Source of Method (USP, FDA or Firm)	FDA
Medium	Acid Stage: 0.1N HCl Buffer Stage: Phosphate buffer pH 6.8 with 5mM SDS
Volume (mL)	Acid Stage: 500 ml Buffer Stage: 900 ml
USP Apparatus type	Apparatus II, (Paddle)
Rotation (rpm)	75
Sampling Times	60 minutes for acid stage followed by 45 minutes for buffer stage, and until 80 of the labeled content is dissolved for buffer stage
DBE-recommended specifications	Acid stage: NMT (b) (4) in 60 minutes Buffer stage: NL % (Q) in 30 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	
Is method acceptable?	**Acceptable**
If not then why?	

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**(T^1) 15 mg vs (T^1) 30 mg**	**(T^1) 15 mg vs (R^1) 15 mg**	**(T^1) 30 mg vs (R^1) 30 mg**
Whole tablet	80.22	65.41	76.32

[1]T = Site Transfer Batch
[2]R = Old ANDA Batch

3.9 Waiver Request(s)

Strengths for which waivers are requested	15 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	**YES**
If not then why?	

3.10 Deficiency Comments

None

3.11 Recommendations

The Division of Bioequivalence accepts the fasting BE study (S08-0114) conducted by Teva Pharmaceuticals on its Lansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg, lot # 2621-015 comparing it to TAP Pharmaceuticals' Prevacid® SoluTab™ (Lansoprazole) Delayed-Release Orally Disintegrating Tablets 30 mg, lot # 578352E22.

Dissolution recommendations:

The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour) at 37ºC ± 0.5ºC using USP apparatus 2 at 75 rpm. The test product should meet the following specifications:

Acid stage: NMT (b) (4) in 60 minutes
Buffer stage: NL % (Q) in 30 minutes

Waiver Request for Solid Oral Dosage Forms

The dissolution testing conducted by TEVA Pharmaceuticals USA on its Lansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg, lot # K2621-015 and Lansoprazole Delayed-Release Orally Disintegrating Tablets 15 mg, lot # K2621-014 is acceptable. The firm has conducted acceptable in vivo bioequivalence testing comparing 30 mg Tablets of the test product (lot # 2621-015) with 30 mg Tablets of the reference product Prevacid® SoluTab™ (lot # 578352E22) manufactured by Tap Pharmaceuticals.
The formulation for the 15 mg strength is proportionally similar to the 30 mg strength of the test product which underwent bioequivalence testing. The 15 mg strength of the test product is deemed bioequivalent to Tap Pharmaceuticals' Prevacid® SoluTab™ (Lansoprazole) Delayed Release Orally Disintegrating Tablets, 15 mg based on the criteria set forth in 21 CFR § 320.24 (b) (6).

3.12 Comments for Other OGD Disciplines

Discipline	Comment
None	

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	S08-0114 (2008-1698)
Study Title	A Relative Bioavailability Study of Lansoprazole 30 mg DR Orally Disintegrating Tablet Versus Prevacid® SoluTab™ 30 mg DR Orally Disintegrating Tablet Under Fasted Conditions
Clinical Site (Name, Address, Phone #)	Cetero Research 400 Fountain Lakes Blvd. St. Charles, MO 63301 (636) 947-1200
Principal Investigator	Deryk L. McDowell, M.D.
Dosing Dates	Period I: April 13, 2008 Period II: April 20, 2008
Analytical Site (Name & Address, Phone #)	(b) (4)
Analysis Dates	April 25, 2008 to May 15, 2008
Analytical Director	(b) (6), M.Sc.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	April 13, 2008 – May 15, 2008 (32 days)

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Lansoprazole, Delayed Release, Orally Disintegrating Tablets	PREVACID® SoluTab™
Manufacturer	Teva Pharmaceuticals, USA	TAP Pharmaceuticals, Inc.
Batch/Lot No.	2621-015	578352E22
Manufacture Date	March 12, 2008	N/A
Expiration Date	N/A	August 2009
Strength	30 mg	30 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A

Production Batch Size	(b) (4)	N/A
Potency (Assay)	106.4%	102.6%
Content Uniformity (mean, %CV)	99.4%, 2.3%	96.8%, 2.2%
Dose Administered	1 x 30 mg capsule	1 x 30 mg capsule
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	110 enrolled 104 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days between each successive Period.
Randomization Scheme	AB: 1, 3, 5, 7, 10, 14, 17, 18, 19, 20, 24, 25, 26, 29, 30, 32, 34, 35, 38, 39, 41, 42, 45, 48, 50, 52, 55, 56, 57, 58, 61, 62, 63, 67, 68, 73, 74, 75, 78, 79, 81, 82, 86, 87, 89, 91, 93, 94, 95, 100, 102, 103, 105, 108, and 110. BA: 2, 4, 6, 8, 9, 11, 12, 13, 15, 16, 21, 22, 23, 27, 28, 31, 33, 36, 37, 40, 43, 44, 46, 47, 49, 51, 53, 54, 59, 60, 64, 65, 66, 69, 70, 71, 72, 76, 77, 80, 83, 84, 85, 88, 90, 92, 96, 96, 97, 98, 99, 101, 104, 106, 107, and 109
Blood Sampling Times	Pre-dose (-1.5), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8,10 and 12 hours post dose
Blood Volume Collected/Sample	6 ml in pre-labeled vacutainers containing K_2EDTA
Blood Sample Processing/Storage	- 20 ± 5°C
IRB Approval	Yes, March 24, 2008
Informed Consent	Yes
Length of Fasting	10 hours
Length of Confinement	Subjects were confined in-house for at least 10 hours prior to each drug administration until 12 hours post-dose.
Safety Monitoring	Blood pressure and heart rate were measured within 90 minutes prior to administration of study product to the first study participant (Hour 0 only), at post dose hours 2, 12 (± 30 minutes), and at the discretion of clinical staff.

Comments on Study Design: The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No.			
		Treatment Groups	
		Test Product (N = 104)	Reference Product (N = 104)
Age (years)	Mean ± SD	31.3 ± 11.9	31.3 ± 11.9
	Range	18-70	18-70
Age Groups	< 18	N/A	N/A
	18 – 40	78 (75%)	78 (75%)
	41 – 64	25 (24.04%)	25 (24.04%)
	65 – 75	1 (0.96%)	1 (0.96%)
	> 75	N/A	N/A
Sex	Male	51 (49%)	51 (49%)
	Female	53 (51%)	53 (51%)
Race*	White	80 (76.9%)	80 (76.9%)
	Asian	2 (1.9%)	2 (1.9%)
	Black	17 (16.3%)	17 (16.3%)
	American Indian or Alaskan	5 (4.8%)	5 (4.8%)
BMI	Mean ± SD	25.6 ± 3.3	25.6 ± 3.3
	Range	18.6-32.0	18.6 – 32.0
Other Factors			
Height (cm)			
Mean ± SD		167.1 ± 28.9	167.1 ± 28.9
Range		114.0-235.0	114.0-235.0
Weight (kg)			
Mean ± SD		67.6 ± 3.5	67.6 ± 3.5
Range		60.0-77.0	60.0-77.0

*Percent of Hispanic or Latino subjects: 5.8%; Percent of Not Hispanic or Latino subjects: 94.2%

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
019	Dropped from the study due to adverse events experienced after receiving the test product	I	No
028	Dropped from the study due to adverse events experienced after receiving the reference product	I	No
044	Dropped from the study due to a death in the family after receiving the reference product	I	No
057	Was dropped from the study due to a positive drugs of abuse test at Period II check-in after receiving the test product	I	No
088	Dropped from the study due to a family emergency after receiving the reference product	I	No
089	Dropped from the study due to a family emergency after receiving the test product	I	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups (Study No: S08-0114)	
	Test N[1] = 110 [2]n(%)	Reference N[1] = 110 [2]n(%)
Body as a whole		
Fatigue	1(0.91%)	
Fever	1(0.91%)	
Nervous System		
Headache/Light-headed		5 (4.55%)
Dizziness	1 (0.91%)	
Renal and Urinary Tract Disorder		
Abnormal Urinalysis	2 (1.82%)	1 (0.91%)
Cardiovascular		
Hypertension	1 (0.91%)	
Respiratory Disorder		
Congestion	1(0.91%)	
Rhinitis		1 (0.91%)
Cough		1 (0.91%)
Hematology Investigation		
Abnormal Blood Glucose level	1(0.91%)	
Total	8 (7.27%)	8 (7.27%)

[1]N = Number of subjects dosed for each treatment
[2]n = Number of subjects reporting at least one incidence of respective adverse event;
(%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N) %)

Comments on Adverse Events: There were a total of 16 adverse events involving 11 subjects in the study. Out of 16 adverse events, 8 were reported for the Test A, 8 for RLD, all of them were considered mild to moderate. There were eight (8) adverse events considered unrelated to the test product. There were three (3) adverse events considered possibly related, and five (5) adverse events considered unrelated to the reference drug, There were no serious adverse events reported during the course of study. Six subjects (18, 36, 57, 88, 89 and 99) were lost to follow up.

The most frequently occurring adverse event reported following administration of the test lansoprazole 30 mg delayed-release orally disintegrating tablets was abnormal urinalysis. The most frequently occurring adverse event reported following administration of Prevacid® SoluTab™ Delayed-Release Orally Disintegrating Tablets 30 mg was headache.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Subjects did not have exit clinical laboratory measurements, exit vital signs, and exit interview obtained due to not returning to the clinic.	088	089
Subjects Period II blood samples were stored and frozen at -26ºC. Per protocol, samples were to be stored and frozen at -20°C ± 5ºC	002, 004, 006, 008, 009, 011, 012, 013, 015, 016, 021, 022, 023, 027, 028	001, 003, 005, 007, 010, 014, 017, 018, 019, 020, 024, 025, 026
Vital sign deviations Period I:	100, 102, 110	096, 098, 104, 106
Blood sample deviations Period I, Hour 0.25	052, 058, 095, 100	N/A
Blood sample deviations Period I, Hour 0.5	052, 081, 093, 100	090, 092
Blood sample deviations Period I, Hour 0.75	N/A	072, 090
Blood sample deviations Period I, Hour 1	025, 035	037, 046, 069
Blood sample deviations Period I, Hour 1.25	075	037, 051
Blood sample deviations Period I, Hour 1.5	010, 093, 100, 108	053, 066, 077, 109
Blood sample deviations Period I, Hour 1.75	N/A	066
Blood sample deviations Period I, Hour 2	035, 061	037, 053
Blood sample deviations Period I, Hour 2.25	061	46
Blood sample deviations Period I, Hour 2.50	058	085, 099
Blood sample deviations Period I, Hour 2.75	062	109
Blood sample deviations Period I, Hour 3	048	065, 104
Blood sample deviations Period I, Hour 3.5	N/A	84
Blood sample deviations Period I, Hour 5	N/A	43
Blood sample deviations Period I, Hour 6	N/A	065, 084

Blood sample deviations Period I, Hour 8	N/A	053
Blood sample deviations Period I, Hour 10	N/A	066
Blood sample deviations Period I, Hour 12	N/A	037, 101
Blood sample deviations Period II, Hour 0.25	084	052, 056, 108
Blood sample deviations Period II, Hour 0.75	N/A	010
Blood sample deviations Period II, Hour 1	006	010, 091, 093, 103
Blood sample deviations Period II, Hour 1.25	006	N/A
Blood sample deviations Period II, Hour 1.75	006	052
Blood sample deviations Period II, Hour 2	N/A	074, 091, 095
Blood sample deviations Period II, Hour 2.25	066	074
Blood sample deviations Period II, Hour 2.5	N/A	058, 074, 093, 103
Blood sample deviations Period II, H our 2.75	004	N/A
Blood sample deviations Period II, Hour 3	043	103
Blood sample deviations Period II, Hour 3.5	N/A	025, 074
Blood sample deviations Period II, Hour 4	008	052, 103
Blood sample deviations Period II, Hour 5	013, 027, 099	074
Blood sample deviations Period II, Hour 6	084	074, 103
Blood sample deviations Period II, Hour 8	037, 070, 099	074, 075
Blood sample deviations Period II, Hour 10	053	058, 074
Blood sample deviations Period II, Hour 12	004, 033, 040	048, 052, 056

Comments on Protocol Deviations:

Primary protocol deviations that occurred during the study consisted of blood sample collection deviations at various time points and storage of blood samples at -26 ºC rather than -20± 5 ºC.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. S08-0114 (2008-1698) Analyte Name: Lansoprazole								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	2.00	4.00	12.0	30.0	100	400	1200	2000
Inter day Precision (%CV)	6.3	3.4	2.6	2.9	2.6	1.7	1.5	0.7
Inter day Accuracy (%Actual)	94.5	95.3	101.7	104.3	104.0	102.0	96.9	101.3
Linearity	0.9988 to 1.0000							
Linearity Range (ng/mL)	2.00 to 2000							
Sensitivity/LOQ (ng/mL)	2.00							

Parameter	Quality Control Samples			
Concentration (ng/mL)	6.00	98.0	1600	500
Inter day Precision (%CV)	4.3	4.0	2.5	3.3
Inter day Accuracy (%Actual)	100.8	105.1	97.9	99.8

Comments on Study Assay Validation:

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
LAB105.05	November 16, 2007	REPEAT SAMPLE ANALYSIS PROCEDURE AND ACCEPTANCE CRITERIA

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

The analysis of samples is complete. The firm submitted the SOPs for analytical run acceptance and repeat analysis. The long term stability data of 163 days cover the entire duration of study samples.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Fasting Bioequivalence Study, Study No. S08-0114										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV %	Min	Max	Mean	CV %	Min	Max	(T/R)
AUCT	ng hr/mL	2025.137	61.69	441.03	9431.46	2030.315	59.46	497.40	9056.34	1.00
AUCI	ng hr/mL	2066.010	67.50	448.27	11401.56	2078.263	62.90	537.05	10541.50	0.99
CMAX	ng/mL	849.712	41.92	136.00	2040.00	900.654	47.20	131.00	2140.00	0.94
*TMAX	hr	2.250	.	1.50	5.00	1.750	.	0.97	5.00	1.29
KE	hr-1	0.640	29.66	0.17	1.14	0.638	29.03	0.18	1.13	1.00
THALF	hr	1.203	38.92	0.61	4.02	1.198	37.41	0.61	3.96	1.00

*T_{max} values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Lansoprazole Dose (1 x 30 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. S08-0114				
Parameter (units)	Test A	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	2025.14	2030.31	99.02	94.35-103.91
AUC∞ (hr *ng/ml)	2060.01	2078.26	99.21	94.54-104.11
Cmax (ng/ml)	849.71	900.65	97.34	89.63-105.72

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Lansoprazole Dose (1 x 30 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. S08-0114				
Parameter (units)	Test A	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	1741.59	1758.89	0.99	94.35-103.91
AUC∞ (hr *ng/ml)	1759.37	1773.38	0.99	94.52104.13
Cmax (ng/ml)	770.76	791.79	0.97	89.63-105.72

Table 17. Additional Study Information, Fasting Study No. S08-0114

Root mean square error, AUC0-t	0.2096	
Root mean square error, AUC∞	0.2082	
Root mean square error, Cmax	0.3587	
	Test A	**Reference**
Kel and AUC∞ determined for how many subjects?	104	103
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test A	104	0.99	0.83	1.00
Reference	103	0.99	0.86	1.00

Comments on Pharmacokinetic and Statistical Analysis:

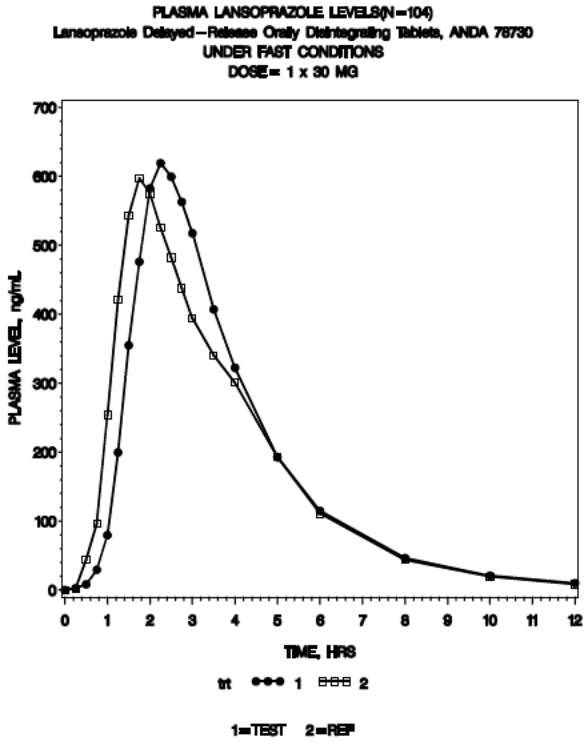
104 of the 110 subjects enrolled completed the study. Six subjects were dismissed from the study prior to Period 2 dosing (See Table 8). The data from these subjects were not included in the final pharmacokinetic and statistical analysis. The reviewer calculated 90% confidence intervals for T/R ratios for LAUCT, LAUCI and LC_{max} of Lansoprazole and the results are within the acceptable limits (80% -125%) and similar to those reported by the firm.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The single-dose fasted bioequivalence study is acceptable.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Analyte: Lansoprazole					
	Test (n=104)		Reference (n=104)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.25	2.54	145.68	2.06	330.26	1.24
0.50	8.41	120.27	43.96	229.91	0.19
0.75	29.36	136.80	95.70	146.46	0.31
1.00	79.54	137.93	254.01	151.67	0.31
1.25	199.67	144.52	421.50	112.98	0.47
1.50	355.00	118.89	543.07	93.63	0.65
1.75	476.14	90.03	597.67	81.17	0.80
2.00	582.45	70.33	575.33	72.90	1.01
2.25	619.28	62.86	525.19	67.16	1.18
2.50	599.43	56.79	482.56	66.01	1.24
2.75	562.92	53.95	437.71	67.27	1.29
3.00	517.52	54.73	393.78	66.39	1.31
3.50	407.19	57.24	340.46	67.15	1.20
4.00	322.44	64.25	300.87	68.47	1.07
5.00	192.77	84.45	192.75	85.10	1.00
6.00	114.70	110.87	111.36	102.21	1.03
8.00	46.39	172.80	43.67	151.54	1.06
10.00	20.86	247.98	19.45	221.64	1.07
12.00	10.16	357.39	8.58	323.31	1.18

Figure 1: Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



Following this page, 6 pages withheld in full - (b)(4) Formulation Data

Reviewer's comment: The change in % age of [redacted] (b) (4) does not change by more than [redacted] (b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	The inactive ingredients are within the acceptable IIG limits. The formulations are acceptable

4.3 Dissolution Data

Dissolution Review Path	N/A

Table 19. Dissolution Data

Dissolution Conditions	**Apparatus:**	Apparatus 2 (Paddle)
	Speed of Rotation:	75 rpm
	Medium:	**Acid Stage:** 0.1N HCl **Buffer Stage:** Phosphate Buffer, pH 6.8 with 5 mM SDS
	Volume:	**Acid Stage:** 500 mL **Buffer Stage:** 900 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	**Acid stage:** NMT [redacted] (b) (4) dissolved in 60 minutes **Buffer stage:** NL [redacted] % (Q) dissolved in 45 minutes	
Dissolution Testing Site (Name, Address)	TEVA Pharmaceuticals USA, 650 Cathill Road, Sellersville, PA 18960	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)		Study Report Location
						Acid Stage	Buffer Stage	

						60 min	5 min	10 min	15 min	20 min	30 min	45 min	
7449-080303-FDA	3/24/09	Lansoprazole Delayed Release Orally Disintegrating Tablets Lot# 2621-014 (Site Transfer Batch) Mfg.:	15 mg Tablets	12	Mean	0.52	16	68	75	77	79	78	Attachment 4
					Range	(b) (4)							
					%CV	104*	34	9	6	5	5	4	
	3/24/09	Lansoprazole Delayed Release Orally Disintegrating Tablets Lot# K-39962 (Old ANDA Batch) Mfg.:	15 mg Tablets	12	Mean	0	14	58	69	74	76	76	Attachment 4
					Range	0	(b) (4)						
					%CV	0	28	13	8	7	5	4	
	8/27/07	[1]Prevacid® SoluTab™ #525552E80 Exp.: 5/09	15 mg Tablets	12	Mean	0	80	84	85	85	84	82	
					Range	0-0	(b) (4)						
					%CV	0	12.7	7.2	3.6	2.8	2.5	2.4	

*Value for %CV not meaningful due to range of 0-1%.

[1]The dissolution data for RLD, 15 mg has been taken from the Biopharmaceutics Review for Lansoprazole Delayed Release Orally Disintegrating Tablets (DFS N 078730 N 000 AB 12-Oct-2007).

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)							Study Report Location
						Acid Stage	Buffer Stage						
						60 min	5 min	10 min	15 min	20 min	30 min	45 min	
7449-090313-FDA	3/24/09	Lansoprazole Delayed Release Orally Disintegrating Tablets Lot# 2621-015 (Site Transfer Batch) Mfg.: March 12, 2008	30 mg Tablets	12	Mean	0	13	63	74	77	79	79	Attachment 4
					Range	0	(b) (4)						
					%CV	0	19	13	7	6	6	5	
	3/24/09	Lansoprazole Delayed Release Orally Disintegrating Tablets Lot# K-39962 (Old ANDA Batch) Mfg.:	30 mg Tablets	12	Mean	0	11	62	77	81	83	82	
					Range	0	(b) (4)						
					%CV	0	16	15	9	8	6	6	
	7/26/07	[1]Prevacid® SoluTab™ Lot# #330269P22 Exp.: April 2008	30 mg Tablets	12	Mean	0	85	91	91	90	88	86	
					Range	0-0	(b) (4)						
					%CV	0	11.1	3.4	2.8	2.8	2.8	2.6	

[1]The dissolution data for RLD, 30 mg has been taken from the Biopharmaceutics Review for Lansoprazole Delayed Release Orally Disintegrating Tablets (DFS N 078730 N 000 AB 12-Oct-2007).

Comparison of profiles using the similarity factor F2

			Site Transfer Batch	Old ANDA Batch
Date	**6/22/2009**		RX- 2621-014	K-39662
	n =	**12**	0.52	0
			16	14
	F2 =	**65.41**	68	58
			75	69
ANDA	**78730**		77	74
Drug	**Lansoprazole**	**15 mg**	79	76
			78	76

Comparison of profiles using the similarity factor F2

			Site Transfer Batch	Old ANDA Batch
			RX-2621-015	K-3966
Date	**6/22/2009**			
	n =	**12**	0	0
			13	11
	F2 =	**76.32**	63	62
			74	77
ANDA	**78730**		77	81
Drug	**Lansoprazole**	**30 mg**	79	83
			79	82

Comparison of profiles using the similarity factor F2

			Site Transfer Batch	Prevacid® SoluTab™
Date	**6/22/2009**		RX-2621-014	525552E80
	n =	**12**	0.52	0
			16	80
	F2 =	**29.64**	68	84
			75	85
ANDA	**78730**		77	85
Drug	**Lansoprazole**	**15 mg**	79	84
			78	82

Comparison of profiles using the similarity factor F2

			Site Transfer Batch	Prevacid® SoluTab™
			RX-2621-015	330269P22
Date	**6/22/2009**			
	n =	**12**	0	0
			13	85
	F2 =	**25.70**	63	91
			74	91
ANDA	**78730**		77	90
Drug	**Lansoprazole**	**30 mg**	79	88
			79	86

Comparison of profiles using the similarity factor F2

			Site Transfer Batch	Site Transfer Batch
Date	**6/22/2009**		RX-2621-014	RX-2621-015
			15 mg	***30 mg***
	n =	**12**	0.52	0
			16	13
	F2 =	**80.22**	68	63
			75	74
ANDA	**78730**		77	77
Drug	**Lansoprazole**	**15 & 30 mg**	79	79
			78	79

On June 23, 2009 firm has acknowledged the FDA-recommended dissolution method and specifications.

Dissolution Comments: The dissolution results submitted by the firm on its 15 mg and 30 mg strengths (Old formulation) in this supplemental application (27-March-2009) indicate that dissolution rate of lansoprazole has decreased as compared to the dissolution rate of the 15 mg and 30 mg strengths (Old formulation) submitted in dissolution amendment dated October 12, 2007 (DFS N 078730 N000 AB 12-Oct-2007).

Figure 2. Dissolution Profiles

4.4 Detailed Regulatory History (If Applicable)

The Division File contains the review of following several relevant documents on this drug product:

(b) (4)

- Control #03-315 (
- Control #04-097 (
- Control #04-1205
- Control #04-813 (
- Control #05-0631
- Control #05-0754
- Control #05-1339
- Control #06-0116
- Control #06-0304
- Control #06-0402
- Control #06-0698
- Control #06-1101
- Control #06-1330
- Control #07-0080
- Control #07-0254
- Control #07-0314
- Control #07-1236
- Control #08-0350
- Control #08-0729

The following ANDAs on this drug product are currently under review:

- ANDA # (b) (4)

4.5 Consult Reviews

N/A

Following this page, 47 pages withheld in full - (b)(4) SAS Data

4.7 Additional Attachments

None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78730

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time.

We acknowledge that you have accepted the following dissolution method and specifications:

The dissolution testing should be conducted in 500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour) at 37°C ± 0.5°C using USP apparatus 2 at 75 rpm. The test product should meet the following specifications:

Acid stage: NMT (b)(4)% in 60 minutes
Buffer stage: NLT (b)(4)% (Q) in 30 minutes

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed product is not approvable.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

COMPLETED ASSIGNMENT FOR 78730 ID: 8622

Productivity:

Reviewer: Kaur, Paramjeet **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
8622	9/15/08	Bioequivalence Study	Fasting Study	1	1	Edit	Delete
8622	3/27/09	Dissolution Data	Dissolution Review	1	1	Edit	Delete
8622	3/27/09	Other	Dissolution Waiver	1	1	Edit	Delete
8622	6/23/09	Other	Dissolution Amendment	0	0	Edit	Delete
				Bean Total:	3		

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

/s/

Paramjeet Kaur
6/24/2009 02:48:11 PM
BIOPHARMACEUTICS

Moheb H. Makary
6/24/2009 02:50:08 PM
BIOPHARMACEUTICS

Barbara Davit
6/24/2009 03:02:40 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78730
Drug Product Name	Lansoprazole Delayed Release Orally Disintegrating Tablet
Strength(s)	15 mg and 30 mg
Applicant Name	Teva Pharmaceuticals USA
Address	1090 Horsham Road, North Wales, PA 19454
Applicant's Point of Contact	Philip Erickson, R.Ph. Senior Director, Regulatory Affairs
Contact's Telephone Number	215-591-3141
Contact's Fax Number	215-591-8812
Original Submission Date(s)	December 27, 2006
Submission Date(s) of Amendment(s) Under Review	September 15, 2008 March 27, 2009 June 23, 2009
Reviewer	Paramjeet Kaur, Ph.D.
Study Number (s)	S08-0114
Study Type (s)	Fasting
Strength (s)	30 mg
Clinical Site	Gateway Medical Research, Inc. – Cetero Research
Clinical Site Address	400 Fountain Lakes Blvd. St. Charles, MO 63301 Deryk L. McDowell, M.D.
Analytical Site	(b) (4)
Analytical Site Address	(b) (4)
OUTCOME DECISION	**INADEQUATE**

OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**INADEQUATE**		
DSI REPORT RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
7	**FASTING STUDY**	**30 MG**	**ADEQUATE**
9	**DISSOLUTION**	**15 MG**	**INADEQUATE**
9	**DISSOLUTION**	**30 MG**	**INADEQUATE**

1 EXECUTIVE SUMMARY

The original application submitted by the firm on December 27, 2006 contained the results of both dissolution testing and single dose fasting and fed bioequivalence studies comparing its test product Lansoprazole Delayed Release Orally Disintegrating Tablets, 30 mg to the corresponding reference product Prevacid® SoluTab™ (Lansoprazole), 30 mg, manufactured by Tap Pharmaceuticals. The firm conducted dissolution testing using its own proposed method (DFS N 078730 N 000 27-Dec-2006), and, was requested to conduct the dissolution testing using the FDA-recommended method. The firm submitted a bioequivalence amendment on October 12, 2007 generating new dissolution profiles for 15 mg and 30 mg strengths of its test product using the FDA-recommended method. Based on the submitted data the Division of Bioequivalence (DBE) recommended the following specifications:

Acid stage: NMT (b) (4) in 60 minutes
Buffer stage: NLT % (Q) in 30 minutes

The bioequivalence (fasting and fed) studies and dissolution method was found acceptable; however, the application was found to be incomplete due to dissolution deficiency (dissolution specifications). The firm was asked to accept and acknowledge the DBE recommended dissolution method and specifications (DFS N 078730 N 000 AB 12-Oct-2007). The firm has not acknowledged DBE-recommended dissolution method and specifications (supplemental application submitted on March 27, 2009).

On March 27, 2009 the firm submitted a supplemental application for Lansoprazole Delayed Release Orally Disintegrating Tablets, 30 mg. This supplement provides for an alternative site (Teva Pharmaceuticals, Sellersville, PA) for the manufacture, analytical testing and packaging from its approved site at Kfar-Saba, Israel; and change in the concentration of (b) (4) and (b) (4) in the formulation. This application was also deemed acceptable with no deficiencies. Based on the dissolution data submitted in the supplemental application (March 27, 2009), firm acknowledged the following FDA-recommended dissolution method and specifications on June 23, 2009.

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Specifications:	Acid stage: NMT (b) (4) in 60 minutes Buffer stage: NL % (Q) in 30 minutes

It is noted that the buffer stage specification of **NLT (b)(4)% (Q) in 45 minutes** was proposed by the firm as its reformulated batches # Rx 2621-014 (15 mg) and Rx 2621-015 (30 mg) manufactured at Sellersville, PA site did not meet the buffer stage criteria. Based on the fact a) that the test formulation did meet the BE 90% confidence interval criteria (DAARTS, ANDA 078730, REV-BIOEQ-01(General Review); final date: 6/24/09) and b) that the DBE in practice allows data driven dissolution specification for modified release products, the DBE proposed specification **of NLT (b)(4)% (Q) in 30 minutes**. However, during course of the CMC review of this supplemental application, the Division of Chemistry 2 noted some discrepancies in the test product formulation as compared to reference listed drug product (for detailed information, please refer to Dr. Wenlei's review and emails in Appendix 1 (4.1.1 and 4.1.2)) and raised concerns with respect to the test product therapeutic equivalence compared to the reference products. These concerns were discussed in an internal meeting between the CMC and DBE 2 on March 10, 2010 (please see the Meeting Minutes attached in Appendix 1: 4.1.3 of this document). The Division of Bioequivalence concurs with Chemistry concerns, and requests the submission of following additional data to ensure that test products Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg manufactured at Sellersville, PA site are therapeutically equivalent to their corresponding reference products Prevacid® SoluTab™ (Lansoprazole), Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg, respectively. From the DBE point of view the application is now considered incomplete pending adequate response to the additional recommendations below:

1. The dissolution testing's of the test Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg exhibit mean dissolution release of less than (b)(4)% compared to the reference Prevacid® SoluTab™ (Lansoprazole) Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg (mean dissolution release more than (b)(4)%) at 30- and 45-minutes. Please provide reasons for incomplete release of the drug from the test products Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg.

2. Please provide the dissolution data obtained from Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg batches kept on accelerated and long-term storage stability conditions.

3. Please conduct comparative dispersibility testing using 20 units of the test and reference 15 mg and 30 mg tablets in oral syringe using 4 mL and 10 mL of water, respectively.

4. Please conduct comparative acid resistance stability testing using 12 units of all strengths of the test and reference products. The stability studies should be conducted using the dispersed tablets with acid resistance as the stability indicator using the following method:

    - Disperse the tablets into water in oral syringe for 15 minutes. Use 4 mL of water for 15 mg tablets and 10 mL for 30 mg tablets.

- Transfer the contents of syringe into dissolution vessel containing 500 mL of 0.1 N HCl maintained at 37 °C ± 0.5 °C.

- Refill the syringe with 2 mL of water for 15 mg tablets and 5 mL for 30 mg tablets, shake gently and transfer any remaining contents into the dissolution media mentioned above.

- Acid resistance testing should be conducted using USP Apparatus II at 75 rpm.

- Analyze the amount of lansoprazole released at 60 minutes.

- Repeat the acid resistance stability testing using combination of a syringe and 8 French nasogastric tube.

5. Please conduct the comparative recovery studies of the dispersed tablets from oral syringe and from a combination of oral syringe and nasogastric tube (8 FR) using 20 units of all strengths of the test and reference listed products using 4 mL of water for 15 mg tablets and 10 mL for 30 mg tablets.

   DBE asks applicants to submit standard operating procedures for dispersibility, stability and recovery testing, individual data, mean values, standard deviations, coefficient of variation (CV%), and plots of percent release of lansoprazole in stability testing in acid medium test.

6. Please note if you want to retain the option of using Kfar-Saba, Israel location as alternate manufacturing site, please provide the data for the tests mentioned in # 1-5 above from the batches manufactured at this site as well.

7. Comments related to the chemistry, manufacturing and controls section will be sent by the chemistry review team.

The objectives of this review are to: (1) provide scientific background justifying the above concerns; and (2) to compare the in vivo performance of the test and reference products with respect to the time to peak plasma concentrations (Tmax). A detailed comparison of test and reference Tmax values was not performed at the time of the original review of the supplemental application of September 15, 2008

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2 TABLE OF CONTENTS

3 ADDITIONAL REVIEW RELATED ISSUES

Since the test product median Tmax and range was found to be slightly different than that of the reference product (Table 1 below), the reviewer compared individual Tmax using a stick-plot approach. The individual subject's concentration versus time profiles (please refer to Appendix II), Tmax distribution and stick-plot are depicted below:

Table 1: Arithmetic mean pharmacokinetic parameters of lansoprazole

Lansoprazole Extended Release Tablets, Dose (1 x 30 mg) Fasting Bioequivalence Study, Study No. S08-0114; N=104										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	2025.137	61.69	441.03	9431.46	2030.315	59.46	497.40	9056.34	1.00
AUCI	ng hr/mL	2066.010	67.50	448.27	11401.56	2078.263	62.90	537.05	10541.5	0.99
CMAX	ng/mL	849.712	41.92	136.00	2040.00	900.654	47.20	131.00	2140.00	0.94
*TMAX	hr	2.250	.	1.50	5.00	1.750	.	0.97	5.00	1.29
KE	hr-1	0.640	29.66	0.17	1.14	0.638	29.03	0.18	1.13	1.00
THALF	hr	1.203	38.92	0.61	4.02	1.198	37.41	0.61	3.96	1.00

*median Tmax represented

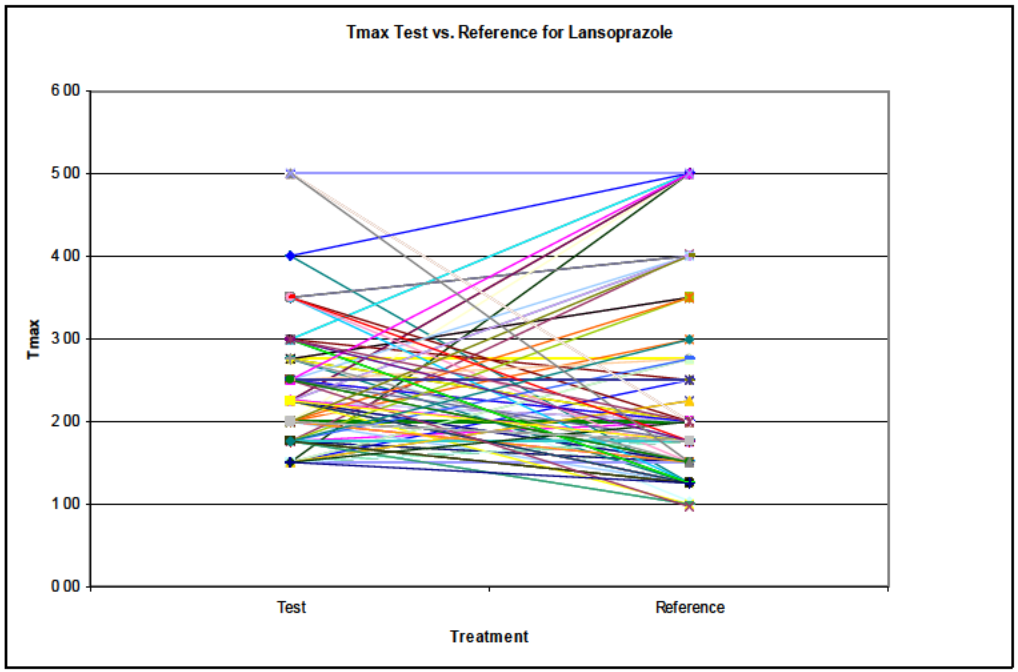
Individual T_{max} Distribution Values for Lansoprazole (Fasting Study No: S08-0114)

Subject #	Test	Reference	Difference Test-Reference	Values in Ascending Order for Difference in (T-R)
1	3.50	4.00	-0.50	-3.50
2	1.75	2.00	-0.25	-3.00
3	2.75	2.75	0.00	-2.75
4	2.00	1.75	0.25	-2.75
5	2.25	2.00	0.25	-2.50
6	1.50	1.75	-0.25	-2.27
7	4.00	1.25	2.75	-2.00
8	1.50	2.50	-1.00	-2.00
9	2.50	1.50	1.00	-2.00
10	3.00	1.03	1.97	-2.00
11	1.75	1.25	0.50	-1.75
12	2.25	1.25	1.00	-1.75
13	2.00	1.25	0.75	-1.75
14	2.75	3.50	-0.75	-1.50
15	2.25	1.25	1.00	-1.50
16	2.00	1.50	0.50	-1.25
17	1.50	1.75	-0.25	-1.25
18	1.75	1.00	0.75	-1.25
20	1.75	1.50	0.25	-1.00
21	1.75	1.25	0.50	-1.00
22	2.25	5.00	-2.75	-1.00
23	2.00	3.00	-1.00	-1.00
24	2.25	1.50	0.75	-0.75
25	1.50	2.75	-1.25	-0.75
26	1.75	1.25	0.50	-0.75
27	2.25	4.00	-1.75	-0.75
29	1.50	5.00	-3.50	-0.50
30	2.75	2.00	0.75	-0.50
31	2.50	1.50	1.00	-0.50
32	3.00	5.00	-2.00	-0.43
33	1.50	2.25	-0.75	-0.25
34	2.75	3.50	-0.75	-0.25
35	2.07	2.50	-0.43	-0.25
36	1.75	1.75	0.00	-0.25

37	1.50	1.75	-0.25	-0.25
38	5.00	5.00	0.00	-0.25
39	2.75	2.00	0.75	-0.02
40	2.00	1.50	0.50	0.00
41	3.00	5.00	-2.00	0.00
42	3.00	2.50	0.50	0.00
43	2.00	2.00	0.00	0.00
45	1.75	1.50	0.25	0.00
46	2.50	2.50	0.00	0.00
47	2.25	1.25	1.00	0.00
48	2.75	1.25	1.50	0.00
49	2.25	1.50	0.75	0.00
50	3.50	4.00	-0.50	0.00
51	1.50	1.50	0.00	0.25
52	1.75	4.02	-2.27	0.25
53	2.00	5.00	-3.00	0.25
54	2.00	4.00	-2.00	0.25
55	2.25	5.00	-2.75	0.25
56	2.50	2.00	0.50	0.25
58	1.75	1.75	0.00	0.25
59	2.25	2.00	0.25	0.25
60	2.25	1.50	0.75	0.25
61	2.27	1.75	0.52	0.50
62	2.25	1.00	1.25	0.50
63	3.00	1.75	1.25	0.50
64	2.25	1.25	1.00	0.50
65	3.50	2.00	1.50	0.50
66	1.75	1.77	-0.02	0.50
67	2.50	2.00	0.50	0.50
68	3.50	1.25	2.25	0.50
69	1.50	1.75	-0.25	0.50
70	1.50	2.75	-1.25	0.50
71	2.25	1.25	1.00	0.50
72	2.50	4.00	-1.50	0.52
73	3.50	1.50	2.00	0.75
74	2.25	4.00	-1.75	0.75
75	2.50	2.75	-0.25	0.75
76	1.75	2.75	-1.00	0.75
77	1.75	1.75	0.00	0.75

78	1.75	3.50	-1.75	0.75
79	1.50	2.25	-0.75	0.75
80	2.00	1.50	0.50	0.75
81	2.00	3.50	-1.50	0.75
82	2.50	1.75	0.75	1.00
83	2.75	1.50	1.25	1.00
84	2.25	1.25	1.00	1.00
85	1.75	1.00	0.75	1.00
86	1.50	2.00	-0.50	1.00
87	1.75	1.25	0.50	1.00
90	5.00	2.00	3.00	1.00
91	2.50	0.97	1.53	1.00
92	2.50	2.50	0.00	1.00
93	3.00	1.25	1.75	1.00
94	5.00	2.00	3.00	1.25
95	3.50	1.75	1.75	1.25
96	3.00	1.25	1.75	1.25
97	4.00	5.00	-1.00	1.25
98	2.25	1.75	0.50	1.50
99	2.50	5.00	-2.50	1.50
100	2.00	1.75	0.25	1.53
101	2.00	1.75	0.25	1.75
102	2.50	1.50	1.00	1.75
103	1.50	1.25	0.25	1.75
104	2.00	4.00	-2.00	1.97
105	3.00	1.75	1.25	2.00
106	1.75	3.00	-1.25	2.25
107	2.00	1.75	0.25	2.75
108	5.00	1.50	3.50	3.00
109	5.00	5.00	0.00	3.00
110	3.00	2.00	1.00	3.50

Stick plot for Lansoprazole T_{max} (Fasting Study No: S08-0114)



Reviewer's Comments:

The mean t_{max} values for the test and reference product are 2.4 ± 0.83 hrs (range: 1.5 -5.0 hrs) and 2.3 ± 1.20 hrs (0.97 -5.0 hrs), respectively. Based on the above data, it is noted that out of 104 subjects only16 subjects had t_{max} value for the test product lower or greater than 2.0 hr than the reference product. The t_{max} range for the test product (1.5 -5.0 hrs) is comparable to that of the reference product (0.97 -5.0 hrs) in the applicants study. However, the mean t_{max} values for test and RLD product in this study are 15 to 35% higher than that reported by the Innovator (See table below).

The median t_{max} values for the test and reference products were 2.25 hrs and 1.75 hrs, respectively. Since, the t_{max} values of the test product are comparable to the range for the reference product in the applicant's bioequivalence study, it should not affect the therapeutic equivalence of the test product.

T_{max} values for RLD product taken from the Original NDA review of Lansoprazole Delayed Release Orally Disintegrating Tablets (Fasting Studies)[1].

[1] DARRTS, NDA 021428, REV-CLINPHARM-01(General Review) by CHEN, TIEN MIEN; final date: 08/08/2008

Study Number	Number of Subjects	Dose	Tmax (hrs)
M021-241	35	30 mg	1.8 ± 0.84
M98-949	59	30 mg	2.0 ± 1.1
M99070	24	30 mg	1.7 ± 0.8

In addition, individual plasma-concentration time profile were obtained using WinNonlin program. These plots are depicted in Appendix 2 of this document. The tmax stick plot pattern between the test and reference treatment is reflected more comprehensively in these individual plots more so in terms of the respective Cmax. Close examinations of each plot reveal a mixed inconsistent pattern of Cmax and Tmax for either of the two treatments, in that while the Tmax is delayed by 1-3 hours and the corresponding Cmax has lower values in some test treatment (for examples, subjects 7, 9,11,12,13,15,24,66…), the reference treatment exhibits similar delay in Tmax and lower Cmax values (for examples, subjects 27, 28, 29, 32, 36, 41, 52, 53, 54, 68…). A similar mixed and inconsistent comparison can be drawn for the AUC parameters as well for the test and reference treatments. Presumably, this inconsistent pattern in the PK parameters between the two treatments (test and reference) is due to the reported high variable nature of the active moiety lansoprazole, rather than a reflection of drug products' formulation. Considering that the drug is taken once daily and has inherent high variability, the inconsistent individual PK profiles (seen evenly with both the test and reference formulations) apparently may not impact the therapeutic equivalence of the test product.

Following this page, 1 page withheld in full - (b)(4) Formulation Data

Reviewer's comment: The amount of (b) (4) remained the same between the site transfer batches 15 mg (lot# Rx 2621-014) and 30 mg (Rx 2621-015) manufactured at Sellerseville, PA and old ANDA batches 15 mg (lot# K-39962) and 30 mg (lot# K-39963) manufactured at Kfar-Saba, Israel, respectively. There was change in amount of (b) (4) excipients, (b) (4) did not change by more than (b) (4)

The composition of RLD formulations (NDA 021248) is provided in the table 2 below:

Table 1: Formulation of Enteric-coated Lansoprazole Microgranules

Excipient	Quantity (mg/30mg tablet)
(b) (4)	

* (b) (4)

[2] SUPAC-MR: Modified Release Solid Oral Dosage Forms – Scale-up and Postapproval Changes: Chemistry, Manufacturing and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (1997)

Table 2: Composition of 15 and 30 mg of Prevacid® (Lansoprazole) Delayed-Release Orally Disintegrating Tablets

Ingredients	Formula per 15mg tablet (mg)	Formula per 30mg tablet (mg)
		(b) (4)
Tablet weight	285.0	570.0

4 APPENDIX

4.1 Appendix I

4.1.1 Review of Lansoprazole Delayed Release ODT (ANDA 78730) by Dr. Wenlei Jiang

Question:

Teva Lansoprazole Delayed Release ODT (ANDA 78730) is bioequivalent to the RLD (Takeda NDA 21428) based on Cmax and AUC. However, its in-vitro dissolution is slower than that of RLD. Therefore, Teva's drug product in the buffer stage needs a dissolution acceptance criterion much lower than that of RLD (Teva NLT (b) (4)% (Q) in 30 minutes versus RLD NLT (b) (4)%(Q)).

Does this slow (or potentially incomplete) dissolution profile raise any concern about therapeutic equivalence of Teva product?

Answers:

1. Teva may have an underestimate of drug dissolution with their current analytical method. Teva's dissolution specification (NLT (b) (4)% (Q) in 30 minutes) may not be discriminative enough to detect a "true slow release or incomplete release" batch.

Both Takeda (RLD) and Teva (ANDA sponsor) use the same FDA recommended method for dissolution testing. When tested by Takeda, the RLD 15 and 30 mg consistently demonstrated 100% release in 30 min at pH 6.8 buffer stage (see Appendix 1). However, when tested by Teva (see Appendix 2), RLD 15 mg and 30 mg could not reach complete

release (min (b) (4)%, max (b) (4)%) even in 45 min. Similarly, Teva products also plateau off around 45 min (min (b) (4)%, max (b) (4)%).

These data suggest that Teva may have an underestimate of drug dissolution with their current analytical method. Teva's dissolution specification (NLT (b) (4)% (Q) in 30 minutes) may not be discriminative enough to detect a "true slow release or incomplete release" batch. (Note: During the RLD product development, formulations with incomplete drug release at pH 6.8 buffer stage ((b) (4)% released in 60 minutes) was considered unacceptable for further development.)

In addition, it is observed that Teva product had slower dissolution at pH 6.8 stage in first 15 min compared to RLD (Appendix 2).

2. If Teva product has comparable complete release to that of RLD, slight slower dissolution at initial time points may not have significant impact on therapeutic equivalence.

PREVACID is a proton pump inhibitor (PPI) which is intended for treatment of ulcers, Gastroesophageal Reflux Disease (GERD), and others. Clinical benefits of prevacid are based on multiple dosing, not immediate onset of the drug. With initial dose, increased gastric pH was seen within 1-2 hours with 30 mg of lansoprazole and 2-3 hours with 15 mg of lansoprazole. After multiple daily dosing, increased gastric pH was seen within the first hour post-dosing with 30 mg of lansoprazole and within 1-2 hours post-dosing with 15 mg of lansoprazole.

Prevacid Solutab 15 or 30 mg tablets were bioequivalent (Appendix 4) to Prevacid delayed release capsules though there are considerable formulation differences in Prevacid Solutab tablet and Prevacid capsules (Appendix 5). In addition, Prevacid delayed release capsules was found to release drug slightly slower in pH 6.8 buffer stage at initial time points compared to Prevacid Solutab (Appendix 3). However, no additional clinical efficacy or safety trials were conducted to support approval of Prevacid Solutab 15 or 30 mg tablets. Prevacid Solutab 15 or 30 mg are approved based on their bioequivalence to Prevacid delayed release capsules.

Prevacid is a BCS class II drug and has an absolute bioavailability over 80%. No regional absorption is reported for this drug. Administration of 30 mg Prevacid Solutab dispersed in 10 ml water and administered by NG tube resulted in similar AUC but around 20% higher Cmax relative to the intact orally disintegrating tablet (Appendix 4). The observed difference on Cmax is considered unlikely of any clinical relevance.

Based on available information, slight difference in initial dissolution of formulations should not cause significant bioavailability and efficacy difference.

3. Teva drug products release slower than RLD possibly because 1) (b) (4) (b) (4); 2) (b) (4) in Teva formulation. (Appendix 5)

Teva and Takeda used the same (b) (4) agent at similar amount. However, their formulations and manufacturing processes differ a great extent. Takeda has relatively

[redacted] (b) (4) to start with for the drug [redacted] (b) (4) process whereas Teva has [redacted] (b) (4) Takeda had performed [redacted] (b) (4) while Teva did [redacted] (b) (4). It is possible that [redacted] (b) (4) in Teva batch gets [redacted] (b) (4), resulting in slower release at initial time points.

In addition, Teva has [redacted] (b) (4) while Takeda has [redacted] (b) (4). In the [redacted] (b) (4), Teva granules used [redacted] (b) (4), which may also cause slower release of drug.

4. Considering the complexity of the drug product and process, the following data should be carefully examined to support the approval of TEVA ANDA:

a. Teva should provide explanations why there is incomplete drug release when using FDA recommended dissolution method.
b. Dissolution profile comparison of delayed release granules before and after tablet [redacted] (b) (4).
c. Dispersibility and stability comparison of Teva ODT and RLD in water, and recovery of the dispersed [redacted] (b) (4) from an oral syringe or from a combination of syringe and NG tube.
d. Any dissolution profile change at accelerated and long term storage conditions
e. Dissolution data of [redacted] (b) (4) and [redacted] (b) (4) batches

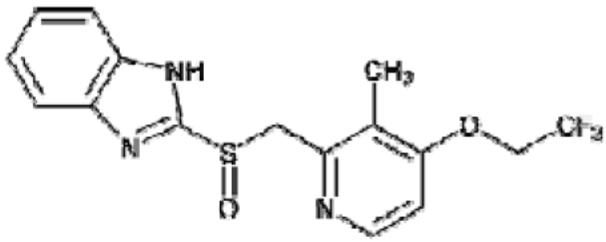
Background

PREVACID® is indicated for short-term treatment (for 4 weeks) for healing and symptom relief of active duodenal ulcer. PREVACID is available as Delayed-Release Capsules (NDA 20406), SoluTab Delayed-Release Orally Disintegrating Tablets (NDA 21428) and Delayed-Release Oral Suspension (NDA 21281, discontinued) in 15 mg and 30 mg strengths (Appendix 6). All these contain enteric-coated granule formulations of lansoprazole to avoid acid degradation of drug substance.

The RLD for ANDA 78730 is SoluTab Delayed-Release Orally Disintegrating Tablets (NDA 21428).

Drug substance

General physico-chemcial properties



Molecular Formula: $C_{16}H_{14}F_3N_3O_2S$
Molecular Weight: 369.37

Lansoprazole is a white to brownish white powder. It is practically insoluble (<0.1 mg/mL) in water below pH 9, becoming slightly soluble at pH 11 and sparingly soluble at pH 13. The rate of degradation of lansoprazole in aqueous solution rapidly increases with decreasing pH. The degradation half-life of the drug substance in aqueous solution at 25°C is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.

Lansoprazole is a BCS class II drug.

Pharmacological action

Lansoprazole) belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by blocking the proton pump [(H+, K+)-ATPase enzyme system] at the secretory surface of the gastric parietal cell. The two active species are not present in the systemic circulation. With initial dose, increased gastric pH was seen within 1-2 hours with 30 mg of lansoprazole and 2-3 hours with 15 mg of lansoprazole. After multiple daily dosing, increased gastric pH was seen within the first hour post-dosing with 30 mg of lansoprazole and within 1-2 hours post-dosing with 15 mg of lansoprazole. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. In addition, Despite a lower bioavailability, enteral lansoprazole suppresses acid in intensive care unit patients to a greater extent than IV lansoprazole[3].

Pharmacokinetics

Lansoprazole PK is linear between 15 mg and 60 mg. The absorption of lansoprazole is rapid, with the mean Cmax occurring approximately 1.7 hours after oral dosing, and the absolute bioavailability is over 80%. Food decreases the absorption.

Lansoprazole is 97% bound to plasma proteins. Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity.

Lansoprazole is a highly variable drug. At fasting state, intra CV 30-40%; At fed state, intra CV (>75%). Wide inter-individual variation in bioavailability of LSP was partly attributed to the variation in the genotype of CYP2C19 and, possible gastric degradation and limited solubility of LSP in water.

[3] OLSEN KM, DEVLIN JW Comparison of the enteral and intravenous lansoprazole pharmacodynamic responses in critically ill patients *Aliment Pharmacol Ther* 28, 326–333

Appendix 1. Dissolution data generated by Takeda (Prevacid solutab (NDA 21428) Annual report Oct 22, 2009 EDR)

Table 4 Long-term Testing at 25°C/60%RH on AG-1749 Tablets (15mg) in Al:Al blisters, Lot No.9010053A

Storage Conditions	Appearance	Dissolution [a] (%)		Assay [b] (%)	Microbial Limit Test		
		Acid stage 60 min	Buffer stage 30 min		T.A.M.C	T.C.M.Y.C	*E. coli*
Initial	Complies	[redacted]					(b) (4)
25°C/60%RH × 3M	Complies						
25°C/60%RH × 6M	Complies						
25°C/60%RH × 9M	Complies						
25°C/60%RH × 12M	Complies						
25°C/60%RH × 18M	Complies						
25°C/60%RH × 24M	Complies						
25°C/60%RH × 36M	Complies						

Table 5 Long-term Testing at 25°C/60%RH on AG-1749 Tablets (30mg) in Al:Al blisters, Lot No. 9010050A

Storage Conditions	Appearance	Dissolution [a] (%)		Assay [b] (%)	Microbial Limit Test		
		Acid stage 60 min	Buffer stage 30 min		T.A.M.C	T.C.M.Y.C	*E. coli*
Initial	Complies	[redacted]					(b) (4)
25°C/60%RH × 3M	Complies						
25°C/60%RH × 6M	Complies						
25°C/60%RH × 9M	Complies						
25°C/60%RH × 12M	Complies						
25°C/60%RH × 18M	Complies						
25°C/60%RH × 24M	Complies						
25°C/60%RH × 36M	Complies						

- In Takeda's test condition, RLD 15 mg and 30 mg has about [redacted] (b) (4) release in acid stage and reach [redacted] (b) (4) % release in 30 min.

Appendix 2. Dissolution data generated by Teva (DBE review)

						60 min	5 min	10 min	15 min	20 min	30 min	45 min	
7449-080303-FDA	3/24/09	Lansoprazole Delayed Release Orally Disintegrating Tablets Lot# 2621-014 (Site Transfer Batch) Mfg.:	15 mg Tablets	12	Mean	0.52	16	68	75	77	79	78	Attachment 4
					Range	(b) (4)							
					%CV	104*	34	9	6	5	5	4	
	3/24/09	Lansoprazole Delayed Release Orally Disintegrating Tablets Lot# K-39962 (Old ANDA Batch) Mfg.:	15 mg Tablets	12	Mean	0	14	58	69	74	76	76	Attachment 4
					Range	(b) (4)							
					%CV	0	28	13	8	7	5	4	
	8/27/07	[1]Prevacid® SoluTab™ #525552E80 Exp.: 5/09	15 mg Tablets	12	Mean	0	80	84	85	85	84	82	
					Range	(b) (4)							
					%CV	0	12.7	7.2	3.6	2.8	2.5	2.4	

*Value for %CV not meaningful due to range of 0-1%.

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) Acid Stage / Buffer Stage							Study Report Location
						60 min	5 min	10 min	15 min	20 min	30 min	45 min	
7449-090313-FDA	3/24/09	Lansoprazole Delayed Release Orally Disintegrating Tablets Lot# 2621-015 (Site Transfer Batch) Mfg.: March 12, 2008	30 mg Tablets	12	Mean	0	13	63	74	77	79	79	Attachment 4
					Range	(b) (4)							
					%CV	0	19	13	7	6	6	5	
	3/24/09	Lansoprazole Delayed Release Orally Disintegrating Tablets Lot# K-39962 (Old ANDA Batch) Mfg.:	30 mg Tablets	12	Mean	0	11	62	77	81	83	82	
					Range	(b) (4)							
					%CV	0	16	15	9	8	6	6	
	7/26/07	[1]Prevacid® SoluTab™ Lot# #330269P22 Exp.: April 2008	30 mg Tablets	12	Mean	0	85	91	91	90	88	86	
					Range	(b) (4)							
					%CV	0	11.1	3.4	2.8	2.8	2.8	2.6	

- In Teva's test condition, both RLD and generic lansoprazol DR ODT 15 mg and 30 mg can not reach (b) (4) % release in 45 min.
- Teva product has slower dissolution in first 15 min that RLD.

Appendix 3. Slower release of Prevacid delayed release capsule compared to Prevacid solutab

Figure 5. **Mean (± SD) Drug Release Profiles of the Lansoprazole 15 mg Fast-Disintegrating Tablet (Biobatch # Z5133061) and the Capsule Formulations Used in Study No. M98-948**

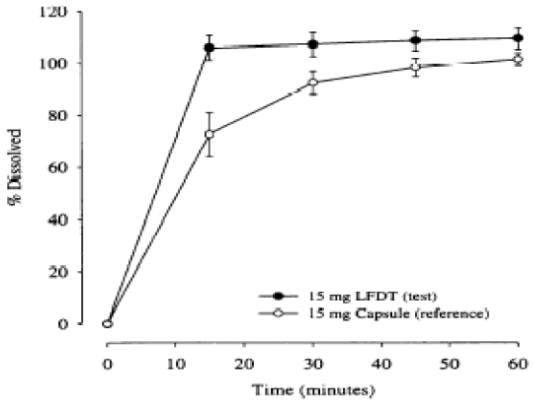
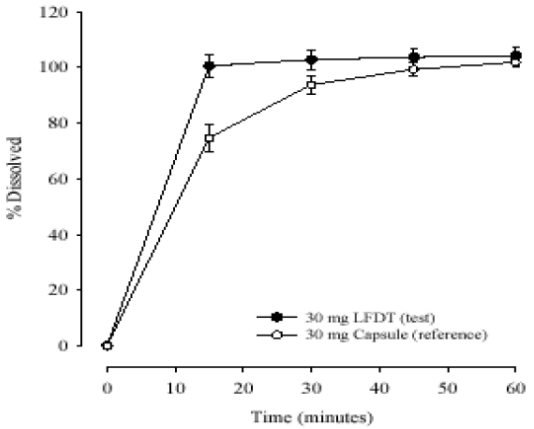


Figure 6. **Mean (± SD) Drug Release Profiles of the Lansoprazole 30 mg Fast-Disintegrating Tablet (Biobatch # Z5134071) and the Capsule Formulations Used in Study No. M98-949**



Appendix 4 Bioequivalence study

1. BE of Prevacid Solutab and Prevacid delayed release capsule

Pharmacokinetic Parameters	Regimen£ A Fast-Disintegrating Tablet	Regimen£ B Capsule
N	59	59
T_{max} (h)	2.0 ± 1.1	2.0 ± 1.0
C_{max} (ng/mL)	1087 ± 470.3	997.2 ± 361.5
AUC_t (ng•h/mL)	2551 ± 1425	2539 ± 1181
AUC_∞ (ng•h/mL)	2597 ± 1500	2583± 1233
$t_{½}$ (h)‡,$	1.18 ± 0.34	1.17 ± 0.37
CL/F (L/h)+	15.2 ± 8.5	15.8 ± 14.6

£ Regimen A: 30 mg lansoprazole fast-disintegrating tablet (test).
Regimen B: 30 mg lansoprazole capsule (reference).
‡ Harmonic mean ± pseudo standard deviation.
$ Evaluations of $t_{½}$ were based on statistical tests for λ.
+ Parameter was not tested statistically.

Pharmacokinetic Parameter	Bioavailability of Lansoprazole Tablet, Relative to Capsule Formulation: 15-mg Strength (Study M98-948) Point Estimate	15-mg Strength 90% Confidence Interval	30-mg Strength (Study M98-949) Point Estimate	30-mg Strength 90% Confidence Interval
C_{max}	1.059	0.909 - 1.235	1.089	0.958 – 1.238
AUC_t	1.042	0.932 - 1.164	0.992	0.900 – 1.092
AUC_∞	1.033	0.928 - 1.150	0.988	0.900 – 1.083

2. BE of Prevacid Solutab with and without water

A 15 mg lansoprazole orally disintegrating tablet dispersed in 2 mL water and administered orally via syringe is not bioequivalent to one 15 mg lansoprazole orally disintegrating tablet administered orally intact without water. The findings suggest that 2 mL of water may not be sufficient to deliver the whole dose of lansoprazole and flushing the remainder of the dispersed tablet is needed.

A 15 mg lansoprazole orally disintegrating tablet dispersed in 4 mL water and administered orally via syringe is not bioequivalent to one 15 mg lansoprazole orally disintegrating tablet administered orally intact without water.

Administration of 30 mg lansoprazole orally disintegrating tablet dispersed in 10 ml water and administered by NG tube resulted in similar AUC but around 20% higher Cmax relative to the intact orally disintegrating tablet. The observed difference on Cmax is concluded to be unlikely of clinical relevance.

15 mg with 4 ml water

Summary of Lansoprazole Pharmacokinetic Parameters by Regimen						
Regimen		t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_∞ (ng·h/mL)	$t_{1/2z}$[a] (h)
LODT Dispersed in Water and Administered Orally via Syringe	N	40	40	40	40	40
	Mean	1.62	480.038	1089.600	1161.999	1.033
	SD	0.92	185.372	765.749	976.560	-
Intact LODT Administered Directly on the Tongue without Water	N	40	40	40	40	40
	Mean	1.61	447.607	1019.138	1066.681	1.034
	SD	0.80	175.506	676.592	792.823	-

a Harmonic mean.

PK Parameter	Least Squares Ratio Mean	90% Confidence Interval
AUC_{0-t}	1.08	1.01-1.15
$AUC_{0-\infty}$	1.08	1.01-1.15
C_{max}	1.08	0.96-1.22

30 mg with 10 ml water

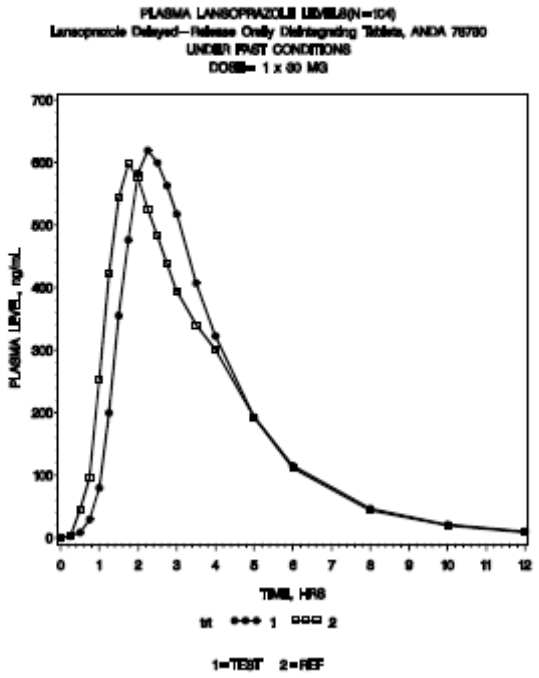
Regimen		t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_∞ (ng·h/mL)	$t_{1/2z}$[a] (h)
LODT Dispersed in Water and Administered by a Nasogastric Tube via Syringe	N	40	40	40	40	40
	Mean	1.33	1215.587	2672.367	2783.777	1.039
	SD	0.56	424.865	1718.635	1997.952	-
Intact LODT Administered Directly on the Tongue without Water	N	40	40	40	40	40
	Mean	1.75	1033.521	2496.907	2611.369	1.019
	SD	0.70	453.660	1671.403	1959.623	-

Table 4. Summary of the bioequivalence analysis calculations

PK Parameter	Least Squares Ratio Mean	90% Confidence Interval
AUC_{0-t}	1.09	1.05-1.13
$AUC_{0-\infty}$	1.09	1.04-1.13
C_{max}	1.21	1.12-1.31

3. BE study of Teva ANDA and RLD
solutab

Figure 1: Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



Fasting Bioequivalence Study, Study No. S08-0114										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV %	Min	Max	Mean	CV %	Min	Max	(T/R)
AUCT	ng hr/mL	2025.137	61.69	441.03	9431.46	2030.315	59.46	497.40	9056.34	1.00
AUCI	ng hr/mL	2066.010	67.50	448.27	11401.56	2078.263	62.90	537.05	10541.50	0.99
CMAX	ng/mL	849.712	41.92	136.00	2040.00	900.654	47.20	131.00	2140.00	0.94
*TMAX	hr	2.250	.	1.50	5.00	1.750	.	0.97	5.00	1.29
KE	hr-1	0.640	29.66	0.17	1.14	0.638	29.03	0.18	1.13	1.00
THALF	hr	1.203	38.92	0.61	4.02	1.198	37.41	0.61	3.96	1.00

*T_{max} values are presented as median, range

Appendix 5

Prevacid solutab Teva	(b) (4)	Dissolution above pH 5.5

	Delay release granule% (relative to tablet weight)	Enteric agent % (relative to tablet weight)	Enteric agent % (relative to delayed release granules)	Enteric agent:Drug ratio	(b) (4) :Drug ratio
Prevacid solutab (NDA 21428)	(b) (4)				
Teva					
Prevacid delayed release capsule (NDA 20406)					

Following this page, 3 pages withheld in full - (b)(4) Formulation Data

Appendix 6

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
PREVACID (NDA # 020406)	CAPSULE, DELAYED REL PELLETS; ORAL	15MG 30MG	Prescription	TAKEDA PHARMS NA
PREVACID (NDA # 021281)	FOR SUSPENSION, DELAYED RELEASE; ORAL	15MG 30MG	Discontinued	TAKEDA PHARMS NA
PREVACID (NDA # 021428)	TABLET, DELAYED RELEASE, ORALLY DISINTEGRATING; ORAL	15MG 30MG	Prescription	TAKEDA PHARMS NA
PREVACID 24 HR (NDA# 022327)	CAPSULE, DELAYED REL PELLETS; ORAL	15MG	Over-the-counter	NOVARTIS

4.1.2 Emails Regarding Lansoprazole Delayed Release ODT (ANDA 78730)

RE: ANDA 78730\Lansoprazole DR- ODT
From: Davit, Barbara M
To: Vehovic, Scott
Cc: Chaurasia, Chandra S; Stier, Ethan; Kaur, Paramjeet

Scott:

Please obtain a copy of Wenlei Jiang's review from her. Please append the review to the meeting request when you set up the meeting; that way the attendees will have a background on the issues.

Chandra, Ethan, Paramjeet: Please see Florence's email below, it explains the issues pretty well.

Barbara

From: Vehovic, Scott
Sent: Tuesday, March 09, 2010 1:08 PM
To: Davit, Barbara M
Subject: FW: ANDA 78730\Lansoprazole DR- ODT

Hi Barbara,

I spoke with Moheb since he signed the general review from Paramjeet, however he's not familiar with the discussions below. Could I have just a couple minutes of your time to discuss the following with you? I'll try to stop by sometime today if you're free.

Thanks,
Scott

From: Fang, Florence S
Sent: Wednesday, February 24, 2010 12:25 PM
To: Davit, Barbara M; Yu, Lawrence
Cc: West, Robert L; Jiang, Wenlei; Buehler, Gary J; Rajagopalan, Radhika; Read, Shanaz; Adams, Richard C; Liu, Theresa
Subject: RE: ANDA 78730\Lansoprazole DR- ODT

Lawrence and Barbara:

To facilitate DBE's review, a *compilation* by Teva of all dissolution data for all batches, including developmental batches, is an excellent idea. Dissolution data for accelerated testing and available room temperature testing are also to be included.
Let's include in our request all the points that Wenlei proposed in No.4 of her document.

In the CMC submissions the dissolution data are scattered in multiple amendments. For example, Teva's November 25, 2009 amendment submitted (b) (4) batches of 15 mg strength and (b) (4) batches of 30 mg strength, which were manufactured after some revisions of the original manufacturing process were made. All the product data including dissolution data are tabulated/graphed in Attachment 8 of that amendment.

I wish to thank Wenlei for the excellent evaluation.

Florence

From: Davit, Barbara M
Sent: Wednesday, February 24, 2010 10:12 AM
To: Yu, Lawrence; Fang, Florence S
Cc: West, Robert L; Jiang, Wenlei; Buehler, Gary J
Subject: RE: ANDA 78730\Lansoprazole DR- ODT

Lawrence:

Good idea, I agree.

Barbara

From: Yu, Lawrence
Sent: Wednesday, February 24, 2010 8:13 AM
To: Davit, Barbara M; Fang, Florence S
Cc: West, Robert L; Jiang, Wenlei; Buehler, Gary J
Subject: RE: ANDA 78730\Lansoprazole DR- ODT

Barbara,

I would suggest that we request the dissolution data for all the batches they have manufactured including development batches if any.

Thanks,

Lawrence

From: Davit, Barbara M
Sent: Tuesday, February 23, 2010 5:57 PM
To: Yu, Lawrence; Fang, Florence S
Cc: West, Robert L; Jiang, Wenlei
Subject: RE: ANDA 78730\Lansoprazole DR- ODT
Importance: High

Lawrence:

Thanks for getting this done so quickly. I think that the proposed requests of Teva are quite reasonable. I concur with them, with the exception of 4(e), only because I do not understand how this is done in practice; would like to hear Florence's or your input on this.

Barbara

From: Yu, Lawrence
Sent: Tuesday, February 23, 2010 5:46 PM
To: Fang, Florence S; Davit, Barbara M
Cc: West, Robert L; Jiang, Wenlei
Subject: FW: ANDA 78730\Lansoprazole DR- ODT

Florence and Barbara,

Wenlei's initial assessment. We probably need to have a meeting to discuss this.

Thanks,

Lawrence

From: Jiang, Wenlei
Sent: Tuesday, February 23, 2010 2:15 PM
To: Yu, Lawrence
Subject: RE: ANDA 78730\Lansoprazole DR- ODT

Lawrence,

Attached please see the document for ANDA78730.

Thanks,

Wenlei

From: Fang, Florence S
Sent: Wednesday, February 03, 2010 1:05 PM
To: Yu, Lawrence
Cc: Adams, Richard C; Rajagopalan, Radhika; Read, Shanaz; Liu, Theresa; Davit, Barbara M
Subject: FW: ANDA 78730\Lansoprazole DR- ODT

Lawrence:

As Radhika has pointed out, Teva's Lansoprazole Delayed Release ODT in the buffer stage needs a dissolution acceptance criterion much lower than the RLD. (generic (b)(4)% in 30 minutes versus RLD (b)(4)%), although the product has been found to be bioequivalent to the RLD. DBE has recommended initially a higher dissolution spec but finally agreed to the spec that TEVA requested. Teva's product simply fails the RLD dissolution specification.

The product is an especially difficult dosage form; it is an orally disintegrating tablet, not to be chewed. If a patient chews the tablet, the enteric coating may be partially destroyed, resulting in the degradation of the acid sensitive lansoprazole. We are concerned that the

slower dissolution rate coupled with loss of active due to acid sensitivity will result in significant difference in effect between Teva's product and the RLD. Should this question arise, a third party doing independent testing will question the slower dissolution of the generic and, therefore, its product performance.

Do you share the chemists' concern? Is the concern serious enough for the Chemistry Division to issue a major deficiency to Teva for the [redacted] (b) (4) resulting in a much slower in vitro dissolution rate?

Thank you for your consideration.

Florence

From: Rajagopalan, Radhika
Sent: Tuesday, February 02, 2010 8:38 AM
To: Fang, Florence S
Cc: Read, Shanaz; Liu, Theresa
Subject: ANDA 78730\Lansoprazole DR- ODT

Florence:

I have been looking at Lansoprazole anda by Teva (78-730, DR-ODT). I will summarize a few sentences in this e-mail and perhaps we can plan on next steps.

- It turns out the generic 15 and 30 mg by Teva is about 30% more in total tablet weight (ODT) compared to RLD-ODT.
- [redacted] (b) (4)
- The proportion of delayed release [redacted] (b) (4) to inactive in the final odt is also different:

  Teva generic: [redacted] (b) (4) % delayed release to [redacted] (b) (4) % inactive (includes flavor)
  RLD: [redacted] (b) (4) % delayed release granules to [redacted] (b) (4) % inactives (includes flavor)

- The most striking difference however comes in buffer stage dissolution\drug release criteria proposed by Teva (and agreed upon by Bio).

  RLD: NLT [redacted] (b) (4) (Q) of Lansoprazole dissolved in 30 minutes
  Teva generic: NLT [redacted] (b) (4) % (Q) in 30 minutes

- We did look at BU issues for some of the newer lots Teva manufactured, along with slower dissolution #s.

Teva product has [redacted] (b) (4), and requires lower Q (slower to release the drug) in buffer stage. It is possible Bio equivalence is a pass based on one lot testing in healthy subjects. Will we have pharmaceutical equivalence\therapeutic equivalence?

4.1.3 Meeting Minutes Regarding Lansoprazole Delayed Release ODT (ANDA 78730)

Subject: Lansoprazole Delayed Release ODT, Teva ANDA 078730
Date: March 10, 2010, 11:00AM – 12:00PM, MPN2 Conference Room B

OGD Attendees:

Barbara Davit
Ethan Stier
Chandra Chaurasia
Paramjeet Kaur
Scott Vehovic
Peter Rickman
Florence Fang
Radhika Rajagopalan
Wenlei Jiang

Background:

This meeting was requested on March 10th, 2010 by Regulatory Support, with input from the Division of Chemistry and the Division of Bioequivalence (DBE II), to discuss dissolution concerns related to Teva's ANDA 078730, Lansoprazole Delayed Release Orally Disintegrating Tablets; specifically the Agency's forthcoming response to the firm.

Discussion:

Barbara opened the meeting by referencing Wenlei's review of ANDA 078730, in particular points noted in item #4 of the review:

a) *Teva should provide explanations why there is incomplete drug release when using FDA recommended dissolution method.*
b) *Dissolution profile comparison of delayed release granules before and after tablet* (b) (4)
c) *Dispersibility and stability comparison of Teva's ODT and RLD in water, and recovery of the dispersed* (b) (4) *from an oral syringe or from a combination of syringe and NG tube.*
d) *Any dissolution profile change at accelerated and long term storage conditions.*
e) *Dissolution data of* (b) (4) *and* (b) (4) *batches.*

It was noted that in-vitro dissolution for Teva's product is slower than that of the RLD, in particular the buffer stage dissolution (RLD NLT (b) (4)% (Q) in 30 minutes versus Teva NLT (b) (4)% (Q) in 30 minutes). Both the RLD and Teva used the same FDA

recommended method for dissolution testing. Chemistry noted discrepancies in the test product formulation and questioned equivalence to the RLD products. It was decided that additional dissolution data be provided for the 15 mg and 30 mg batches, both under accelerated and LTS stability conditions. Dispersability, recovery, and stability testing was discussed and it was determined that studies should be provided from testing of tablets from an oral syringe and combination syringe/NG tube.

Location of product data batch manufacturing was discussed between attendees. It was unclear as to the manufacturing location of product for the original fasting and fed bio studies. A Sellersville, PA site was also designated by Teva as a site for the manufacture, testing, and packaging of product. It is unclear if Teva is using the Pennsylvania site as an alternate site while using the Israel site as the active site for manufacturing. Teva manufactured batches where their location was not noted (Israel or Pennsylvania site).

Conclusion:

The Division of Chemistry II, Division of Bioequivalence II, and DLPS provided discussion points relating to dissolution/testing specification for ANDA 078730.

After review of all information presented, it was determined that additional dissolution testing and other dispersibility, resistence, and stability testing was warranted. Official notification to Teva will be made on behalf of the Division of Bioequivalence II upon review of the most recently submitted data.

Following this page, 52 pages withheld in full - (b)(4)

BIOEQUIVALENCE DEFICIENCIES

ANDA: 078730

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

The Division of Bioequivalence (DBE) has completed its review and has identified the following deficiencies:

1. The dissolution testings of your test product Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg exhibit mean dissolution release of less than (b)(4)% compared to the reference listed drug (RLD) Prevacid® SoluTab™ (Lansoprazole) Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg (mean dissolution release more than (b)(4)%) at 30- and 45-minutes. Please provide reasons for incomplete release of the drug from the test products Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg.
2. Please provide the dissolution data obtained from Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg batches kept on accelerated and long-term storage stability conditions.
3. The approved labeling for the RLD states that the product may be administered via an oral syringe. The RLD labeling also states that the product may be administered by nasogastric tube. Therefore, we request that you perform the following in vitro tests to compare the performance of your product to that of the RLD under these conditions of use.

    a. Please conduct comparative dispersibility testing using 20 units of the test and reference 15 mg and 30 mg tablets in oral syringe using 4 mL and 10 mL of water, respectively.

    b. Please conduct comparative acid resistance stability testing using 12 units of all strengths of the test and reference products. The stability studies should be conducted using the dispersed tablets with acid resistance as the stability indicator using the following method:

- Disperse the tablets into water in oral syringe for 15 minutes. Use 4 mL of water for 15 mg tablets and 10 mL for 30 mg tablets.
- Transfer the contents of syringe into dissolution vessel containing 500 mL of 0.1 N HCl maintained at 37 °C ±0.5 °C.
- Refill the syringe with 2 mL of water for 15 mg tablets and 5 mL for 30 mg tablets, shake gently and transfer any remaining contents into the dissolution media mentioned above.
- Acid resistance testing should be conducted using USP Apparatus II at 75 rpm.
- Analyze the amount of lansoprazole released at 60 minutes.
- Repeat the acid resistance stability testing using combination of a syringe and nasogastric (8 FR) tube.

c. Please conduct the comparative recovery studies of the dispersed tablets from oral syringe and from a combination of oral syringe and 8 French nasogastric tube using 20 units of all strengths of the test and reference listed products using 4 mL of water for 15 mg tablets and 10 mL for 30 mg tablets.

4. Please submit standard operating procedures for dispersibility, stability and recovery testing, individual data, mean values, standard deviations, coefficient of variation (CV%), and plots of percent release of lansoprazole in stability testing in acid medium test.

5. Please note if you want to retain the option of using Kfar-Saba, Israel location as alternate manufacturing site, please provide the data for the tests mentioned in # 1-4 above from the batches manufactured at this site as well.

6. Comments related to the chemistry, manufacturing and controls section will be sent by the chemistry review team.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME PAGE

Completed Assignment for 78730 ID: 10673

Productivity:

Reviewer: Kaur, Paramjeet **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
10673	9/15/08	Other	Addendum	1	1	Edit	Delete
				Bean Total:	1		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

PARAMJEET KAUR
03/22/2010

CHANDRA S CHAURASIA
03/22/2010

BARBARA M DAVIT
03/22/2010

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78730	
Drug Product Name	Lansoprazole Delayed Release Orally Disintegrating Tablet	
Strength(s)	15 mg and 30 mg	
Applicant Name	Teva Pharmaceuticals USA	
Address	1090 Horsham Road, North Wales, PA 19454	
Applicant's Point of Contact	Philip Erickson, R.Ph. Senior Director, Regulatory Affairs	
Contact's Telephone Number	215-591-3141	
Contact's Fax Number	215-591-8812	
Original Submission Date(s)	December 27, 2006	
Submission Date(s) of Amendment(s) Under Review	September 15, 2008 March 27, 2009 May 7, 2010	
Reviewer	Paramjeet Kaur, Ph.D.	
Study Number (s)	S08-0114	
Study Type (s)	Fasting	
Strength (s)	30 mg	
Clinical Site	Gateway Medical Research, Inc. – Cetero Research	
Clinical Site Address	400 Fountain Lakes Blvd. St. Charles, MO 63301 Deryk L. McDowell, M.D.	
Analytical Site	(b) (4)	
Analytical Site Address		
OUTCOME DECISION	**ADEQUATE**	

OVERALL REVIEW RESULT	**ADEQUATE**		
WAIVER REQUEST RESULT	**ADEQUATE**		
DSI REPORT RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
7	**FASTING STUDY**	**30 MG**	**ADEQUATE**
22	**DISSOLUTION**	**15 MG and 30 MG**	**ADEQUATE**

REVIEW OF AN AMENDMENT

1 EXECUTIVE SUMMARY

Teva Pharmaceuticals has submitted this amendment in response to the Agency's deficiency letter dated 3/23/2010 for its Lansoprazole Delayed Release Orally Disintegrating (ODT) Tablets, 15 mg and 30 mg. The original application submitted by the firm on December 27, 2006 contained the results of both dissolution testing and single dose fasting and fed bioequivalence studies comparing its test product Lansoprazole Delayed Release Orally Disintegrating Tablets, 30 mg to the corresponding reference product Prevacid® SoluTab™ (Lansoprazole), 30 mg, manufactured by Tap Pharmaceuticals. The firm conducted dissolution testing using its own proposed method (DFS N 078730 N 000 27-Dec-2006), and, was requested to conduct the dissolution testing using the FDA-recommended method. The firm submitted a bioequivalence amendment on October 12, 2007 generating new dissolution profiles for 15 mg and 30 mg strengths of its test product using the FDA-recommended method. Based on the submitted data the Division of Bioequivalence (DBE) recommended the following specifications:

Acid stage: NMT (b) (4) in 60 minutes
Buffer stage: NLT % (Q) in 30 minutes

The bioequivalence (fasting and fed) studies and dissolution method was found acceptable; however, the application was found to be incomplete due to dissolution deficiency (dissolution specifications). The firm was asked to accept and acknowledge the DBE recommended dissolution method and specifications (DARRTS, ANDA 078730, REV-BIOEQ-01(General Review); final date 12/21/2007).

On March 27, 2009 the firm submitted a supplemental application for Lansoprazole Delayed Release Orally Disintegrating Tablets, 30 mg. This supplement provided for an alternative site (Teva Pharmaceuticals, Sellersville, PA) for the manufacture, analytical testing and packaging from its approved site at Kfar-Saba, Israel; and change in the concentration of (b) (4) and (b) (4) in the formulation. This application was also deemed acceptable with no deficiencies. Based on the dissolution data submitted in the supplemental application (March 27, 2009), firm acknowledged the following FDA-recommended dissolution method and specifications on June 23, 2009.

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Specifications:	Acid stage: NMT (b) (4) in 60 minutes Buffer stage: NL % (Q) in 30 minutes

It is noted that the buffer stage specification of **NLT** (b) (4) **% (Q) in 45 minutes** was proposed by the firm as its reformulated batches # Rx 2621-014 (15 mg) and Rx 2621-015 (30 mg) manufactured at Sellersville, PA site did not meet the buffer stage criteria. Based on the fact a) that the test formulation did meet the BE 90% confidence interval criteria (DAARTS, ANDA 078730, REV-BIOEQ-01(General Review); and b) that the DBE in practice allows data driven dissolution specification for modified release products, the DBE proposed specification **of NLT** (b) (4) **% (Q) in 30 minutes**. However, during course of the CMC review of this supplemental application, the Division of Chemistry 2 noted some discrepancies in the test product formulation as compared to reference listed drug product. The Division of Bioequivalence concurred with Chemistry concerns, and requested the submission of additional in vitro data to ensure that test Lansoprazole Delayed Release ODT, 15 mg and 30 mg manufactured at Sellersville, PA site are therapeutically equivalent to their corresponding reference products Prevacid® SoluTab™ (Lansoprazole) Delayed-Release ODT, 15 mg and 30 mg, respectively (DAARTS, ANDA 078730, REV-BIOEQ-01(General Review).

In the current submission (submitted: May 7, 2010), the firm has indicated that Sellersville, PA site was withdrawn via a quality minor amendment dated March 22, 2010.

In addition, the firm has submitted data from following in vitro tests on Lansoprazole Delayed Release ODT, 15 mg and 30 mg batches[1] manufactured at Teva's Kfar Saba, Israel site in response to the deficiencies cited by the Division:

1. Dissolution testing in support of incomplete release of the drug from the test products Lansoprazole Delayed Release ODT.
2. Dissolution data obtained from Lansoprazole Delayed Release ODT, 15 mg and 30 mg batches kept on accelerated and long-term storage stability conditions.
3. Comparative dispersibility testing in oral syringe.
4. Comparative acid resistance stability testing of all strengths of the test and reference products using the dispersed tablets with acid resistance as the stability indicator using the FDA-recommended method.
5. Comparative recovery studies of the dispersed tablets from oral syringe and from a combination of oral syringe and 8 French nasogastric tube.

The submitted dissolution data indicates that Teva's test products, 15 mg and 30 mg consistently meet the dissolution specification **of NLT** (b) (4) **% (Q) in 30 minutes at B1 or B2 level.** The results of dissolution data obtained from both strengths kept on long-term storage stability conditions indicate that test products consistently meet the dissolution specification of **NLT** (b) (4) **% (Q) in 30 minutes at B1 level** throughout the proposed two-year shelf life.

[1] The components and composition of these batches is similar to batches (15 mg batch# 2621-014 and 30 mg batch 2621-015) manufactured at Sellersville, PA site as submitted on 9/15/2008 and 3/27/2009 except the change in %age ratios of (b) (4) and (b) (4).

The dispersion time of test products in water using oral syringe is less than 30 sec. In vitro acid resistance stability studies demonstrated that acid media does not adversely impact the integrity of the enteric coating of dispersed test products, and dispersed test products meet the dissolution specification at A2 level in acid media. In addition, in vitro recovery studies indicate that loss of drug from test products is similar to reference products during administration via oral syringe or a combination of oral syringe and nasogastric tube.

The application is complete with no deficiencies.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Review of Submission

Deficiency Comment #1:

The dissolution testings of your test product Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg exhibit mean dissolution release of less than (b)(4)% compared to the reference listed drug (RLD) Prevacid® SoluTab™ (Lansoprazole) Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg (mean dissolution release more than (b)(4)%) at 30- and 45-minutes. Please provide reasons for incomplete release of the drug from the test products Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg.

Firm's Response to the Deficiency Comment #1:

Regarding drug product dissolution, we refer you to the dissolution data provided to the Chemistry division in a March 22, 2010 minor amendment. These data were obtained from ten recent commercial scale batches manufactured at Teva's Kfar Saba, Israel facility. These data demonstrate that Teva's product not only consistently meets the FDA-recommended dissolution specification, with mean dissolution release values of approximately (b)(4)% at 30 and 45 minutes, but also demonstrate comparability to the values presented for the brand product within our original ANDA. The data from the more recent batches are re-provided in Attachment 2 for ease of reference.

As Teva's product has been demonstrated to be bioequivalent to the brand product in the in-vivo studies supportive of this ANDA, we feel the slight variations observed between the two during the buffer stage of dissolution testing to be inconsequential. It is our belief that these slight variations can be attributed to differences in the products' manufacturing technologies.

Review of the Firm's Data Submitted in Response to Deficiency #1:

The firm has submitted the following dissolution data for ten recent batches of lansoprazole DR Orally Disintegration Tablets,

- 3 batches of 15 mg tablets: L61008, L61009 and L61010
- 7 batches of 30 mg tablets: L60033, L60034, L60035, L60036, L60037, L60038 and L60039

Table 1: Dissolution Data for Lansoparazole delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg batches

Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location
				Acid Stage	Buffer Stage			
				60	30	45	60	
L61008	15 mg Tablets	6	Mean	0	85	86	86	Attachment 2
			Range	(b) (4)				
			%CV	245	7	6	6	
L61009	15 mg Tablets	12	Mean	0	78	79	78	Attachment 2
			Range	(b) (4)				
			%CV	160	12	12	10	
L61010	15 mg Tablets	12	Mean	0	77	80*	79	Attachment 2
			Range	(b) (4)				
			%CV	234	12	12	12	
L60033	30 mg Tablets	6	Mean	1	88*	89	88	Attachment 2
			Range	(b) (4)				
			%CV	167	6	5	4	
L60034	30 mg Tablets	6	Mean	0	89	89	86	Attachment 2
			Range	(b) (4)				
			%CV	245	8	5	4	
L60035	30 mg Tablets	6	Mean	0	90	90	88*	Attachment 2
			Range	(b) (4)				
			%CV	155	4	4	3	
L60036	30 mg Tablets	6	Mean	0	87	89	87	Attachment 2
			Range	N/A	(b) (4)			
			%CV	N/A	5	4	5	
L60037	30 mg Tablets	6	Mean	0	92	93	89	Attachment 2
			Range	(b) (4)				
			%CV	155	5	6	4	
L60038	30 mg Tablets	6 for acid stage, 12 for buffer stage	Mean	1	84	86	84	Attachment 2
			Range	(b) (4)				
			%CV	110	11	8	8	
L60039	30 mg Tablets	6	Mean	1	87	88	89	Attachment 2
			Range	N/A	(b) (4)			
			%CV	N/A	10	3	3	

*Typographical errors corrected by reviewer

Reviewer's Comment on the Deficiency #1:

As shown in the **Table 1** above (please refer to Appendix 5.1 for individual tablet dissolution data), lansoprazole delayed release orally disintegrating tablets, 15 mg meet the dissolution specification of (b) (4)% (Q) in 30 minutes at B2 level in buffer stage.

Lansoprazole Delayed Release Orally Disintegrating Tablets, 30 mg meet the dissolution specification of (b)(4)% (Q) in 30 minutes at B1 level in buffer stage for all batches expect 1 tablet for batch# L60039, and batch# 60038 which meet the dissolution specification of (b)(4)% (Q) in 30 minutes at B2 level in buffer stage.

All 10 batches for 15 mg and 30 mg strengths consistently meet the dissolution specification of (b)(4)% (Q) in 30 minutes at B1 or B2 level in buffer stage with mean dissolution release of >76% at 30 and 45-min in buffer stage. The mean dissolution release values for reformulated test products are lower as compared to original ANDA batch and brand products as shown in the table below:

Dissolution Data for original ANDA test and reference products[2]:

Dissolution Conditions	**Apparatus:**	Apparatus 2 (Paddle)
	Speed of Rotation:	75rpm
	Medium:	Acid Stage: 0.1N HCl Volume: 500mL Buffer Stage: Medium: Phosphate Buffer, pH 6.8, with 5mM SDS
	Volume:	Acid Stage: 500mL Buffer Stage: 900mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	**Not Applicable**	
Dissolution Testing Site (Name, Address)	Teva Pharmaceutical Industries, Ltd., Hashikma Street, Industrial Area, Kfar-Saba 44102, ISRAEL	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)							Study Report Location
						Acid Stage	Buffer Stage						
						60 min	5 min	10 min	15 min	20 min	30 min	45 min	
CDP-1702/01	July 26, 2007	Lansoprazole D.R. ODT K-36985 Mfg.: 6/06	15 mg D.R Orally Disintegrating Tablets	12	Mean	0	10	66	80	83	85	85	Attachment 2
					Range	0-0	(b) (4)						
					%CV	0	51.5	13.4	10.7	8.2	7.5	6.6	
	Aug. 7, 2007	Prevacid® SoluTab™ #525552E80 Exp.: 5/09	15 mg D.R Orally Disintegrating Tablets	12	Mean	0	80	84	85	85	84	82	
					Range	0-0	(b) (4)						
					%CV	0	12.7	7.2	3.6	2.8	2.5	2.4	
CDP-1703/01	July 26, 2007	Lansoprazole D.R. ODT K-36986 Mfg.: 6/06	30 mg D.R Orally Disintegrating Tablets	12	Mean	0	6	69	83	85	86	84	Attachment 2
					Range	0-0	(b) (4)						
					%CV	0	41.2	10.4	6.2	5.2	4.7	6.0	
	July 26, 2007	Prevacid® SoluTab™ #330269P22 Exp.: 4/08	30 mg D.R Orally Disintegrating Tablets	12	Mean	0	85	91	91	90	88	86	
					Range	0-0	(b) (4)						
					%CV	0	11.1	3.4	2.8	2.8	2.8	2.6	

Since reformulated test product, 30 mg was found to be bioequivalent to reference product in fasting bioequivalence study # S08-0114[3] and test products, 15 mg and 30 mg consistently meet the dissolution specification of NLT (b)(4)% (Q) at 30 minutes at B1 or B2 levels in buffer stage, the reviewer concurs with the firm's opinion that slight variations observed between the two during the buffer stage of dissolution testing to be inconsequential. The firm's response is adequate, and in the reviewer's opinion, a slight slower dissolution rate from the test product as compared to reference products (NDA specifications: NLT (b)(4)% (Q) at 30 min[4]) might not have an impact on the therapeutic equivalence of the test products.

[2] DARRTS, ANDA 078730, REV-BIOEQ-01(General Review); final date 12/21/07
[3] DAARTS, ANDA 078730, REV-BIOEQ-01(General Review); final date: 6/24/09
[4] DARRTS, NDA 021428, REV-CLINPHARM-01(General Review) by CHEN, TIEN MIEN; final date: 08/08/2002

Deficiency Comment #2: Please provide the dissolution data obtained from Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg batches kept on accelerated and long-term storage stability conditions.

Firm's Response to the Deficiency Comment #2: Provided in Attachment 3, please find accelerated and CRT stability reports for Teva's Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg which include the requested dissolution data. Please note, the buffer stage dissolution specifications listed in the accelerated stability study reports reflect the 45-minute Q time which was in effect at the time the batches were manufactured and tested. These stability data support the quality of Teva's drug product throughout the proposed two-year shelf life.

Review of the Firm's Data Submitted in Response to Deficiency #2:

The firm has submitted the following data:

Table 2: Stability data for 15 mg strength at 40 ± 2°C/ 75 ± 5% RH

Batch No.	Test Date	Time (months)	Dosage Strength & Form	No. of Dosage Units		Collection Times		Study Report Location
						Acid Stage	Buffer Stage	
						60 min	45 min	
Conditions: 40 ± 2°C/ 75 ± 5% RH								
K-39662	1/29/08	Zero	15 mg Tablets	12	Mean	0	81	Attachment 3
					Range	0	(b) (4)	
					%CV	0	7.2	
K-39662	3/9/08	1	15 mg Tablets	6	Mean	0	78	Attachment 3
					Range	0	(b) (4)	
					%CV	0	6.5	
K-39662	3/31/08	2	15 mg Tablets	6	Mean	0	77	Attachment 3
					Range	0	(b) (4)	
					%CV	0	7.5	
K-39662#	4/30/08	3	15 mg Tablets	6	Mean	0	84	Attachment 3
					Range	0	(b) (4)	
					%CV	0	2.4	

Table 3: Stability data for 15 mg strength at 25 ± 2°C/ 60 ± 5% RH

Batch No.	Test Date	Time (months)	Dosage Strength & Form	No. of Dosage Units		Collection Times		Study Report Location
						Acid Stage	Buffer Stage	
						60 min	30 min	
Conditions: 25 ± 2°C/ 60 ± 5% RH								
K-39662	1/29/08	0	15 mg Tablets	12	Mean	0	81	Attachment 3
					Range	0	(b) (4)	
					%CV	0	7.2	
K-39662	4/30/08	3	15 mg Tablets	6	Mean	0	78	Attachment 3
					Range	0	(b) (4)	
					%CV	0	6.9	
K-39662	7/30/08	6	15 mg Tablets	6	Mean	0	83	Attachment 3
					Range	0	(b) (4)	
					%CV	0	4.5	
K-39662	10/28/08	9	15 mg Tablets	6	Mean	0	78	Attachment 3
					Range	0	(b) (4)	
					%CV	0	6.8	
K-39662	1/29/09	12	15 mg Tablets	6	Mean	0	87	Attachment 3
					Range	0	(b) (4)	
					%CV	0	5.5	
K-39662	8/06/09	18	15 mg Tablets	6	Mean	0	72	Attachment 3
					Range	0	(b) (4)	
					%CV	0	2.9	
K-39662#	3/01/10	24	15 mg Tablets	6	Mean	0	87	Attachment 3
					Range	0	(b) (4)	
					%CV	0	7.0	

Table 4: Stability data for 30 mg strength at 40 ± 2°C/ 75 ± 5% RH

Batch No.	Test Date	Time (months)	Dosage Strength & Form	No. of Dosage Units		Collection Times		Study Report Location
						Acid Stage	Buffer Stage	
						60 min	45 min	
Conditions: 40 ± 2°C/ 75 ± 5% RH								
K-39663	1/29/08	0	30 mg Tablets	12	Mean	0	79	Attachment 3
					Range	0	(b) (4)	
					%CV	0	7.8	
K-39663	3/9/08	1	30 mg Tablets	6	Mean	0	80	Attachment 3
					Range	0	(b) (4)	
					%CV	0	3.9	
K-39663	3/31/08	2	30 mg Tablets	12	Mean	0	80	Attachment 3
					Range	0	(b) (4)	
					%CV	0	8.9	
K-39663	4/30/08	3	30 mg Tablets	6	Mean	0	79	Attachment 3
					Range	0	(b) (4)	
					%CV	0	8.0	

Table 5: Stability data for 30 mg strength at 25 ± 2°C/ 60 ± 5% RH

Batch No.	Test Date	Time (months)	Dosage Strength & Form	No. of Dosage Units		Collection Times		Study Report Location
						Acid Stage	Buffer Stage	
						60 min	30 min	
Conditions: 25 ± 2°C/ 60 ± 5% RH								
K-39663	1/29/08	0	30 mg Tablets	12	Mean	0	79	Attachment 3
					Range	0	(b) (4)	
					%CV	0	7.8	
K-39663	4/30/08	3	30 mg Tablets	6	Mean	0	77	Attachment 3
					Range	0	(b) (4)	
					%CV	0	4.9	
K-39663	7/30/08	6	30 mg Tablets	6	Mean	0	76	Attachment 3
					Range	0	(b) (4)	
					%CV	0	8.4	
K-39663	10/28/08	9	30 mg Tablets	6	Mean	0	76	Attachment 3
					Range	0	(b) (4)	
					%CV	0	5.7	
K-39663	1/29/09	12	30 mg Tablets	6	Mean	0	79	Attachment 3
					Range	0	(b) (4)	
					%CV	0	6.9	
K-39663	08/06/09	18	30 mg Tablets	6	Mean	0	77	Attachment 3
					Range	0	(b) (4)	
					%CV	0	5.1	
K-39663#	3/01/10	24	30 mg Tablets	6	Mean	0	92	Attachment 3
					Range	0	(b) (4)	
					%CV	0	5.2	

The reformulated batches# K-39662 (15 mg) and # K-39663 (30 mg) manufactured at Teva's Kfar-Saba, Israel site have same components and composition as batches# 2621-014 (15 mg) and # 2621-015 (30 mg), respectively manufactured at Sellersville, PA site, except the change in %age ratios of [redacted] (b) (4) and [redacted] (b) (4).

For batches# 2621-014 (15 mg) and # 2621-015 (30 mg), [redacted] (b) (4)

For batches# K-39662 (15 mg) and # K-39663 (30 mg), [redacted] (b) (4)

Please refer to additional attachments section 4 for components and composition of reformulated batches# K-39662 (15 mg) and # K-39663 (30 mg).

Reviewer's Comment on the Deficiency # 2:

Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg consistently meet the dissolution specification of (b) (4)% (Q) in 45 min at B1 or B2 level at accelerated conditions, 40 ± 2°C/ 75 ± 5% RH for 3 months.

Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg consistently meet the dissolution specification of (b) (4)% (Q) in 30 min at B1 level at 25 ± 2°C/ 60 ± 5% RH for 2 years.

Firm's response to deficiency comment# 2 is acceptable.

Deficiency Comment #3: The approved labeling for the RLD states that the product may be administered via an oral syringe. The RLD labeling also states that the product may be administered by nasogastric tube. Therefore, we request that you perform the following in vitro tests to compare the performance of your product to that of the RLD under these conditions of use.

a. Please conduct comparative dispersibility testing using 20 units of the test and reference 15 mg and 30 mg tablets in oral syringe using 4 mL and 10 mL of water, respectively.

b. Please conduct comparative acid resistance stability testing using 12 units of all strengths of the test and reference products. The stability studies should be conducted using the dispersed tablets with acid resistance as the stability indicator using the following method:

   - Disperse the tablets into water in oral syringe for 15 minutes. Use 4 mL of water for 15 mg tablets and 10 mL for 30 mg tablets.

   - Transfer the contents of syringe into dissolution vessel containing 500 mL of 0.1 N HCl maintained at 37 °C ± 0.5 °C.

- Refill the syringe with 2 mL of water for 15 mg tablets and 5 mL for 30 mg tablets, shake gently and transfer any remaining contents into the dissolution media mentioned above.

- Acid resistance testing should be conducted using USP Apparatus II at 75 rpm.

- Analyze the amount of lansoprazole released at 60 minutes.

- Repeat the acid resistance stability testing using combination of a syringe and nasogastric (8 FR) tube.

c. Please conduct the comparative recovery studies of the dispersed tablets from oral syringe and from a combination of oral syringe and 8 French nasogastric tube using 20 units of all strengths of the test and reference listed products using 4 mL of water for 15 mg tablets and 10 mL for 30 mg tablets.

Firm's Response to the Deficiency Comment #3:

As requested, the following *in-vitro* testing was conducted to compare the performance of Teva's drug product to that of the RLD product under the specified conditions of use. Data reports are provided in **Attachment 5** which serves to demonstrate the comparability of the two products.

a. Comparative dispersibility testing was conducted using 20 units of each strength of both the test and reference products. The 15 mg tablets were dispersed using 4 mL of water, and the 30 mg tablets were dispersed using 10 mL of water, in an oral syringe.

b. Comparative acid resistance stability testing was conducted using 12 units of each strength of both the test and reference products. The dispersed tablets were introduced to the dissolution vessel using 1) the oral syringe and 2) a combination of the oral syringe with a nasogastric tube (8 FR). In accord with your request, acid resistance was used as the stability indicator.

c. Comparative recovery studies of the dispersed tablets were conducted using 20 units of each strength of both the test and reference products. The 15 mg tablets were dispersed using 4 mL of water, and the 30 mg tablets were dispersed using 10 mL of water. The recovery was measured from 1) the oral syringe and 2) a combination of the oral syringe with the nasogastric tube (8 FR).

Review of the Firm's Data Submitted in Response to Deficiency #3:

The firm has provided the following data:

The following batches were used for the dispersibility, acid resistance stability and recovery studies

Lansoprazole DR ODT 15mg – Lot. L61001 TEVA, Exp. 12/2010
Lansoprazole DR ODT 30mg – Lot. L60008 TEVA, Exp. 02/2011
Lansoprazole DR ODT 15mg – Lot. 811092E22 Prevacid, Exp. 09/2012
Lansoprazole DR ODT 30mg – Lot. 845292E21 Prevacid, Exp. 08/2012

Dispersibility test: For dispersibility test, 15 mg and 30 mg tablets were dissolved into 4 mL and 10 mL of water, respectively in a 20cc oral syringe. Syringe was gently shaken to disperse the tablet and time from the beginning of the shaking to the complete dispersion of the tablet was measured using a stopwatch or suitable timer.

Table 6: Dispersion time (sec) for 15 mg and 30 mg test and reference products

Dispersion Time (sec)				
#	**Lansoprazole DR ODT 15 mg**	**Prevacid ODT 15 mg**	**Lansoprazole DR ODT 30 mg**	**Prevacid ODT 30 mg**
	Lot# L61001	**Lot# 811092E22**	**Lot# L60008**	**Lot# 845292E21**
1	(b) (4)	(b) (4)	(b) (4)	(b) (4)
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
Avg.	**18**	**10**	**20**	**10**
SD	0.8	0.6	1.1	0.8
CV	4.3	6.6	5.4	8.0
Max.	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Min.				

Comments on dispersibility test: Although, the dispersion time for lansoprazole delayed release orally tablets, 15 mg and 30 mg is slightly higher than that of

corresponding reference products, this is less than the disintegration time of 30 second as specified for orally disintegrating tablets[5]. In addition, the RLD label states that

- Prevacid® SoluTab™ typically disintegrate in less than 1 minutes, and
- For administration via oral syringe and nasogastric tube, shake the 15 mg and 30 mg tablets into 4 mL and 10 mL of water, respectively in oral syringe and inject the tablet within 15 min after the tablet dispersion.

Since the dispersion time for the test products is less than 25 sec and tablets are administrated after complete dispersion, the 8-10 second difference in dispersion times of test versus reference products should not have any impact on the therapeutic equivalence of the test products.

Acid Resistance Stability Test: The firm conducted the acid resistance stability testing using the FDA-recommend method as described under deficiency comment #3b

Table 7: Acid resistance stability data for 15 mg tablets dispersed in water using oral syringe only

#	Lansoprazole DR ODT Lot# L61001		Prevacid ODT Lot# 811092E22	
	Assay After 1h 0.1N HCL (%)	Release in Acid Medium* (%)	Assay After 1h 0.1N HCL (%)	Release in Acid Medium (%)*
1	(b) (4)	(b) (4)	(b) (4)	(b) (4)
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Avg.	**93**	**4**	**91**	**2**
SD	2.2	2.2	2.2	2.2
CV	2.5	50.8	2.5	138.2
Max.	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Min.				

*Calculated as a difference between the average lansoprazole results from the recovery tests and lansoprazole content after 1 hour in acid conditions.

[5] Guidance for Industry: Orally Disintegrating Tablets (December 2008)

Table 8: Acid resistance stability data for 30 mg tablets dispersed in water using oral syringe only

#	Lansoprazole DR ODT Lot# L60008		Prevacid ODT Lot# 845292E21	
	Assay After 1h 0.1N HCL (%)	Release in Acid Medium* (%)	Assay After 1h 0.1N HCL (%)	Release in Acid Medium (%)*
1	(b) (4)	(b) (4)	(b) (4)	(b) (4)
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Avg.	**96**	**6**	**92**	**7**
SD	4.6	4.6	1.4	1.4
CV	4.8	79.2	1.5	18.7
Max.	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Min.				

*Calculated as a difference between the average lansoprazole results from the recovery tests and lansoprazole content after 1 hour in acid conditions.

Table 9: Acid resistance stability data for 15 mg tablets dispersed in water using a combination of oral syringe and 8 FR nasogastric tube

#	Lansoprazole DR ODT, Lot# L61001		Prevacid ODT, Lot# 811092E22	
	Assay After 1h 0.1N HCL (%)	Release in Acid Medium (%)*	Assay After 1h 0.1N HCL (%)	Release in Acid Medium (%)*
1	(b) (4)	(b) (4)	(b) (4)	(b) (4)
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Avg.	**90**	**5**	**89**	**4**
SD	4.5	4.5	2.2	2.2
CV	5	88.6	2.4	61.2
Max.	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Min.				

*It is also calculated as a difference between the average lansoprazole results from the recovery tests and lansoprazole content after 1 hour in acid conditions (typographical error corrected by reviewer).

Table 10: Acid resistance stability data for 30 mg tablets dispersed in water using a combination of oral syringe and 8 FR nasogastric tube

#	Lansoprazole DR ODT, Lot# L60008		Prevacid ODT, Lot# 845292E21	
	Assay After 1h 0.1N HCL (%)	Release in Acid Medium (%)*	Assay After 1h 0.1N HCL (%)	Release in Acid Medium (%)*
1	(b) (4)	(b) (4)	(b) (4)	(b) (4)
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Avg.	**92**	7	**93**	**4**
SD	6	6	1.9	1.9
CV	6.5	89.9	2	42.2

Max.		(b) (4)			(b) (4)			(b) (4)			(b) (4)
Min.											

* Calculated as a difference between the average lansoprazole results from the recovery tests and lansoprazole content after 1 hour in acid conditions.

Reviewer's Comment on Acid Resistance Stability Test:

Analysis of data for % lasnoprazole released into acid media calculated based on difference between the average lansoprazole results from the recovery tests and lansoprazole content after 1 hour in acid conditions (**Tables 7, 8, 9 and 10 above**) indicates that reference products, 15 mg and 30 mg meet the dissolution specifications at A1 level (No individual value exceeds (b) (4)% dissolved) in acid media using oral syringe or combination of oral syringe and 8 FR nasogastric tube, however, test products meet dissolution specifications at A2 level (average of 12 units (A1 + A2) is not more than (b) (4)% dissolved, and no individual unit is greater than (b) (4)% dissolved) in acid stage except for 15 mg strength using oral syringe that meet dissolution specification at A1 level.

This data indicates that acid media does not adversely impact the integrity of enteric coating of dispersed tablets when administrated using the oral syringe or a combination of oral syringe and nasogastric tube.

Recovery Test

Recovery Test for Dispersed Tablets, 15 mg strengths using *oral syringe only*						
#	Lansoprazole DR ODT Lot# L61001			Prevacid ODT Lot# 811092E22		
	Lansoprazole (%)	UOC (%)	Recovery vs. Avg. UOC (%)	Lansoprazole (%)	UOC (%)	Recovery vs. Avg. UOC (%)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						

(b) (4)

18						
19						
20						
Avg.	**97.1**	**100.2**	**96.9**	**93.2**	**94.8**	**98.3**
SD	2.6	3.4	2.6	2.7	1.5	2.8
CV	2.7	3.4	2.7	2.9	1.6	2.9
Min.						
Max.						

(b) (4)

Recovery Test for Dispersed Tablets, 30 mg strengths using *oral syringe only*						
#	**Lansoprazole DR ODT, Lot# L60008**			**Prevacid ODT, Lot# 845292E21**		
	Lansoprazole (%)	UOC (%)	Recovery vs. Avg. UOC (%)	Lansoprazole (%)	UOC (%)	Recovery vs. Avg. UOC (%)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
Avg.	**101.6**	**103.3**	**98.4**	**99.3**	**97.0**	**102.4**
SD	3.2	2.4	3.2	1.8	1.8	1.9
CV	3.2	2.3	3.3	1.8	1.8	1.8
Min.						
Max.						

(b) (4)

Recovery Test for 15 mg Dispersed Tablets Using a *Combination of Oral Syringe and 8 FR Nasogastric tube*						
#	Lansoprazole DR ODT, Lot# L61001			Prevacid ODT, Lot# 811092E22		
	Lansoprazole (%)	UOC (%)	Recovery vs. Avg. UOC (%)	Lansoprazole (%)	UOC (%)	Recovery vs. Avg. UOC (%)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
Avg.	**94.7**	**100.2**	**94.5**	**92.6**	**94.8**	**97.7**
SD	3.8	3.4	3.8	3.1	1.5	3.3
CV	4.1	3.4	4.0	3.4	1.6	3.4
Min.						
Max.						

(b) (4)

Recovery Test for 30 mg Dispersed Tablets Using a *Combination of Oral Syringe and 8 FR Nasogastric tube*						
#	Lansoprazole DR ODT, Lot# L60008			Prevacid ODT, Lot# 845292E21		
	Lansoprazole (%)	UOC (%)	Recovery vs. Avg. UOC (%)	Lansoprazole (%)	UOC (%)	Recovery vs. Avg. UOC (%)
1						
2						
3						
4						
5						
6						
7						
8						
9						

(b) (4)

10	(b) (4)					
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
Avg.	**99.1**	**103.3**	**95.9**	**97.4**	**97**	**100.4**
SD	3.2	2.4	3.1	1.9	1.8	2.0
CV	3.2	2.3	3.2	2.0	1.8	2.0
Min.	(b) (4)					
Max.						

Reviewer's Comment on Recovery Test:

For recovery of dispersed tablets (15 mg and 30 mg) using oral syringe only and a combination of oral syringe and 8 FR nasogastric tube, firm used additional 5 mL of water to transfer the contents from the syringe and syringe + nasogastric tube into media used for analysis.

The results for dispersed test and reference products, 15 mg and 30 mg using oral syringe indicates that average recovery of the drug based on the % lansoprazole released and recovery vs. average uniformity of contents is > 93% and 96%, respectively, and the lowest value obtained is (b) (4) % for reference product, 15 mg.

The results for dispersed test and reference products, 15 mg and 30 mg using combination of oral syringe and 8 French nasogastric tube indicates that average recovery of the drug based on the % lansoprazole released and recovery vs. average uniformity of contents is > 92% and 94%, respectively, and the lowest value obtained is (b) (4) % for reference product, 15 mg.

This data indicates that the recovery of the test products is similar to that of reference products using oral syringe or a combination of nasogastric tube and oral syringe.

Deficiency Comment #4: Please submit standard operating procedures for dispersibility, stability and recovery testing, individual data, mean values, standard deviations, coefficient of variation (CV%), and plots of percent release of lansoprazole in stability testing in acid medium test.

Firm's Response to the Deficiency Comment #4: Provided in **Attachment 4**, please find the procedure manual describing the sample preparation and analytical procedures used for performing the dispersibility, stability, and recovery testing. As noted above, a

report detailing the results of the requested comparative *in-vitro* studies is provided in **Attachment 5**.

Reviewer's Comment on the Deficiency #4: Firm's response to deficiency comment# 4 is acceptable.

Deficiency Comment #5: Please note if you want to retain the option of using Kfar-Saba, Israel location as alternate manufacturing site, please provide the data for the tests mentioned in # 1-4 above from the batches manufactured at this site as well.

Firm's Response to the Deficiency Comment #5: The batches used for the comparative in vitro testing were manufactured at Teva's Kfar Saba, Israel location. Please note that Kfar Saba, Israel is the only intended site of commercial manufacture for Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg. The Sellersville, PA site, proposed in September 2008 as an additional site of manufacture, was later withdrawn via a Quality Minor Amendment dated March 22, 2010.

Reviewer's Comment on the Deficiency #5: The DBE acknowledges that firm will use *only Teva's Kfar Saba, Israel location* for manufacture of Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg, and Sellersville, PA site has been withdrawn.

3.2 Waiver Request(s)

Strengths for which waivers are requested	15 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	**WAIVERS GRANTED**
If not then why?	

3.3 Deficiency Comments

None

3.4 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study (S08-0114) conducted by Teva Pharmaceuticals USA on its Lansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg, lot # 2621-015 comparing it to TAP Pharmaceuticals' Prevacid® SoluTab™ (Lansoprazole) Delayed-Release Orally Disintegrating Tablets 30 mg, lot # 578352E22.

2. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour) at 37ºC ± 0.5ºC using USP apparatus 2 at 75 rpm. The test product should meet the following specifications:

   Acid stage: NMT (b)(4)% in 60 minutes
   Buffer stage: NLT (b)(4)% (Q) in 30 minutes

3. The dissolution testing conducted by TEVA Pharmaceuticals USA on its Lansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg, lot # K2621-015 and Lansoprazole Delayed-Release Orally Disintegrating Tablets 15 mg, lot # K2621-014 is acceptable. The firm has conducted acceptable in vivo bioequivalence testing comparing 30 mg Tablets of the test product (lot # 2621-015) with 30 mg Tablets of the reference product Prevacid® SoluTab™ (lot # 578352E22) manufactured by Tap Pharmaceuticals.

4. The formulation for the 15 mg strength is proportionally similar to the 30 mg strength of the test product which underwent bioequivalence testing. The 15 mg strength of the test product is deemed bioequivalent to Tap Pharmaceuticals' Prevacid® SoluTab™ (Lansoprazole) Delayed Release Orally Disintegrating Tablets, 15 mg based on the criteria set forth in 21 CFR § 320.24 (b)(6).

5. The Division of Bioequivalence deems the test product Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg, manufactured by Teva Pharmaceuticals USA, to be bioequivalent to the reference products, Prevacid® SoluTab™, 15 mg and 30

mg, respectively, manufactured by TAP Pharmaceuticals under the provisions of 21 CFR § 320.24(b)(6).

3.5 Comments for Other OGD Disciplines

Discipline	Comment
	none

4 ADDITIONAL ATTACHEMNTS

NOTE: As specified in the bioequivalence reviews (DAARTS, ANDA 078730, REV-BIOEQ-01(General Review); final date: 6/24/09 and 3/22/10) under formulation data there is an erroneous entry in lot number's for old ANDA batches, 15 mg and 30 mg. The lot# for old ANDA batches should be lot# K-36985 and K-36986 for 15 mg and 30 mg strengths, respectively.

On March 27, 2009, the dissolution data submitted by the firm (DAARTS, ANDA 078730, REV-BIOEQ-01(General Review); final date: 6/24/09) was on site transfer batches# 2621-014 (15 mg) and batches# 2621-015 (30 mg) manufactured at Sellersville, PA and amended batches# K-39662 (15 mg) and K-39663 (30 mg) manufactured at Kfar-Saba, Israel. The batch# K-39662 (15 mg) and K-39663 (30 mg) were used as reference ANDA batches for comparisons of dissolution data with site transfer batches# 2621-014 (15 mg) and 2621-015 (30 mg), respectively.

The formulation composition of batches K-39662 (15 mg) and K-39663 (30 mg) is provided in the table below[6]:

Ingredient	Amount (mg) / Tablet (K-39662)		Amount (%) / Tablet (K-39663)	
	15 mg strength	30 mg strength	15 mg strength	30 mg strength
(b) (4)				

[6] ANDA 078730, Jacket Volume 8.1, Submission 1 of 2, Pages# 9-11.

Following this page, 1 page withheld in full - (b)(4) Formulation Data

5 APPENDIX

5.1 Individual Tablet Dissolution Data

Strength	Batch	Interval (min)	Individual results (%)	Average (%)
15mg	L61008- Acid	60	(b) (4)	0
	L61008- Buffer	30		85
		45		86
		60		86
	L61009- Acid	60		0
	L61009- Buffer	30		78
		45		79
		60		78
	L61010 - Acid	60		0
	L61010- Buffer	30		77
		45		79
		60		79
30mg	L60033 - Acid	60		1
	L60033- Buffer	30		89
		45		89
		60		88
	L60034 - Acid	60		0
	L60034- Buffer	30		89
		45		89
		60		86
	L60035 - Acid	60		0
	L60035 -Buffer	30		90
		45		90
		60		87
	L60036 - Acid	60		0
	L60036- Buffer	30		87
		45		89
		60		87

30mg	**L60037 - Acid**	**60**	(b) (4)		0
	L60037- Buffer	**30**			92
		45			93
		60			89
	L60038 - Acid	**60**			1
	L60038- Buffer	**30**			84
		45			86
		60			84
	L60039 - Acid	**60**			1
	L60039- Buffer	**30**			87
		45			88
		60			89

Following this page, 4 pages withheld in full - (b)(4)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78730

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time.

Your dissolution testing is acceptable. The Division of Bioequivalence acknowledges that you will conduct your dissolution testing using the following FDA-recommended method:

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Specifications:	Acid stage: NMT (b)(4)% in 60 minutes Buffer stage: NLT (b)(4)% (Q) in 30 minutes

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

6 OUTCOME PAGE

ANDA: 078730

Completed Assignment for 78730 ID: 11172

Reviewer: Kaur, Paramjeet **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
11234	5/7/2010	Other	Study Amendment - Dissolution	1	1	Edit	Delete
11234	5/7/2010	Other	Study Amendment – Recovery Test	1	1	Edit	Delete
11234	5/7/2010	Other	Study Amendment-Acid resistance stability test	1	1	Edit	Delete
				Bean Total:	3		

IVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment	
Study Amendment-Deficiency comments-dated 5/7/2010	1
Study Amendment-Recovery Test-dated 3/26/2010	1
Study Amendment-Acid Resistance Stability Test-dated 3/26/2010	1
Total number of Complexity Points	3

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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/s/

PARAMJEET KAUR
05/25/2010

CHANDRA S CHAURASIA
05/25/2010

BARBARA M DAVIT
05/25/2010

M E M O R A N D U M

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

DATE: July 20, 2010

FROM: Barbara M. Davit, Ph.D., J.D.
Acting Director, Division of Bioequivalence II
Office of Generic Drugs

TO: ANDA 078730 – Teva Pharmaceuticals USA
Lansoprazole Delayed-Release Orally Disintegrating Tablet
15 mg, 30 mg

SUBJECT: Summary review of in-house dissolution data

On 6/11/10, Teva Pharmaceuticals USA (Teva) submitted an amendment to ANDA 078730 in response to an information request from the Office of Generic Drugs (OGD), made 6/4/10. The Division of Bioequivalence II (DBE II) was asked to review the amendment and to compare dissolution from Teva's Lansoprazole Delayed-Release (DR) Orally Disintegrating Tablet (ODT) with other in-house dissolution data. The following review presents a summary of (1) bioequivalence (BE) data; (2) Teva's dissolution data; and (3) a comparison of in-house dissolution data on the lansoprazole DR ODT. A separate DBE II review of the 6/11/10 amendment is being prepared separately and will incorporate some of the recommendations in this memorandum.

All DBE II reviews referred to in this memorandum are archived electronically in DARRTS.

Bioequivalence

Teva's Lansoprazole DR ODT is bioequivalent to the corresponding reference listed drug (RLD) Prevacid® SoluTab under fasting and fed conditions.

Parameter	Test	Reference	Ratio	90% CI
Fasting BE study, N = 87 subjects, Teva's Lansoprazole DR ODT 30 mg versus Prevacid® SoluTab 30 mg				
AUC0-t (ng*hr/mL)	2166.79	2218.08	0.98	93.3-102.3
AUC∞ (ng*hr/mL)	2204.75	2256.84	0.98	93.3-102.3
Cmax (ng/mL)	876.55	955.10	0.92	85.1-98.9
Fed BE study, N = 80 subjects, Teva's Lansoprazole DR ODT 30 mg versus Prevacid® SoluTab 30 mg				
AUC0-t (ng*hr/mL)	1655.25	1561.35	1.06	98.5-114.1
AUC∞ (ng*hr/mL)	1715.59	1587.38	1.08	100.3-116.4
Cmax (ng/mL)	421.73	369.64	1.12	101.7-124.2

Summary statistics of Teva's Lansoprazole DR ODT BE studies are shown below. The fed BE study was conducted first and was designed as a 3-way crossover study to compare 2 different lansoprazole DR ODT formulations. The formulation of Batch No. 36986 was developed and used in the fasting BE study. The formulation of Batch No. 36295 was not developed further.

A detailed analysis of Tmax values from individual subjects (see DBE II review dated 3/22/10) showed no difference in test and RLD Tmax values in the fasting BE study.

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (CV%)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng*h/mL)	AUC∞ (ng*h/mL)	T½ (hr)	Kel (hr-1)	
2006-1270	A Single-Dose, Comparative Bioavailability Study of Three Formulations of Lansoprazole 30 mg Delayed-Release Orally Disintegrating Tablets Under Fed Conditions	Randomized, single-dose, crossover	LANSOPRAZOLE DR OD, 30 mg Tab., p.o. [Batch # K-36295] LANSOPRAZOLE DR OD, 30 mg Tab., p.o. [Batch # K-36986] PREVACID® SoluTab™ DR OD, 30 mg, Tab., p.o. [Lot # 140089P22]	80 completing (41M/39F) Healthy subjects Age (yrs): 36 (18-55)	563.92 (74) 549.41 (71) 454.71 (65)	4.60 (45) 4.44 (42) 3.80 (43)	2733.06 (109) 2687.05 (109) 2413.89 (108)	2858.73 (113) 2845.15 (113) 2542.85 (112)	2.04 (85) 2.05 (81) 2.10 (80)	0.4973 (48) 0.4957 (46) 0.4791 (48)	Synopsis p. 1 008
2006-1287	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Lansoprazole 30 mg Delayed-Release Orally Disintegrating Tablets Under Fasting Conditions	Randomized, single-dose, crossover	LANSOPRAZOLE DR OD, 30 mg Tab., p.o. [Batch # K-36986] PREVACID® SoluTab™ DR OD, 30 mg, Tab., p.o. [Lot # 330269P22]	87 completing (41M/46F) Healthy subjects Age (yrs): 37 (19-60)	937.86 (34) 1012.84 (33)	2.21 (33) 1.89 (50)	2488.11 (59) 2502.37 (51)	2593.70 (70) 2589.50 (57)	1.43 (57) 1.42 (54)	0.5616 (31) 0.5680 (33)	Synopsis p. 1 008

Dissolution data on Teva's Lansoprazole DR ODT

The DBE asked Teva to use the same dissolution method as used by the manufacturer of the RLD. The method is shown below.

Apparatus	USP Apparatus II (paddles)
Speed of rotation	75 rpm throughout
Medium	Acid Stage: 0.1 N HCl for one hour, followed by Buffer Stage: Phosphate buffer, pH 6.8, with 5 mM SDS
Volume	Acid Stage: 500 mL Buffer Stage: 900 mL
Temperature	37°C throughout
Specifications (for RLD)	Acid Stage: NMT (b) (4) in 60 minutes Buffer Stage: NLT in 30 minutes

Both test and reference product perform the same during the Acid Stage, therefore, the same Acid Stage specification as used for the RLD can be used for Teva's product.

However, as tested by Teva, neither Teva's product nor the RLD would meet the RLD specification of NLT (b) (4)% in 30 minutes at the B1 level. Initially, based on a review of the dissolution performance of Teva's product, DBE II recommended a specification of NLT (b) (4)% in 30 minutes for the Buffer Stage (see DBE II review dated 6/23/09). The original Buffer Stage dissolution data, generated in July-August of 2007, using the 30-mg strength biobatch and a fresh batch of the 15-mg strength are shown below.

Dissolution testing of the 30-mg strength of the biobatch of Teva's Lansoprazole DR ODT and RLD Batch #330269P22 (Expiration April 2008), using the FDA-recommended method, was conducted on 7/26/07. For details, see the DBE II review dated 12/21/07.

The dissolution of the 15-mg strength of Teva's Lansoprazole DR ODT, Batch No. K-36985, was tested on 7/26/07, using the FDA-recommended method. Note that Prevacid® 15-mg tablets were not tested until 8/7/07 (expiration of Lot #525552E80 was May, 2009).

Dissolution testing of Teva's Lansoprazole DR ODT and Prevacid® SoluTabs 30 mg; 500 mL 0.1 N HCl used for Acid Stage (60 min); 900 mL phosphate buffer + 5 mM SDS used for Buffer Stage; USP Apparatus II (paddles) at 75 rpm; date of testing 7/26/2007

Product Name: LANSOPRAZOLE D.R. ORALLY DISINTEGRATING TABLETS 30mg

Analysis No: CDP-1703/01

TAB. #	% OF LABELED AMOUNT DISSOLVED							
	ACID STAGE		BUFFER STAGE					
	60 MINUTES 0.1N HCl		5 MINUTES		10 MINUTES		15 MINUTES	
	TEVA K-36986	PREVACID® SoluTab™ 330269P22	TEVA K-36986	PREVACID® SoluTab™ 330269P22	TEVA K-36986	PREVACID® SoluTab™ 330269P22	TEVA K-36986	PREVACID® SoluTab™ 330269P22
1	0	0						
2	0	0						
3	0	0						
4	0	0						
5	0	0						
6	0	0						
7	0	0						
8	0	0						
9	0	0						
10	0	0						
11	0	0						
12	0	0						
Mean	0	0	6	85	69	91	83	91
RSD (%)	0	0	41.2	11.1	10.4	3.4	6.2	2.8

(b) (4)

Dissolution testing of Teva's Lansoprazole DR ODT and Prevacid® SoluTabs 30 mg; 500 mL 0.1 N HCl used for Acid Stage (60 min); 900 mL phosphate buffer + 5 mM SDS used for Buffer Stage; USP Apparatus II (paddles) at 75 rpm; date of testing 7/26/07

TAB. #	% OF LABELED AMOUNT DISSOLVED					
	BUFFER STAGE					
	20 MINUTES		30 MINUTES		45 MINUTES	
	TEVA K-36986	PREVACID® SoluTab™ 330269P22	TEVA K-36986	PREVACID® SoluTab™ 330269P22	TEVA K-36986	PREVACID® SoluTab™ 330269P22
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	85	90	86	88	84	86
RSD (%)	5.2	2.8	4.7	2.8	6.0	2.6

(b) (4)

Dissolution testing of Teva's Lansoprazole DR ODT and Prevacid® SoluTabs 15 mg; 500 mL 0.1 N HCl used for Acid Stage (60 min); 900 mL phosphate buffer + 5 mM SDS used for Buffer Stage; USP Apparatus II (paddles) at 75 rpm; date of testing 7/26/07 for test product and 8/7/07 for RLD

TAB. #	% OF LABELED AMOUNT DISSOLVED					
	BUFFER STAGE					
	20 MINUTES		30 MINUTES		45 MINUTES	
	TEVA K-36985	PREVACID® SoluTab™ 525552E80	TEVA K-36985	PREVACID® SoluTab™ 525552E80	TEVA K-36985	PREVACID® SoluTab™ 525552E80
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	83	85	85	84	85	82
RSD (%)	8.2	2.8	7.5	2.5	6.6	2.4

Comments on Teva's dissolution data:

- Teva's product dissolves more slowly than the RLD.
- Variability is greater with Teva's product than with the RLD.
- The 30-mg strength of Teva's product and the RLD meet a specification of NLT (b) (4)% at the B2 level.
- The 15-mg strength of the RLD meets a specification of NLT (b) (4)% at the B2 level.
- The 15-mg strength of Teva's product meets a specification of NLT (b) (4)% at the B3 level.

Comparison of In-house Dissolution Data on Prevacid® SoluTabs

To address concerns about the dissolution performance of Teva's Lansoprazole DR ODT, DBE II compared dissolution data on the RLD generated by four different firms. Using 900 mL phosphate buffer, pH 6.8 with 5 mM SDS, Teva, (b) (4), and Takeda obtained the following dissolution data for the RLD. (b) (4) used a paddle speed of 100 rpm; all others used 75 rpm.

% of labeled amount of lansoprazole dissolved, 30 minutes in Buffer Stage, Prevacid SoluTab 30 mg			
Firm	**Takeda**	**Teva**	(b) (4)
ANDA/NDA	21428	78730	
Mean	102	88	
Lowest	Not in review	(b) (4)	
Highest	Not in review		
% CV	1.8	2.8	

% of labeled amount of lansoprazole dissolved, 30 minutes in Buffer Stage, Prevacid SoluTab 15 mg			
Firm	**Takeda**	**Teva**	(b) (4)
ANDA/NDA	21428	78730	
Mean	102	84	
Lowest	Not in review	(b) (4)	
Highest	Not in review		
% CV	41.8	2.5	

Comments on in-house dissolution data on the Prevacid® SoluTab:

- (b) (4) will be asked to repeat testing using 75 rpm.
- The OGD issued to (b) (4).
- According to Takeda (innovator) lansoprazole from the Prevacid® SoluTab was essentially 100% dissolved by 15 minutes in the Buffer Stage.
- It is unclear why, during the Buffer Stage, only the innovator (Takeda) achieved 100% lansoprazole dissolution in 30 minutes, whereas two generic firms, using the same method, achieved only (b) (4)% dissolution by 30 minutes.
- (b) (4) achieved an average of (b) (4)% lansoprazole dissolution by 30 minutes in the Buffer Stage, but used a higher paddle speed (100 rpm) than the other two generic firms and the innovator.
- The DBE 2 Acting Director discussed this issue with the CDER liaison to the USP on 7/14/2008.
- Since NDA 21248 was submitted on 10/30/01 and approved on 8/30/02, it is unclear if the different dissolution performance of the Prevacid® SoluTab generated by the 4 different firms reflects changes in the RLD product or differences in how the three generic firms and Takeda conducted the dissolution testing; for example, if Takeda and the three generic firms used different assays.

Conclusions

(1) Teva's Lansoprazole DR ODT is bioequivalent to Prevacid® SoluTab, and there appears to be no significant difference in the test versus RLD lansoprazole rate of absorption, as reflected by comparative Cmax and Tmax data.
(2) It is reasonable to propose a tentative dissolution specification of NLT (b) (4)% in 30 minutes for the Buffer Stage of dissolution testing for Teva's Lansoprazole DR ODT to control individual tablet dissolution variability and thereby ensure product quality.
(3) The OGD may consider investigating why three generic firms could not achieve the same dissolution performance of the Prevacid® SoluTab as the innovator achieved (as evidenced in the original 2001 NDA 21248 submission).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

BARBARA M DAVIT
07/20/2010

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78730
Drug Product Name	Lansoprazole Delayed Release Orally Disintegrating Tablet
Strength(s)	15 mg and 30 mg
Applicant Name	Teva Pharmaceuticals USA
Address	1090 Horsham Road, North Wales, PA 19454
Applicant's Point of Contact	Philip Erickson, R.Ph. Senior Director, Regulatory Affairs
Contact's Telephone Number	215-591-3141
Contact's Fax Number	215-591-8812
Original Submission Date(s)	December 27, 2006
Submission Date(s) of Amendment(s) Under Review	September 15, 2008 March 27, 2009 June 23,2009 May 7, 2010 June 11, 2010
Reviewer	Paramjeet Kaur, Ph.D.
Study Number (s)	S08-0114
Study Type (s)	Fasting
Strength (s)	30 mg
Clinical Site	Gateway Medical Research, Inc. – Cetero Research
Clinical Site Address	400 Fountain Lakes Blvd. St. Charles, MO 63301 Deryk L. McDowell, M.D.
Analytical Site	(b) (4)
Analytical Site Address	(b) (4)
OUTCOME DECISION	**INADEQUATE**

OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**INADEQUATE**		
DSI REPORT RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
7	**FASTING STUDY**	**30 MG**	**ADEQUATE**
24	**DISSOLUTION**	**15 MG and 30 MG**	**INADEQUATE**

1 EXECUTIVE SUMMARY

The original application submitted by the firm on December 27, 2006 contained the results of both dissolution testing and single dose fasting and fed bioequivalence studies comparing its test product Lansoprazole Delayed Release (DR) Orally Disintegrating Tablets (ODT), 30 mg to the corresponding reference product Prevacid® SoluTab™ (Lansoprazole), 30 mg, manufactured by Tap Pharmaceuticals. The firm conducted dissolution testing using its own proposed method (DFS N 078730 N 000 27-Dec-2006), and, was requested to conduct the dissolution testing using the FDA-recommended method. The firm submitted a bioequivalence amendment on October 12, 2007 generating new dissolution profiles for 15 mg and 30 mg strengths of its test product using the FDA-recommended method. Based on the submitted data the Division of Bioequivalence (DBE) recommended the following specifications:

Acid stage: NMT (b) (4) in 60 minutes
Buffer stage: NL % (Q) in 30 minutes

The bioequivalence (fasting and fed) studies and dissolution method was found acceptable; however, the application was found to be incomplete due to a dissolution deficiency (dissolution specifications). The firm was asked to accept and acknowledge the DBE recommended dissolution method and specifications (DARRTS, ANDA 078730, REV-BIOEQ-01(General Review); final date 12/21/2007).

On March 27, 2009 the firm submitted a supplemental application – additional manufacturing site at Sellersville, PA - for Lansoprazole DR ODT Tablets, 30 mg. Based on the dissolution data submitted in the supplemental application (March 27, 2009), firm acknowledged the following FDA-recommended dissolution method and specifications on June 23, 2009.

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Specifications:	Acid stage: NMT (b) (4) in 60 minutes Buffer stage: NL % (Q) in 30 minutes

However, during course of the CMC review of this supplemental application, the Division of Chemistry 2 (DC 2) noted some discrepancies in the test product formulation compared to the reference listed drug (RLD) product. On May 7, 2010, the firm submitted the additional in vitro data in response to deficiency letter dated April 23, 2010 sent to the firm and indicated that Sellersville, PA site was withdrawn.

Initially, the DBE proposed that the buffer stage dissolution specification for Teva's test products, 15 mg and 30 mg could be NLT (b) (4) % (Q) in 30 minutes. However, since dissolution testing of Teva's test Lansoprazole DR ODT, 15 mg (batches # L61009 and

L61010) exhibit mean lansoprazole release only about (b)(4)% at 60 minutes in the buffer stage, the OGD ANDA 78730 review team, at an internal meeting, raised concerns about this apparent incomplete dissolution (Since this is an ODT, it was expected that lansoprazole from this dosage form would be 100% dissolved at 60 minutes). The team asked Teva to provide the possible reasons for incomplete drug release (for detailed information, please refer to record of telephone conversation in additional attachment section 3.9.1).

On June 11, 2010, the firm submitted additional dissolution data in response to the June 4, 2010 information request. In addition to reviewing this amendment submitted by Teva, the reviewer evaluated and compared the dissolution data of the test and reference products from various lansoprazole DR ODT regulatory submissions in-house.

The firm conducted comparative dissolution testing using the USP Apparatus (II) with PEAK vessels and regular vessels for test product, 15 mg, noting that the DBE had apparently found acceptable the proposal to use PEAK vessels (b) (4) (b) (4). Teva will be informed that the DBE does not recommend the use of PEAK vessels for dissolution testing of the lansoprazole DR ODT. (b) (4) (b) (4)

Based on the summary review of all in-house dissolution data on the lansoprazole DR ODT by OGD management (please refer to DARRTS, ANDA 078730, REV-BIOEQ-01(General Review) final date 7/20/10 and email communications in presented in additional attachment section 3.9.2), the OGD review team concluded that Teva's test product can be approved provided the firm agrees to accept the interim dissolution specification of **NLT (b)(4)% at 30 minutes** in the buffer stage. The DBE and DC 2 conclude that this specification is optimal to ensure consistent product quality.

The application is incomplete, pending the firm's acceptance of the FDA-recommended dissolution method and following specifications: NMT (b)(4)% in 60 minutes in the acid stage and NLT (b)(4)% (Q) in 30 minutes in the buffer stage.

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[1] DARRTS, ANDA (b) (4) COR-ANDADE-06(Quality Major Deficiencies); final date: (b) (4)

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3 SUBMISSION SUMMARY

3.1 Review of Submission

Deficiency Comment #1:

The drug product is not 100% dissolved, we would like to know where the rest of the drug is. Two lots were given as examples: L-61010 and L-61009. Possible reasons for not reaching 100%: analytical methods, degradation, or it just never dissolved. TEVA is requested to respond to this question as a telephone amendment to the office.

Firm's Response to the Deficiency Comment #1 is summarized below:

Teva states that the dissolution conditions are less than optimal for use with this particular drug substance and dosage form based on the fact that both Teva's product and the RLD have overall low dissolution results as it can be observed in the comparative dissolution profile data provided in **Attachment 1**. Due to the consistent low dissolution release rate observation, one is led to question if the method and/or dissolution conditions are ideally suited to the drug itself.

The first point considered by Teva was the appropriateness of the dissolution media employed. Teva submitted a study report (previously submitted to Canadian health authorities, to justify the use of a pH 6.8 phosphate buffer as the dissolution media) in **Attachment 2.** Based on results of this study, Teva concluded that the rate of degradation of the lansoprazole increases with a decrease in pH in aqueous solutions. The degradation half life of lansoprazole in an aqueous solution at 25°C was ≅ 0.5 hours at pH 5.0, while at pH 7.0 the observed $t_{1/2}$ was ≅ 18 hours. Considering this lack of stability, one can certainly question the overall dissolution values considering the product experiences 1 hour in the aqueous acid media followed by an additional 30 minutes at pH 6.8. Any drug released during this 90 minutes time frame would be subjected to a less than optimal environment for its stability.

The stability of the lansoprazole in the FDA designated media is further questioned by the results of an acid resistance test that had been requested by the Agency's DBE (provided in **Attachment 3**). The results of acid resistance test comparison suggests that the drug product formulations may release some amount of drug (b) (4)%) in the acid stage, albeit less than the (b) (4)%. However, based on the stability study referenced earlier in **Attachment 2**, any drug so released in the acid stage would be expected to rapidly degrade and therefore, would not be included in the overall dissolution value obtained. Additionally, it is suggested that drug that may be in solution during the 30 minute pH 6.8 buffer stage could also experience degradation, albeit to a lesser extent.

Additionally, to determine if the vessel itself could be affecting the overall dissolution results, a preliminary test was performed using all existing conditions and parameters with the exception that the USP vessel was replaced with a PEAK vessel **(Attachment 4)**.

In order to assure that the dissolution results in question are not indicative of either an assay or uniformity issue, Teva submitted the finished product certificates of analysis for Lots# L61010 and L61009 in **Attachment 5**, which establish that the drug product potency and uniformity results are acceptable and around 100%. Additionally in-process data obtained on the delayed release coated (b) (4) lot LAP015 (which was used to manufacture the two finished drug product lots mentioned above), was reviewed **(Attachment 6)**. All data obtained (b) (4) was very consistent and well within specification. Therefore, the product quality, potency and uniformity have been confirmed. This consistency in both the in-process and finished product uniformity data is not consistent with the few lower than typical dissolution results that have been observed which would again lead one to question if the dissolution test is optimal. Please note that the individual values referenced still meet the USP L2 testing criteria of Q-15% and are therefore, fully USP compliant.

Review of the Firm's Data Submitted in Attachment# 1 in Response to Deficiency #1: The firm has submitted the following dissolution data and profiles comparing Teva's original ANDA batches to the RLD:

Study Ref. No.	Product ID/Batch No.	Dosage form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)								Study Report Location
						Acid stage	Buffer stage						
						60 min	5 min	10 min	15 min	20 min	30 min	45 min	
CDP-1531/01	Lansoprazole K-36985	15 mg D.R Orally Disintegrating Tablets	**Dissolution:** Apparatus 2 (Paddle) Speed of Rotation: 75 rpm Temperature: 37°C ± 0.5°C **Acid Stage**: Medium: 0.1N HCl Volume: 500mL, Tolerance: (b) (4) dissolved in 60 minutes **Buffer Stage:** Medium: Phosphate Buffer pH 6.8 Volume: 900 mL Tolerance: (b) (4) (Q) dissolved in 45 minutes.	12		0 (0-0)	19	59	70	74	78	80 (b) (4)	Original ANDA Section V1.3
					RSD (%)	0	30.2	17.5	13.2	12.7	12.3	11.1	
	Prevacid® SoluTab™ # 130169P22	15 mg D.R Orally Disintegrating Tablets				0 (0-0)	86	87	87	86	85	83 (b) (4)	
					RSD (%)	0%	2.6	3.5	3.1	3.0	2.9	4.5	
CDP-1477/01	Lansoprazole K-36986	30 mg D.R Orally Disintegrating Tablets		12		0	9	43	67	73	77	81 (b) (4)	
					RSD (%)	Not Relevant	64.3	29.0	9.5	8.8	8.8	7.8	
	Prevacid® SoluTab™ #140089P22	30 mg D.R Orally Disintegrating Tablets				0	81	82	80	81	80	78 (b) (4)	
					RSD (%)	0	3.9	4.7	3.7	4.2	4.8	2.8	

Figure 1: Comparative dissolution profiles for 15 mg strengths

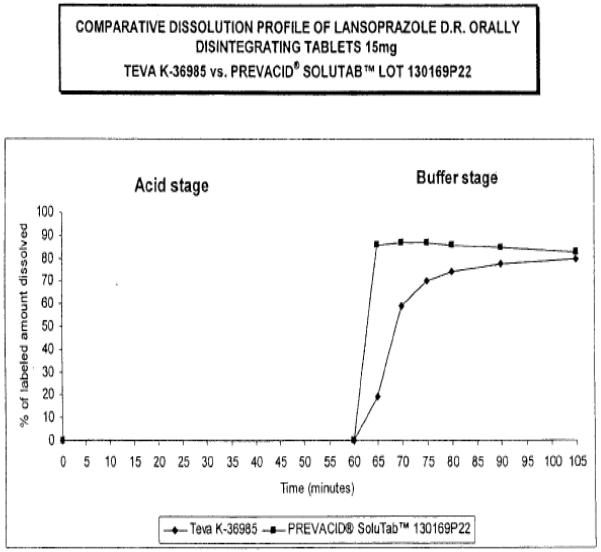
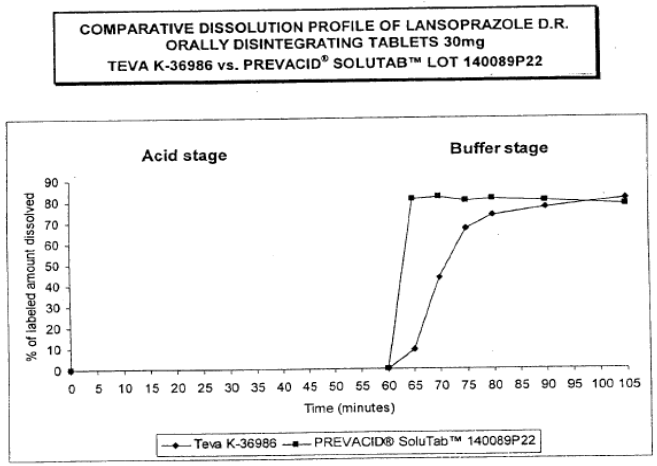


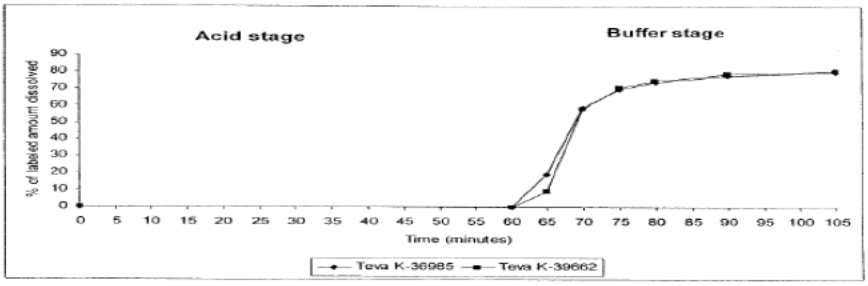
Figure 2: Comparative dissolution profiles for 30 mg strengths



The firm has also submitted the following dissolution data and profiles comparing the original ANDA batches to the reformulated batches in Attachment 1:

Study Ref. No.	Product ID/Batch No.	Dosage form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)								Study Report Location
						Acid stage	Buffer stage						
						60 min	5 min	10 min	15 min	20 min	30 min	45 min	
CDP-1799/01	Lansoprazole K-36985	15 mg D.R Orally Disintegrating Tablets	**Dissolution:** Apparatus 2 (Paddle) Speed of Rotation: 75 rpm Temperature: 37°C ± 0.5°C **Acid Stage**: Medium: 0.1N HCl Volume: 500mL, Tolerance: (b) (4) dissolved in 60 minutes **Buffer Stage**: Medium: Phosphate Buffer pH 6.8 Volume: 900 ml Tolerance (b) (4) (Q) dissolved in 45 minutes.	12		0 (0-0)	19	59	70	74	78	80 (b) (4)	
					RSD (%)	0	30.2	17.5	13.2	12.7	12.3	11.1	
	Lansoprazole K-39662	15 mg D.R Orally Disintegrating Tablets				0 (0-0)	9	58	71	75	79	81 (b) (4)	
					RSD (%)	0%	56.5	21.7	13.3	10.8	9.2	7.2	
CDP-1798/01	Lansoprazole K-36986	30 mg D.R Orally Disintegrating Tablets		12		0	9	43	67	73	77	81 (b) (4)	
					RSD (%)	Not Relevant	64.3	29.0	9.5	8.8	8.8	7.8	
	Lansoprazole K-39663	30 mg D.R Orally Disintegrating Tablets				0 (0-0)	8	58	72	76	79	71 (b) (4)	
					RSD (%)	0	47.7	23.9	15.2	11.8	9.5	7.8	

COMPARATIVE DISSOLUTION PROFILE OF LANSOPRAZOLE D.R. ORALLY DISINTEGRATING TABLETS 15mg
TEVA K-36985 vs. TEVA K-39662



COMPARATIVE DISSOLUTION PROFILE OF LANSOPRAZOLE D.R. ORALLY DISINTEGRATING TABLETS 30mg
TEVA K-36986 vs. TEVA K-39663

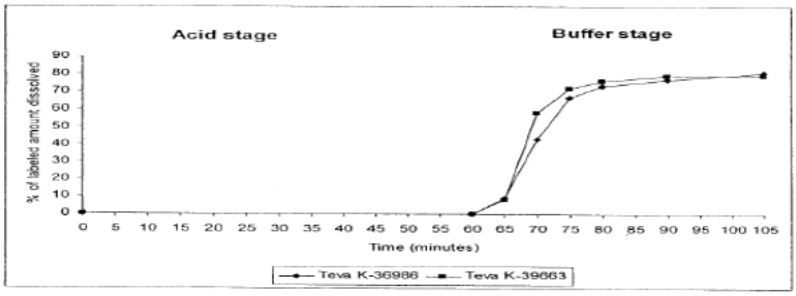
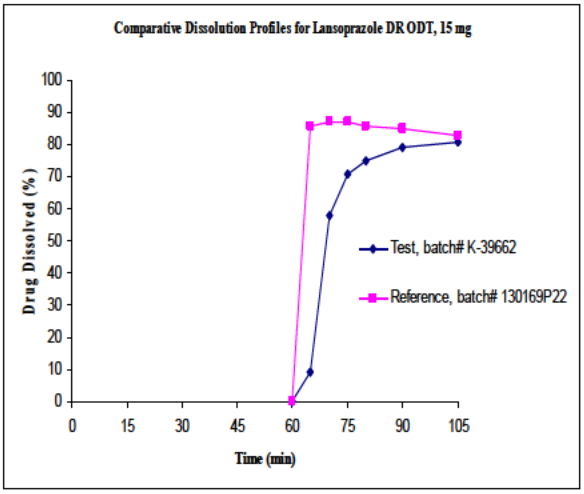
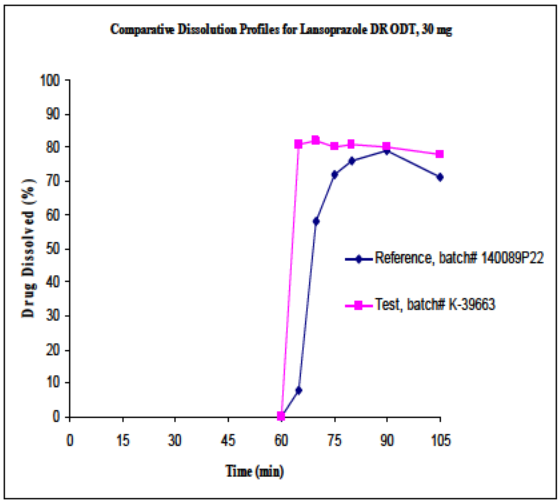


Figure 3: Comparative dissolution profiles for 15 and 30 mg strengths





Reviewer's Comment on Dissolution Data Submitted in Attachment# 1:

The firm's response that both Teva's product and the RLD have overall low release is not acceptable because inadequate data are submitted at this time to support this claim. As shown in the **Figures 1, 2 and 3 above,** the original ANDA batches (K-36985, 15 mg and K-36986, 30 mg) and reformulated test batches (K-39662, 15 mg and K-39663, 30 mg) exhibit slower release in buffer stage as compared to RLD products except at 45-min in buffer stage. The dissimilarity in dissolution profiles of test vs. reference products is further supported by the f2 values of < 30 as shown in the table below:

F2 metric, biostudy strengths compared to other strength(s); ANDA 078730 (Teva); Firm's Method: USP Apparatus II; 75 rpm, Acid Stage: 500 mL 0.1N HCl, Buffer Stage: 900 mL Phosphate Buffer, pH 6.8			
Biostudy Strength	**(T^1) 15 mg vs. (R^2) 15 mg**	**(T^1) 30 mg vs. (R^2) 30 mg**	**(T^1) 15 mg vs. (T^1) 30 mg**
Whole tablet	27.10	25.06	56.78
Biostudy Strength	**(T^2) 15 mg vs. (R^2) 15 mg**	**(T^2) 30 mg vs. (R^2) 30 mg**	**(T^2) 15 mg vs. (T^2) 30 mg**
Whole tablet	24.70	26.58	70.09

T^1: batches# K-36985, 15 mg and # K-36986, 30 mg; T^2: batches# K-39662, 15 mg and K-39663, 30 mg; R^2: Reference

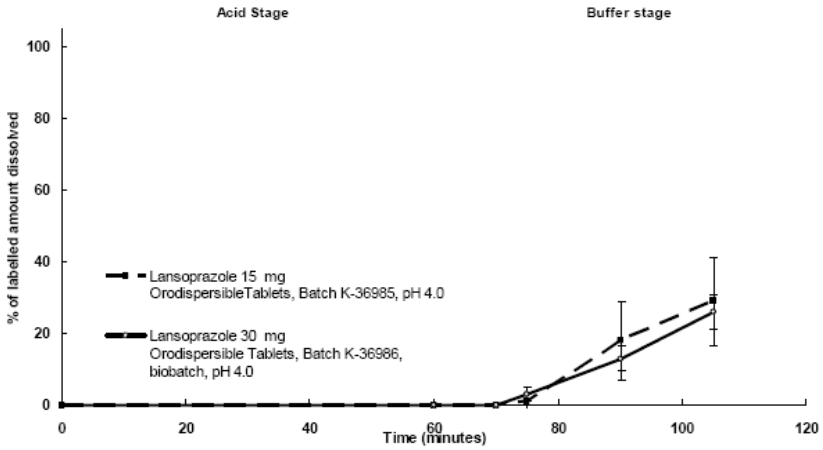
However, since a detailed Tmax analysis previously conducted by this reviewer showed that Teva's product and the RLD do not have a significant difference in the rate of absorption, the significance of the slower absorption rate of Teva's product before 45 minutes is not clear.

Review of the Firm's Data Submitted in Attachments# 2 and 3 in Response to Deficiency #1:

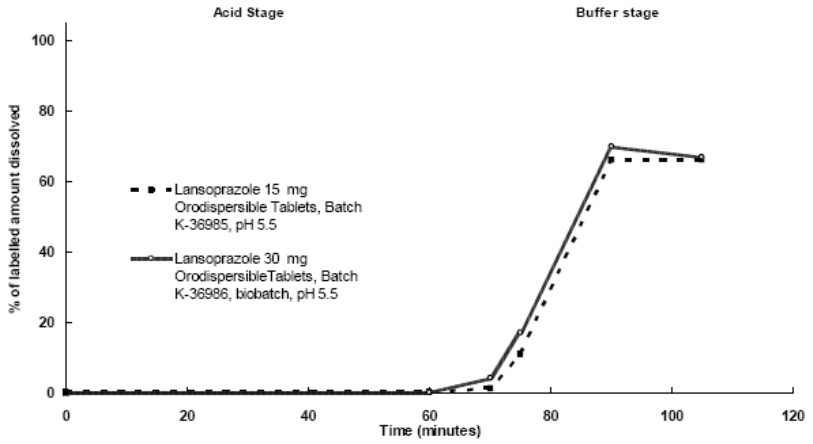
The firm used the following dissolution media in the buffer stage in order to study the influence of pH on lansoprazole release, using Lansoprazole 15 & 30 mg Orodispersible Tablets, batches# K- 36985 and K-36986, respectively:

1) Phosphate Buffer, pH 4.0; 2) Phosphate Buffer, pH 5.5; and 3) Phosphate Buffer, pH 6.8, and provided the following comparative dissolution profiles in different pH media:

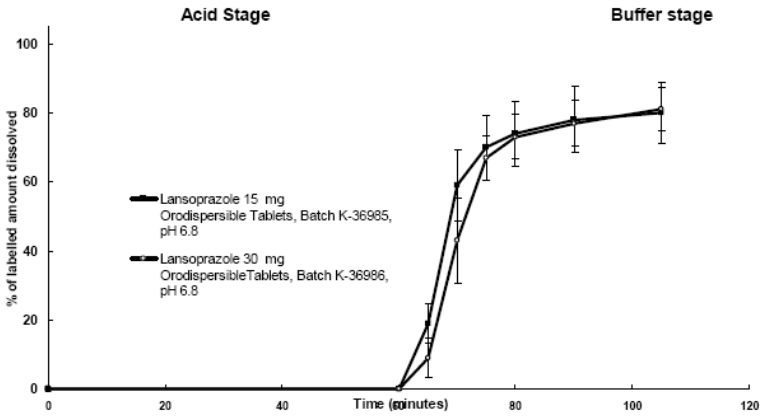
The two strengths of Teva Lansoprazole Orodispersible Tablets (buffer pH 4.0)



The two strengths of Teva Lansoprazole Orodispersible Tablets (buffer pH 5.5)



The two strengths of Teva Lansoprazole Orodispersible Tablets (buffer pH 6.8)



The firm stated, "It is confirmed that lansoprazole is unstable in all solutions with acidic pH. In solutions with pH lower than 6, the degradation rate of lansoprazole is almost equal to its release rate from the (b) (4) Based on the above data, phosphate buffer pH 6.8 was chosen as a medium for buffer stage of the dissolution testing in which the (b) (4) of the coated (b) (4) is dissolved and the product is released".

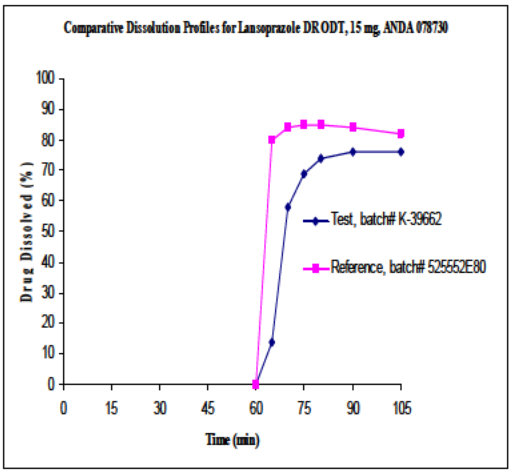
Reviewer's Comment on Data Submitted in Attachments# 2 and 3:

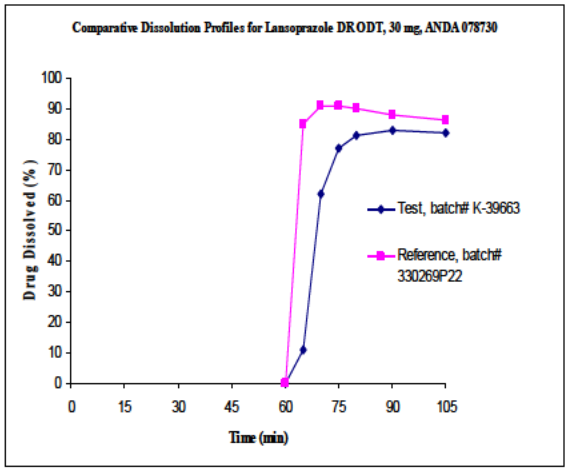
Based on the above data, it is evident that % of lansoprazole dissolved increases with the increase in pH 4.0 to pH 6.8 in buffer stage media.

Considering that test products, 15 mg and 30 mg meet dissolution specification at A1 level in acid stage, and dispersed test products, 15 mg and 30 mg meet dissolution specifications at A2 level in acid stage using oral syringe (DARRTS: ANDA 078730, REV-BIOEQ-01(General Review); final date: 5/25/10); the firm's explanation that any drug released in the acid stage would be expected to rapidly degrade and therefore, would not be included in the overall dissolution value seems reasonable.

Since, degradation is a property of drug substance after its release form the drug product, degradation rate of drug may be expected to be similar for the test and reference products in buffer stage. However, the dissolution profiles (**Figures 4**) indicates that during buffer stage, the mean % of drug released from test products is slower than reference products. These observations do not support the firm's explanation about the impact of stability on slower dissolution release of drug in the buffer stage. In addition, firm has not submitted any data supporting its claim that lansoprazole degrades in the buffer media (pH 6.8).

Figure 4: Comparative Dissolution Profile for Lansoprazole DR ODT, 15 mg and 30 mg (Using FDA-recommended method)





Review of the Firm's Data Submitted in Attachment# 4 in Response to Deficiency #1:

The firm has submitted the following comparative dissolution testing data generated using USP Apparatus II (paddle) with regular vessels vs. PEAK vessels.

Lot # L61009								
Dissolution (% Released)								
Vessel Type	Peak	USP	Peak	USP	Peak	USP	Peak	USP
Time (min)	0.1N HCl		900mL pH 6.8 Phosphate Buffer; Paddle 75 rpm					
	60		30		45		60	
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Avg. (%)	0	0	87	78	85	79	82	78
RSD (%)	N/R		9.8	12.08	10.3	11.79	10.1	10.51

Lot # L61010								
Dissolution (% Released)								
Vessel Type	Peak	USP	Peak	USP	Peak	USP	Peak	USP
	0.1N HCl		900mL pH 6.8 Phosphate Buffer; Paddle 75 rpm					
Time (min)	60		30		45		60	
1	[redacted] (b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Avg. (%)	0	0	82	77	84	79	82	79
RSD (%)	N/R		18.6	11.75	8.8	12.15	9.6	12.30

The firm has mentioned that, "while the differences in overall dissolution were not drastic, a consistent increase in overall dissolution was observed for both Teva's product and the RLD. Further study would be needed to confirm these observations and determine the extent to which this may be a contributing factor."

Reviewer's Comment on Data Submitted in Attachment# 4: The submitted dissolution data indicates that:

1. During buffer stage, there is an overall increase in dissolution rate of test product, 15 mg (batches# L61009 and L61010) using PEAK vessels ([redacted] (b) (4)) as compared to regular vessels ([redacted] (b) (4)).
2. Furthermore, a consistent decrease in drug release rate is observed from 30 – 60 minutes during buffer stage with the use of PEAK vessel.
3. The dissolution data submitted by Teva using PEAK vessels is inconclusive as the firm has not provided a comparative dissolution on the reference Lansoprazole (Prevacid® SoluTabTM) 15 mg and 30 mg tablets. In addition, the firm used only 6 units for the test 15 mg tablets using the PEAK vessel. The limited data on the 15 mg test strength (N=6), doesn't meet the NLT [redacted] (b) (4)% (Q) even at 60 minutes in the buffer stage at B1 for either of the two batches under the PEAK Vessel conditions.
4. It is further noted that the OGD issued a [redacted] (b) (4) letter on the [redacted] (b) (4) [redacted] (see the discussion of ANDA [redacted] (b) (4) dissolution data in this review). Therefore, the argument that

PEAK vessels should be suitable for dissolution testing for Teva's product because they are (b) (4) is moot.

Reviewer's Comment on Data Submitted in Attachments# 5 and 6:

The data submitted in the attachments# 5 and 6 will be reviewed by the chemistry division.

3.2 In Vitro Dissolution Method

The FDA-recommend dissolution method for lansoprazole delayed release orally disintegrating tablets available at FDA's website http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm is as follow:

Source of Method (USP, FDA or Firm)	FDA
Medium	Acid Stage: 0.1N HCl Buffer Stage: Phosphate buffer, pH 6.8 with 5 mM Sodium Dodecyl Sulfate
Volume (mL)	Acid Stage: 500 mL Buffer Stage: 900 mL
USP Apparatus type	Apparatus II, (Paddle)
Rotation (rpm)	75
Sampling Times (minutes)	Acid Stage: 60 minutes Buffer Stage: 10, 20, 30 and 45 minutes
DBE-recommended specifications	

[2]The NDA dissolution specifications for Prevacid ® SoluTab™ (Lansoprazole) Delayed Release Orally Disintegrating Tablets: NMT (b)(4)% in 60 minutes during acid stage; and NLT (b)(4)% (Q) in 30 minutes during buffer stage.

The DBE has recommended the following dissolution specifications for ANDA (b) (4) (b) (4) at: NMT (b)(4)% in 60 minutes during acid stage, and NLT (b)(4)% (Q) in 30 minutes during buffer stage (b) (4)

The DBE has recommended the following dissolution specifications for ANDA 078730 (Teva) at: NMT (b)(4)% in 60 minutes during acid stage, and NLT (b)(4)% (Q) in 30 minutes during buffer stage.

Lansoprazole delayed release orally disintegrating tablets, (b) (4) (b) (4) meet the following specifications: NMT (b)(4)% in 60 minutes during acid stage, and NLT (b)(4)% (Q) in 30 minutes during buffer stage (b) (4) (b) (4)

[2] DARRTS, NDA 021428, REV-CLINPHARM-01(General Review), final date: 08/08/02.

3.3 Review of Dissolution Data

Dissolution data from NDA 021428 (Takeda)[3]*:*

OCPB Reviewer's Comment: During the acid resistance stage (60 min): the % of lansoprazole released were (b) (4)% and (b) (4) % for Solutab 15 mg (batch# Z5133061) and 30 mg biobatch (batch # Z5134071) tablets, respectively; and during the buffer stage (at 15, 30, 45, and 60 min), Prevacid Solutab 15 and 30 mg tablets all showed rapid and nearly complete dissolution in 15 min ((b) (4)% and (b) (4)%, respectively).

For Prevacid Solutab 15 mg and 30 mg tablets, additional data at earlier time points of 5 and 10 min during the buffer stage (6 tablets per batch) were obtained upon the Agency's request and the results are shown below in **Table 1** below.

Table 1: Drug Release Profiles for 15 mg (Lot A1274) and 30 mg ((Lot A1224) Lansoprazole Tablets in buffer stage

Time (min)	Drug Release (%); n=6, 15 mg		Drug Release (%); n=6, 30 mg	
	Mean	SD (CV%)	Mean	SD (CV%)
5	66.2	20.2 (30.5%)	64.5	23.3 (36%)
10	92.3	6.8 (7.4%)	88.3	12.0 (14%)
15	99.2	1.8 (1.8%)	99.4	1.7 (1.7%)
30	102.	1.8 (1.8%)	99.0	2.3 (2.3%)
45	103.	1.7 (1.7%)	99.7	1.9 (1.9%)

[3] DARRTS, NDA 021428, REV-CLINPHARM-01(General Review), final date: 08/08/02.

Dissolution Data for ANDA 078730 (Teva) [4]

Dissolution Conditions		
	Apparatus:	Apparatus 2 (Paddle)
	Speed of Rotation:	75 rpm
	Medium:	**Acid Stage:** 0.1N HCl **Buffer Stage:** Phosphate Buffer, pH 6.8 with 5 mM SDS
	Volume:	**Acid Stage:** 500 mL **Buffer Stage:** 900 mL
	Temperature:	37.0°C ± 0.5°C
Firm's Proposed Specifications	**Acid stage:** NMT (b) (4) dissolved in 60 minutes; **Buffer stage:** NLT (b) (4) (Q) dissolved in 45 minutes	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)							Study Report Location
						Acid Stage	Buffer Stage						
						60 min	5 min	10 min	15 min	20 min	30 min	45 min	
7448-090323-FDA	3/24/09	Lansoprazole Delayed Release Orally Disintegrating Tablets Lot# K-39662 (Kfar Saba, Israel site)	15 mg Tablets	12	Mean	0	14	58	69	74	76	76	Attachment 4
					Range	0	(b) (4)						
					%CV	0	28	13	8	7	5	4	
	8/27/07	[1]Prevacid® SoluTab™ #525552E80 Exp.: 5/09	15 mg Tablets	12	Mean	0	80	84	85	85	84	82	
					Range	0-0	(b) (4)						
					%CV	0	12.7	7.2	3.6	2.8	2.5	2.4	
7449-090313-FDA	3/24/09	Lansoprazole Delayed Release Orally Disintegrating Tablets Lot# K-39663 (Kfar Saba, Israel site)	30 mg Tablets	12	Mean	0	11	62	77	81	83	82	Attachment 4
					Range	0	(b) (4)						
					%CV	0	16	15	9	8	6	6	
	7/26/07	[1]Prevacid® SoluTab™ Lot# 330269P22 Exp.: 4/08	30 mg Tablets	12	Mean	0	85	91	91	90	88	86	
					Range	0-0	(b) (4)						
					%CV	0	11.1	3.4	2.8	2.8	2.8	2.6	

[4] DARRTS, ANDA 078730, REV-BIOEQ-01(General Review), final date: 06/24/2009

Dissolution data for test products manufactured at Teva' Kfar-Saba, Israel Site submitted as a part of original ANDA submission (location: DARRTS, ANDA 078730, REV-BIOEQ-01(General Review); final date: 12/21/2007):

Dissolution Conditions	**Apparatus:**	Apparatus 2 (Paddle)
	Speed of Rotation:	75rpm
	Medium:	Acid Stage: 0.1N HCl Volume: 500mL Buffer Stage: Medium: Phosphate Buffer, pH 6.8, with 5mM SDS
	Volume:	Acid Stage: 500mL Buffer Stage: 900mL
	Temperature:	37°C ± 0.5°C
Dissolution Testing Site (Name, Address)	Teva Pharmaceutical Industries, Ltd., Hashikma Street, Industrial Area, Kfar-Saba 44102, ISRAEL	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						Acid Stage	**Buffer Stage**						
						60 min	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	
CDP-1702/01	July 26, 2007	Lansoprazole D.R. ODT K-36985 Mfg.: 6/06	15 mg D.R Orally Disintegrating Tablets	12	Mean	0	10	66	80	83	85	85	Attachment 2
					Range	0-0	[redacted] (b) (4)						
					%CV	0	51.5	13.4	10.7	8.2	7.5	6.6	
	Aug. 7, 2007	Prevacid® SoluTab™ #525552E80 Exp.: 5/09	15 mg D.R Orally Disintegrating Tablets	12	Mean	0	80	84	85	85	84	82	
					Range	0-0	[redacted] (b) (4)						
					%CV	0	12.7	7.2	3.6	2.8	2.5	2.4	
CDP-1703/01	July 26, 2007	Lansoprazole D.R. ODT K-36986 Mfg.: 6/06	30 mg D.R Orally Disintegrating Tablets	12	Mean	0	6	69	83	85	86	84	Attachment 2
					Range	0-0	[redacted] (b) (4)						
					%CV	0	41.2	10.4	6.2	5.2	4.7	6.0	
	July 26, 2007	Prevacid® SoluTab™ #330269P22 Exp.: 4/08	30 mg D.R Orally Disintegrating Tablets	12	Mean	0	85	91	91	90	88	86	
					Range	0-0	[redacted] (b) (4)						
					%CV	0	11.1	3.4	2.8	2.8	2.8	2.6	

Following this page, 5 pages withheld in full - (b)(4)

Table 2: f2 Values for Lansoprazole Delayed Release Orally Disintegrating Tablets

F2 metric, biostudy strengths compared to other strength(s); ANDA 078730 (Teva)			
Biostudy Strength	**(T^1) 15 mg vs. (R^2) 15 mg**	**(T^1) 30 mg vs. (R^2) 30 mg**	**(T^1) 15 mg vs. (T^1) 30 mg**
Whole tablet	27.59	25.57	62.08
F2 metric, biostudy strengths compared to other strength(s); ANDA			(b) (4) **PEAK Vessel**
Biostudy Strength			(b) (4)
Whole tablet			
F2 metric, biost			
Biostudy Strength			
Whole tablet			
F2 metr			
Biostudy Strength			
Whole tablet			

T^1 = Test; R^2= Reference

Reviewer's Comments on the Comparative Dissolution Release for the 3 ANDAs Currently being Reviewed by the OGD:

1. (b) (4)

2.

3.

Table 3: Comparative Dissolution Data for Lansoprazole DR ODT, 15 mg (ANDA 078730; Teva; (b) (4) and 021428, Takeda)

Dissolution Conditions:
Apparatus: USP II (Paddle)
Buffer Stage: Phosphate Buffer, pH 6.8 with 5 mM SDS, 900 mL
Speed of Rotation: 75 rpm for (b) (4) Teva and Takeda; 100 rpm for (b) (4)

Vessel Type	Regular			Regular	Regular	Regular	PEAK		PEAK
Time (min)	Teva			(b) (4)		Takeda (RLD/NDA)	Teva		(b) (4)
	Batch# K-39662 n = 12	*Batch# L61009 n = 12*	*Batch# L61010 n = 12*			*n = 6*	*Batch# L61009 n = 6*	*Batch# L61010 n = 6*	
5	14 (b) (4)					66.2			
10	58 (b) (4)					92.3			
15	69 (b) (4)					99.2			
20	74 (b) (4)					-			
30	76	78	77 (b) (4)			102.	87	82 (b) (4)	
45	**76**	**79**	**79** (b) (4)			**103.**	**85**	**84** (b) (4)	
60		78	79 (b) (4)				82	82 (b) (4)	

Table 4: Comparative Dissolution Data for Lansoprazole DR ODT, 30 mg (ANDA 078730; Teva; (b) (4) and 021428, Takeda)

Dissolution Conditions: **Apparatus:** USP II (Paddle) **Buffer Stage:** Phosphate Buffer, pH 6.8 with 5 mM SDS, 900 mL **Speed of Rotation:** 75 rpm for (b) (4) Teva and Takeda; 100 rpm for (b) (4)					
Vessel Type	**Regular**	**Regular**	**Regular**	**Regular**	**PEAK**
Time (min)	**Teva**	(b) (4)		**Takeda (RLD/NDA)**	(b) (4)
	Batch# K-39663 n = 12			***n = 6***	
5	11 (b) (4)			64.5	
10	62 (b) (4)			88.3	
15	77 (b) (4)			99.4	
20	81 (b) (4)				
30	83 (b) (4)			99.0	
45	**82** (b) (4)			**99.7**	
60					

3.4 Geometric Means and 90% Confidence Intervals

In this review, only the results of fasting BE studies are summarized below:

ANDA 078730; Teva[9]

Lansoprazole Orally Disintegrating DR Tablets, 30 mg Fasting Bioequivalence Study No. (S08-0114), N=104 (Male=51 and Female=53) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (hr *ng/ml)	1741.59	1758.89	0.99	94.35-103.91
AUC_{∞} (hr *ng/ml)	1759.37	1773.38	0.99	94.52-104.13
C_{max} (ng/ml)	770.76	791.79	0.97	89.63-105.72

Note: In the fasting BE study, Lansoprazole Delayed Release Orally Disintegrating Tablets; 30 mg, lot # 2621-015 manufactured at Sellersville, PA was compared with the Prevacid® SoluTab™, 30 mg. The lansoprazole DR ODT, 30 mg, lot# 39663 manufactured at Teva's Kfar-Saba, Israel site have same components and composition as batch# 2621-015 (30 mg) manufactured at Sellersville, PA site, except the change in % age ratios of (b) (4) and (b) (4). For batches# 2621-015 (30 mg), (b) (4) (b) (4), whereas for batch# K-39663 (30 mg), (b) (4) (b) (4)

The results of PK and statistical analysis from the fasting study comparing the original ANDA formulation manufactured at Teva's Kfar-Saba, Israel site with the RLD are provided in the table below[10]:

Parent Drug, Dose Lansoprazole, 30 mg Fasting Bioequivalence Study No. 2006-1287, N=87 (Male=41 and Female=46) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	**Test Teva lot K36986**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng·hr/mL)	2166.79	2218.08	0.98	93.25 – 102.33
AUC∞ (ng·hr/mL)	2204.75	2256.84	0.98	93.32 – 102.27
Cmax (ng/mL)	876.55	955.10	0.92	85.13 – 98.94

[9] DARRTS, ANDA 078730, REV-BIOEQ-01(General Review), final date: 06/24/09
[10] DARRTS, ANDA 078730, REV-BIOEQ-01(General Review) by CHERSTNIAKOVA, SVETLANA A, final date: 12/21/07

ANDA (b) (4)

Lansoprazole Orally Disintegrating DR Tablets, 30 mg Fasting Bioequivalence Study No (b) (4) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng·hr/mL)	(b) (4)			
AUC∞ (ng·hr/mL)				
Cmax (ng/mL)				

ANDA (b) (4)

Lansoprazole Orally Disintegrating DR Tablets, 30 mg Fasted Bioequivalence Study (b) (4) Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Parameter	**Test**	**Reference**	**Ratio**	**90%CI**
AUCt (ng·hr/mL)	(b) (4)			
AUCi (ng·hr/mL)				
Cmax (ng/mL)				

3.5 Summary and Conclusions

Based on the summary review of in-house dissolution data by OGD management (DARRTS, ANDA 078730, REV-BIOEQ-01(General Review); final date 7/20/10) and internal discussions (please refer to email communications in additional attachment section 3.9.2), it was concluded that Teva's test product can be approved, if the firm agrees to accept the FDA-recommended interim dissolution method and following specifications: acid stage: NMT (b) (4) in 60 minutes; and buffer stage: NLT (b) (4) (Q) in 30 minutes. The OGD review team concluded that the specification of NLT (b) (4) (Q) in 30 minutes should assure consistent product quality. However, a final dissolution specification will not be set until review of production batch data.

3.6 Deficiency Comments

1. The firm will be informed that DBE does not recommend the use of PEAK vessels for dissolution testing of lansoprazole delayed release ODT, 15 mg and 30 mg.

2. In the current [June 11, 2010] submission Attachment 1, firm has submitted the dissolution testing data generated using its own-proposed method (without inclusion of 5 mM SDS in buffer media). It is unclear why the firm did not include in the June 11 submission dissolution data obtained in phosphate buffer with 5 mM SDS, since these data were previously submitted to the OGD. The firm will be asked to acknowledge the following FDA-recommended dissolution method and specifications:

   Medium: 500 mL of 0.1 N HCl for the first hour followed by 900 mL

[11] DARRTS, ANDA (b) (4)
[12] DARRTS, ANDA

	phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37 °C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Specifications:	Acid stage: NMT (b) (4) % in 60 minutes
	Buffer stage: NLT % (Q) in 30 minutes

3.7 Recommendations

The Division of Bioequivalence accepts the fasting BE study (S08-0114) conducted by Teva Pharmaceuticals USA on its Lansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg, lot # 2621-015 comparing it to TAP Pharmaceuticals' Prevacid® SoluTab™ (Lansoprazole) Delayed-Release Orally Disintegrating Tablets 30 mg, lot # 578352E22. However, the application is incomplete pending firm's response to the deficiency# 2 mentioned above.

3.8 Comments for Other OGD Disciplines

Discipline	Comment
	None

BIOEQUIVALENCE DEFICIENCIES

ANDA: 078730

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

The Division of Bioequivalence (DBE) has completed its review and has identified the following deficiencies:

1. The DBE acknowledges your submission of dissolution data using PEAK Vessels. We concluded that we do not recommend the use of the PEAK Vessel for dissolution testing of Lansoprazole Delayed Release Orally Disintegrating Tablets. [redacted] (b) (4) the use of PEAK Vessels for dissolution testing for Lansoprazole Delayed-Release Orally Disintegrating Tablets.

2. Your application is incomplete pending your acceptance of following FDA-recommended interim dissolution method and specifications:

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Specifications:	Acid stage: NMT [redacted] (b) (4) in 60 minutes Buffer stage: NLT [redacted] (b) (4) % (Q) in 30 minutes

Please indicate whether you accept the above interim dissolution method and specifications.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.

Acting Director, Division of
Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

3.9 Additional Attachments

3.9.1 Record of Telephone Conversation[13]

After internal discussion, TEVA was contacted for the following question: The drug product is not 100% dissolved, we would like to know where is the rest of the drug. Two lots were given as examples: L-61010 and L-61009. Possible reasons for not reaching 100%: analytical methods, degradation, or it just never dissolved. TEVA is requested to respond to this question as a telephone amendment to the office.	**Date:** 6/4/10 **ANDA Number:** 078730 **Product Name:** Lansoprazole DR ODT **Firm Name:** TEVA **Firm Representative:** Philip Erickson **Phone Number:** 215-591-3141 **FDA Representatives:** Lawrence Yu Barbara Davit Chaurasia Chandra Robert Lionberger Wenlei Jiang Glen Smith Radhika Rajagopalan Theresa Liu **Endorsements:**

[13] DARRTS, ANDA 078730, COR-ANDAIR-01(Advice/Information Request) by LIU, THERESA C, final date: 06/14/2010

3.9.2 Email Communications NOT TO BE RELEASED UNDER FOI

3.9.2.1 E-mail Correspondence from Dr. Florence Fang

From: Fang, Florence S
Sent: Tuesday, July 20, 2010 1:04 PM
To: Davit, Barbara M
Cc: Chaurasia, Chandra S; Stier, Ethan; Kaur, Paramjeet; Yu, Lawrence; Smith, Glen J; Rajagopalan, Radhika; Jiang, Wenlei; Lionberger, Robert; Rickman, William P; Read, Shanaz; West, Robert L; Nice, Frank
Subject: RE: draft memo, observations on the Teva lansoprazole DR ODT dissolution data and other issues

Barbara:

We thank you for the observations and summary. For our scientific curiosity, we would like to have OTR use the one and same dissolution method to test all the lansoprazole ODT products (RLD, Teva and (b) (4) and compare the data. Please note (b) (4) does not have a (b) (4)

The OTR testing effort will take some time. In the meantime, the CMC review team would recommend the approval of Teva's ANDA if Teva agrees to what you stated:

(2) a specification of NLT (b) (4) % in 30 minutes is reasonable for the buffer stage to ensure product quality

We also feel this dissolution acceptance criterion should be a good quality control for the manufacturing of Teva's product. Teva will probably not be able to release a certain percentage of their production batches.

We are asking the input from the Science team.

If we all agree , we can schedule a tcon with Teva (bio and chemistry both participate) and bring closure to the ANDA.

Thank you,

Florence

From: Davit, Barbara M
Sent: Monday, July 19, 2010 8:07 PM
To: Chaurasia, Chandra S; Stier, Ethan; Kaur, Paramjeet; Yu, Lawrence; Fang, Florence S; Smith, Glen J; Rajagopalan, Radhika; Jiang, Wenlei; Lionberger, Robert; Rickman, William P
Subject: draft memo, observations on the Teva lansoprazole DR ODT dissolution data and other issues

Hello:

I am not sure if I cc'd everyone.

Please see the following preliminary draft.

These are my observations on the Teva lansoprazole dissolution data, including a comparison of dissolution data generated by various firms.

Please see my tentative conclusions.

Basically

(1) the in vivo BE study appears robust and I do not see any evidence that differences in early dissolution rate in the buffer phase will be reflected by differences in lansoprazole rate of absorption;
(2) a specification of NLT(b) (4)% in 30 minutes is reasonable for the buffer stage to ensure product quality; and
(3) only the innovator has been able to achieve 100% dissolution by 30 minutes on Prevacid Solutabs. Although the generics only achieve (b) (4)% dissolution in 30 minutes for their respective products, in their hands the RLD is also only (b) (4)% dissolved by 30 minutes.

Thanks to Paramjeet and Chandra for collecting all the dissolution data.

Please advise how to proceed, should we have another meeting?

Barbara
<< File: ANDA 78730 Lansoprazole DR ODT Bio.doc >>

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
CDER/FDA
240-276-8819

3.9.2.2 E-mail Correspondence from Dr. Lawrence Yu

From: Yu, Lawrence
Sent: Tuesday, July 20, 2010 5:39 PM
To: Fang, Florence S; Davit, Barbara M
Cc: Chaurasia, Chandra S; Stier, Ethan; Kaur, Paramjeet; Smith, Glen J; Rajagopalan, Radhika; Jiang, Wenlei; Lionberger, Robert; Rickman, William P; Read, Shanaz; West, Robert L; Nice, Frank
Subject: RE: draft memo, observations on the Teva lansoprazole DR ODT dissolution data and other issues

Barbara,

Agree with your conclusion.

Florence,

Agree to ask OTR to test these lansoprazole ODT products.

Many thanks to all!

Lawrence

From: Fang, Florence S
Sent: Tuesday, July 20, 2010 1:04 PM
To: Davit, Barbara M
Cc: Chaurasia, Chandra S; Stier, Ethan; Kaur, Paramjeet; Yu, Lawrence; Smith, Glen J; Rajagopalan, Radhika; Jiang, Wenlei; Lionberger, Robert; Rickman, William P; Read, Shanaz; West, Robert L; Nice, Frank
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The OTR testing effort will take some time. In the meantime, the CMC review team would recommend the approval of Teva's ANDA if Teva agrees to what you stated:

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To: Chaurasia, Chandra S; Stier, Ethan; Kaur, Paramjeet; Yu, Lawrence; Fang, Florence S; Smith, Glen J; Rajagopalan, Radhika; Jiang, Wenlei; Lionberger, Robert; Rickman, William P
Subject: draft memo, observations on the Teva lansoprazole DR ODT dissolution data and other issues

Hello:

I am not sure if I cc'd everyone.

Please see the following preliminary draft.

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Please see my tentative conclusions.

Basically

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(2) a specification of NLT (b)(4)% in 30 minutes is reasonable for the buffer stage to ensure product quality; and
(3) only the innovator has been able to achieve 100% dissolution by 30 minutes on Prevacid Solutabs. Although the generics only achieve (b)(4)% dissolution in 30 minutes for their respective products, in their hands the RLD is also only (b)(4)% dissolved by 30 minutes.

Thanks to Paramjeet and Chandra for collecting all the dissolution data.

Please advise how to proceed, should we have another meeting?

Barbara
<< File: ANDA 78730 Lansoprazole DR ODT Bio.doc >>

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
CDER/FDA
240-276-8819

Following this page, 4 pages withheld in full - (b)(4)

4 OUTCOME PAGE

ANDA: 78730

Completed Assignment for 78730 ID: 11468

Reviewer: Kaur, Paramjeet **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
11468	6/11/2010	Other	Study Amendment	1	1	Edit	Delete
11468	6/11/2010	Other	Dissolution Data Review from Other ANDAs	1	1	Edit	Delete
				Bean Total:	2		

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment	
Study Amendment-deficiency comments-dated 6/11/2010	1
Dissolution Data Review from Other ANDAs	1
Total number of Complexity Points	2

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

PARAMJEET KAUR
07/27/2010

CHANDRA S CHAURASIA
07/27/2010

BARBARA M DAVIT
07/27/2010

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78730
Drug Product Name	Lansoprazole Delayed Release Orally Disintegrating Tablet
Strength(s)	15 mg and 30 mg
Applicant Name	Teva Pharmaceuticals USA
Address	1090 Horsham Road, North Wales, PA 19454
Applicant's Point of Contact	Philip Erickson, R.Ph. Senior Director, Regulatory Affairs
Contact's Telephone Number	215-591-3141
Contact's Fax Number	215-591-8812
Original Submission Date(s)	December 27, 2006
Submission Date(s) of Amendment(s) Under Review	September 15, 2008; March 27, 2009; June 23,2009; May 7, 2010; June 11, 2010; *September 8, 2010 and September 15, 2010*
Reviewer	Paramjeet Kaur, Ph.D.
Study Number (s)	S08-0114
Study Type (s)	Fasting
Strength (s)	30 mg
Clinical Site	Gateway Medical Research, Inc. – Cetero Research
Clinical Site Address	400 Fountain Lakes Blvd. St. Charles, MO 63301 Deryk L. McDowell, M.D.
Analytical Site	(b) (4).
Analytical Site Address	(b) (4)
OUTCOME DECISION	**ADEQUATE**

OVERALL REVIEW RESULT	**ADEQUATE**		
WAIVER REQUEST RESULT	**ADEQUATE**		
DSI REPORT RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
7	**FASTING STUDY**	**30 MG**	**ADEQUATE**
26 & 28	**DISSOLUTION**	**15 MG and 30 MG**	**ADEQUATE**

Review of Two Amendments

1 EXECUTIVE SUMMARY

The original application submitted by the firm on December 27, 2006 contained the results of both dissolution testing and single dose fasting and fed bioequivalence studies comparing its test product Lansoprazole Delayed Release (DR) Orally Disintegrating Tablets (ODT), 30 mg to the corresponding reference product Prevacid® SoluTab™ (Lansoprazole), 30 mg, manufactured by Tap Pharmaceuticals. The firm conducted dissolution testing using its own proposed method (DFS N 078730 N 000 27-Dec-2006), and, was requested to conduct the dissolution testing using the FDA-recommended method. The firm submitted a bioequivalence amendment on October 12, 2007 generating new dissolution profiles for 15 mg and 30 mg strengths of its test product using the FDA-recommended method. Based on the submitted data the Division of Bioequivalence (DBE) recommended the following specifications:

Acid stage: NMT (b) (4) % in 60 minutes
Buffer stage: NLT (Q) in 30 minutes

The bioequivalence (fasting and fed) studies and dissolution method was found acceptable; however, the application was found to be incomplete due to a dissolution deficiency (dissolution specifications). The firm was asked to accept and acknowledge the DBE recommended dissolution method and specifications (DARRTS, ANDA 078730, REV-BIOEQ-01(General Review); final date 12/21/2007).

On March 27, 2009 the firm submitted a supplemental application – additional manufacturing site at Sellersville, PA - for Lansoprazole DR ODT Tablets, 30 mg. Based on the dissolution data submitted in the supplemental application (March 27, 2009), firm acknowledged the FDA-recommended dissolution method and following specifications on June 23, 2009.

Specifications: Acid stage: NMT (b) (4) % in 60 minutes
Buffer stage: NLT % (Q) in 30 minutes

However, during course of the CMC review of this supplemental application, the Division of Chemistry 2 (DC 2) noted some discrepancies in the test product formulation compared to the reference listed drug (RLD) product. On May 7, 2010, the firm submitted the additional in vitro data in response to deficiency letter dated April 23, 2010 sent to the firm and indicated that Sellersville, PA site was withdrawn.

Initially, the DBE proposed that the buffer stage dissolution specification for Teva's test products, 15 mg and 30 mg could be NLT (b) (4) % (Q) in 30 minutes. However, since dissolution testing of Teva's test Lansoprazole DR ODT, 15 mg (batches # L61009 and L61010) exhibit mean lansoprazole release only about (b) (4) % at 60 minutes in the buffer stage[1], the OGD ANDA 78730 review team, at an internal meeting, raised concerns about

[1] DARRTS; ANDA 78730, supporting document# 22, final date: 5/7/10

this apparent incomplete dissolution (Since this is an ODT, it was expected that lansoprazole from this dosage form would be 100% dissolved at 60 minutes). The team asked Teva to provide the possible reasons for incomplete drug release[2]. On June 11, 2010, the firm submitted additional dissolution data, including use of PEAK vessels in response to the June 4, 2010 information request, which was found unacceptable; and based on the summary review of all in-house dissolution data on the lansoprazole DR ODT by OGD management and internal discussions (please refer to DARRTS, ANDA 078730, REV-BIOEQ-01(General Review) final date 7/20/10, and 7/27/2010), the firm was informed that FDA does not recommend the use of PEAK vessel and to acknowledge the FDA-recommended dissolution method and following specifications[3]:

Specifications: Acid stage: NMT (b) (4) % in 60 minutes
Buffer stage: NLT % (Q) in 30 minutes

On August 26, 2010, a teleconference took place between the Teva and FDA representatives in response to Teva's request regarding the clarification on dissolution specification for the buffer stage of NLT (b) (4) % (Q) in 30 minutes. During teleconference, firm was requested to submit the following information to gain understanding about the possible reasons for slow dissolution of lansoprazole from the test and reference products during buffer stage of dissolution: 1) if paddle rotation speed is stopped while changing from acid stage to buffer stage, 2) pH values of the dissolution media at different sampling times, 3) effect of rate of addition of buffer phase, 4) recovery data of the assay method used for dissolution testing, and 5) dissolution testing data for test and reference products in acid and buffer stages, conducted separately.[4]

On 9/08/10 and 9/15/10, firm responded to deficiency letter dated 7/28/2010 and information requested during teleconference on 8/26/10. Teva has mentioned that, "the root cause for the low dissolution values obtained during drug product dissolution testing was due to a bias in the analytical method used for testing the dissolution samples. In an effort to improve the overall repeatability of the dissolution method, the procedure has been modified to specify that paddle rotation is maintained while the buffer solution is added to the acid media, and a more accurate UV method is proposed for analysis of the dissolution sample". The firm's response is acceptable.

The firm has conducted acceptable comparative dissolution testing on all strengths using the FDA-recommended dissolution method (this review). On September 8, 2010, the firm has acknowledged its acceptance of the following FDA-recommended dissolution method and specifications:

Specifications: Acid stage: NMT (b) (4) % in 60 minutes
Buffer stage: NLT % (Q) in 30 minutes

[2] DARRTS; ANDA 078730, COR-ANDAIR-01(Advice/Information Request); final date: 6/14/2010
[3] DARRTS, ANDA 078730, COR-ANDADE-01(Bio Incomplete Deficiencies); final date: 7/28/2010
[4] For detailed information please refer to DARRTS, ANDA 078730, FRM-MINUTES-01(Internal Meeting Minutes), final date: 8/30/10

The formulation for 15 mg strength is proportionally similar to the 30 mg strength of the test product which underwent bioequivalence testing. The DBE deems the test lansoprazole delayed release orally disintegrating tablets, 15 mg, bioequivalent to the reference Prevacid® SoluTab™ (Lansoprazole), 15 mg based on criteria set forth in section 21 CFR § 320.24 (b) (6).

The application is acceptable with no deficiencies.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Review of Submission

REVIEW OF AMENDMENT SUBMITTED ON SEPTEMBER 08, 2010:

Review of Deficiency letters sent to firm on July 28, 2010:

Deficiency Comment #1:

The DBE acknowledges your submission of dissolution data using PEAK Vessels. We concluded that we do not recommend the use of the PEAK Vessel for dissolution testing of Lansoprazole Delayed Release Orally Disintegrating Tablets. (b) (4) the use of PEAK Vessels for dissolution testing for Lansoprazole Delayed Release Orally Disintegrating Tablets.

Firm's Response to the Deficiency Comment #1:

Please be advised that Teva does not propose the use of PEAK vessels for routine testing of the drug product. The data obtained using PEAK dissolution vessels was presented as additional information for the purpose of investigating the cause of low dissolution values obtained while testing the drug product with the recommended dissolution method.

Reviewer's Comment on the Deficiency# 1:

The firm's response to deficiency comment# 1 is acceptable.

Deficiency Comment #2:

Your application is incomplete pending your acceptance of following FDA-recommended interim dissolution method and specifications:

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Specifications:	Acid stage: NMT (b) (4) % in 60 minutes Buffer stage: NLT % (Q) in 30 minutes

Please indicate whether you accept the above interim dissolution method and specifications.

Firm's Response to the Deficiency Comment #2:

We hereby accept the recommended interim dissolution method and specification as follows:

Medium:	500mL of 0.1N HCl for the first hour followed by 900mL phosphate buffer pH 6.8 with 5mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75rpm
Specifications:	Acid Stage: NMT (b) (4) % in 60 minutes Buffer Stage: NLT % (Q) in 30 minutes

Reviewer's Comment on the Deficiency# 2:

Firm's response to FDA-recommended dissolution method and specifications is acceptable.

<u>Review of Information Requested from Teva during teleconference on August 26, 2010:</u>

Deficiency Comment #1

It was requested that Teva provides information whether paddle rotation was stopped when changing from acid stage to buffer stage?

Firm's Response to Deficiency Comment #1:

In performing the method as originally proposed, the dissolution apparatus was stopped during the addition of the buffer phase. The method has been revised to specify the paddles continue to rotate while the buffer is added to the acid phase.

Reviewer's Comment on Deficiency #1:

The DBE acknowledges that dissolution method has been revised to specify the paddles continue to rotate while the buffer is added to the acid phase.

Deficiency Comment #2

Please provide the pH of the buffer media at the beginning, and throughout the buffer stage at each sampling time point.

Firm's Response to Deficiency Comment #2:

To determine if the pH of the individual vessels were influenced over time, two sets of 6- unit dissolution tests were performed to monitor the dissolution medium pH of each dissolution vessel at each time point after addition of the buffer medium. The following pH results were obtained:

15mg Batch L-61001				30mg Batch L-60002			
Buffer stage-Time (min.)				Buffer stage-Time (min.)			
0	10	20	30	0	10	20	30
							(b) (4)

The pH of the dissolution medium, after addition of the buffer, is stable over the duration of the dissolution test.

Reviewer's Comment on Deficiency #2:

As shown in the above table, the pH of dissolution media for lansoprazole DR ODT, 15 mg (batch# L-61001) and 30 mg (batch# L-60002) after addition of buffer stage over 30 minutes does not change by more than ± 0.04.

The firm's response to deficiency comment# 2 is acceptable.

Deficiency Comment #3:

Please provide the information if firm has evaluated the effect of the rate of buffer addition to the acid media during dissolution testing.

Firm's Response to Deficiency Comment #3:

The addition of buffer solution to the acid media occurs in less than a minute. As such, further studies related to addition rate were deemed unnecessary.

Reviewer's Comment on Deficiency #3:

The firm's response to deficiency # 3 is acceptable.

Deficiency Comment #4:

Please provide data where the acid stage and the buffer stage dissolutions are run as standalone tests 12 units of both Teva's product and the RLD product.

Firm's Response to Deficiency Comment #4:

Twelve-unit dissolution profiles were conducted on both the Teva product and the RLD product using new tablets for the buffer stage test. The resulting dissolution profiles demonstrated comparability between the two products, but did not achieve significant improvement in the buffer stage. Individual data is provided in Attachment 4 and is summarized as follows:

	Acid Stage	Buffer Stage		
	60 min	30 min	45 min	60 min
15 mg Teva Average	0%	88	90	90
15 mg Prevacid Average	0%	93	92	90
30 mg Teva Average	0%	85	90	90
30 mg Prevacid Average	0%	92	93	91

Reviewer's Comment on Deficiency #4:

The firm has provided the following data in Attachment 4 and has mentioned that acid stage and buffer stage were performed separately.

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Acid stage (60 min)	Collection Times (Buffer Stage)			Study Report Location
					30 min	45 min	60 min	
Lansoprazole Delayed-release Orally Disintegrating Tablets, Batch No: L-61001	15 mg Tablets	12	Mean	0	88	90	90	Attachment 4
			Range	0-0	(b) (4)			
			%CV	0	6.6	4.9	4.3	
Prevacid® Solu Tab ™ (Lansoprazole) Delayed-release Orally Disintegrating Tablets, Batch No: 856662E21	15 mg Tablets	12	Mean	0	93	92	90	Attachment 4
			Range	0-0	(b) (4)			
			%CV	0	4.0	3.1	3.0	
Lansoprazole Delayed-release Orally Disintegrating Tablets, Batch No: L-60002	30 mg Tablets	12	Mean	0	85	90	90	Attachment 4
			Range	0-0	(b) (4)			
			%CV	0	11.0	4.7	4.5	
Prevacid® Solu Tab ™ (Lansoprazole) Delayed-release Orally Disintegrating Tablets, Batch No: 811472E23	30 mg Tablets	12	Mean	0	92	93	91	Attachment 4
			Range	0-0	(b) (4)			
			%CV	0	3.9	3.5	3.3	

As shown in the above table, for dissolution testing conducted in buffer stage separately, the reference products, 15 mg and 30 mg meet specification of NLT (b) (4) % (Q) in 30 minutes in buffer stage except one tablet for 15 mg at 60 minutes. However, the test products, 15 mg and 30 mg do not meet the DBE recommended specification of NLT (b) (4) % (Q) in 30 minutes in buffer stage at S1 level.

Deficiency Comment #5:

Please provide recovery data of the assay method of dissolution samples.

Firm's Response to Deficiency Comment #5:

The original accuracy studies were conducted by comparison of dissolution results obtained using 2 different HPLC methods. Additional accuracy studies were conducted by spiking placebo samples with known levels of Lansoprazole. The results of the recovery study revealed a negative bias of approximately 10% when using an HPLC method for analysis of dissolution samples.

The following table summarizes the findings of the recovery study using the HPLC method:

Spiked concentration (% labeled amount)	50%	100%	120%
% Recovery	93%	90%	93%

As a result of these findings, a new analytical method utilizing UV detection was developed for this product. The method is based on the analytical method specified in the USP monograph for Lansoprazole Delayed-Release Capsules. A recovery study was performed using the UV method, with the following values obtained:

Spiked concentration (% labeled amount)	50%	100%	120%
% Recovery	103%	99%	99%

The analytical method has been subsequently validated. The validation report is provided in **Attachment 5**.

Reviewer's Comment on Deficiency #5:

The results of UV method for determination of lansoprazole in the buffer stage of dissolution testing as provided in Attachment 5 are listed in the table below:

<table>
<tr><th>Information Requested</th><th>Analyte: lansoprazole</th></tr>
<tr><td>Method validation report location</td><td>Supporting Document 26, Attachment 5</td></tr>
<tr><td>Study Report Number/Method No</td><td>QDP0022119</td></tr>
<tr><td>Analyte</td><td>Lansoprazole</td></tr>
<tr><td>Method description</td><td>UV at 285 nm</td></tr>
<tr><td>Standard curve concentrations (mg/mL)</td><td>0.001253, 0.002505, 0.006265, 0.01253, 0.01504, 0.02005, 0.02506, 0.03007, 0.04010</td></tr>
<tr><td>Accuracy (recovery)</td><td>Average recovery and RSD for each duplicate is as follow:
<table>
<tr><td>Analyte</td><td>50%</td><td>100%</td><td>120%</td></tr>
<tr><td>% lansoprazole</td><td>103%</td><td>99%</td><td>99%</td></tr>
</table></td></tr>
<tr><td>Method repeatability and intermediate precision</td><td>
<table>
<tr><td>Dosage unit</td><td>% Dissolved* (RSD %)</td><td>% Dissolved** (RSD %)</td><td>Relative Difference (%)</td></tr>
<tr><td>15 mg tablets (n = 6)</td><td>99 (3.1)</td><td></td><td></td></tr>
<tr><td>30 mg tablets (n = 6)</td><td>91 (1.8)</td><td>97 (5.4)</td><td>6%</td></tr>
</table>
*Method Repeatability ** Intermediate Precision</td></tr>
<tr><td>Stability of standard solution</td><td>24 hours @ RT*</td></tr>
<tr><td>Stability of samples solution</td><td>12 hours @ RT*</td></tr>
<tr><td>Specificity</td><td>The placebo response was less than 2% of the nominal working concentration. The method was found to be specific.</td></tr>
<tr><td>Effect of pH of dissolution media</td><td>Effect of pH of buffer media at pH 6.6 and 6.9 on the dissolution rate was evaluated and compared to pH 6.8 (according to method), the results of which are summarized in the below table:
<table>
<tr><td></td><td>% Lansoprazole Dissolved Labeled Amount</td></tr>
<tr><td>pH of dissolution media</td><td>Avg (%)</td></tr>
<tr><td>According to method</td><td>91</td></tr>
<tr><td>pH 6.6</td><td>96</td></tr>
<tr><td>pH 6.9</td><td>93</td></tr>
<tr><td>% Max relative difference between average results</td><td>5%</td></tr>
</table></td></tr>
</table>

*RT = Room temperature,

The analytical method is acceptable.

Deficiency Comment #6

Please provide samples of both the test and reference products to FDA for evaluation.

Firm's Response to Deficiency Comment #6:

The requested samples are currently in transit from our site in Israel, and will be provided to your attention under separate cover, as soon as they are available.

Reviewer's Comment on Deficiency #6:

The DBE acknowledges that firm will send the samples of both the test and RLD product to FDA for evaluation.

Additional Comments

Teva mentioned that, **"***they have determined the root cause for the low dissolution values obtained during drug product dissolution testing is due to a bias in the analytical method used for testing the dissolution samples. In an effort to improve the overall repeatability of the dissolution method, the procedure has been modified to specify that paddle rotation is maintained while the buffer solution is added to the acid media, and a more accurate UV method is proposed for analysis of the dissolution samples*"**.**

Firm's response to reasons for low dissolution of lansoprazole is acceptable.

In Attachment 6, firm has provided the revised analytical method for dissolution testing of enteric coated (b) (4) and Attachment 7 contains the revised analytical method for dissolution testing of final drug product, which mentions that during acid stage, sample will be analyzed by HPLC method; and during buffer stage by UV spectrophotometer determination.

<u>REVIEW OF AMENDMENT SUBMITTED ON SEPTEMBER 15, 2010</u>

On September 15, 2010 Teva Pharmaceuticals USA submitted an addendum to Bioequivalence Amendment dated September 8, 2010 to fulfill a commitment to submit comparative dissolution data comparing 12 units of each strength of Teva's product to the RLD product, using the revised method. Firm provided Attachment 1 and 2, containing bioequivalence summary table 5 and comparative dissolution profile report, respectively.

Review of Firm's data submitted in Attachments# 1 and #2 dated 9/15/10:

The firm has provided the following dissolution summary table in Attachment 1

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddles)
	Speed of Rotation:	75rpm
	Medium:	500mL of 0.1N HCl for the first hour followed by 900mL phosphate buffer pH 6.8 with 5mM SDS (second hour)
	Volume:	500mL (Acid Stage), 900mL (Buffer Stage)
	Temperature:	37°C
Firm's Proposed Specifications	Acid Stage: NMT (b) (4) in 60 minutes Buffer Stage: NLT (Q) in 30 minutes	
Dissolution Testing Site (Name, Address)	Teva Pharmaceuticals Industries Kfar Saba, Israel	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 0min	10min	20min	30min	45min	60min	Study Report Location
	September 12, 2010	Lansoprazole Delayed-Release Orally Disintegrating Tablets Batch L61001 Mfg Date: June 3, 2009	15 mg Tablet	12	Mean	0	65	92	98	99	100	Attachment 2
					Range	0	(b) (4)					
					%CV	0	21	11	4	5	4	
	September 12, 2010	Prevacid SoluTab Batch 8856662E21 Exp. Date: July 2013	15 mg Tablet	12	Mean	0	97	98	97	97	98	Attachment 2
					Range	0	(b) (4)					
					%CV	0	5	5	5	5	5	
	September 12, 2010	Lansoprazole Delayed-Release Orally Disintegrating Tablets Batch L60002 Mfg Date: June 3, 2009	30 mg Tablet	12	Mean	0	54	87	95	95	95	Attachment 2
					Range	0	(b) (4)					
					%CV	0	19	13	4	4	4	
	September 12, 2010	Prevacid SoluTab Batch 811472E23 Exp. Date: November 2011	30 mg Tablet	12	Mean	0	77	91	95	96	97	Attachment 2
					Range	0	(b) (4)					
					%CV	0	18	11	7	4	3	

*For the 60-min sampling time point of Batch L60002, the data reflects n=6 units; due to technical problem data are missing for 6 tablets.

In Attachment 2, firm has mentioned that analytical method used for the determination of lansoprazole is HPLC and UV during the acid stage and buffer stage, respectively. It should be noted that after sampling 20 mL of the acid stage samples from each vessel, 420 mL of the buffer stage concentrated buffer were added in each vessel *without stopping paddles rotation*.

The data provided in the Attachment 2 does not mention whether 5 mM SDS was added to phosphate buffer, pH 6.8 or not. Although, above table provided in Attachment 1 indicates that 5 mM SDS has been added to phosphate buffer, pH 6.8.

Lansoprazole DR ODT, 15 mg exhibit high variability (% CV) at 10 and 20- min in buffer stage (10.9% - 20.5%) as compared to Prevacid® DR ODT, 15 mg (4.5%- 5.1%). In addition, as shown in the table below, one tablet for the reference product and two tablets for the test product, 15 mg release more than 105% of lansoprazole in the buffer media.

TEVA 15mg tablets Batch # L61001					
Tablet #	% Lansoprazole of Labeled Claim Dissolved				
	Sampling Time (minutes)				
	10	20	30	45	60
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
% Avg.	65	92	98	99	100
% RSD	20.5	10.9	4.0	4.9	4.1

Pravacid 15mg tablets Lot # 8856662E21					
Tablet #	% Lansoprazole of Labeled Claim Dissolved				
	Sampling Time (minutes)				
	10	20	30	45	60
1					(b) (4)
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
% Avg.	97	98	97	97	98
% RSD	5.1	4.5	4.9	5.3	4.9

The lansoprazole DR ODT, 15 mg and 30 mg meet the DBE recommended specifications:

Acid stage: NMT (b) (4) % in 60 minutes
Buffer stage: NLT % (Q) in 30 minutes

The firm's response to FDA-recommended dissolution method and specifications is acceptable.

3.2 Deficiency Comments

None

3.3 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study (S08-0114) conducted by Teva Pharmaceuticals USA on its Lansoprazole Delayed-Release Orally Disintegrating Tablets 30 mg, lot # 2621-015 comparing it to TAP Pharmaceuticals' Prevacid® SoluTab™ (Lansoprazole) Delayed-Release Orally Disintegrating Tablets 30 mg, lot # 578352E22.

2. The firm's in vitro dissolution testing is acceptable. We acknowledge that the firm will conduct dissolution testing using the following FDA-recommended method

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm

   The test product should meet the following specifications: acid stage: NMT (b)(4)% in 60 minutes, and buffer stage: NLT (b)(4) % (Q) in 30 minutes.

3. The dissolution testing conducted by Teva Pharmaceuticals on its Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg, lot #L61001; and 30 mg, lot# 60002 is acceptable. The firm has conducted acceptable in vivo bioequivalence testing (submission date: September 15, 2008) comparing 30 mg of lansoprazole delayed-release orally disintegrating tablets of the test product with 30 mg tablets of the reference product Prevacid® SoluTab™ manufactured by Tap Pharmaceuticals. The formulation for the 15 mg strength is proportionally similar to the 30 mg strength of the test product which underwent bioequivalence testing. The DBE deems the test lansoprazole delayed release orally disintegrating tablets, 15 mg bioequivalent to the reference Prevacid® SoluTab™ (Lansoprazole), 15 mg under Section 21 CFR § 320.24 (b) (6).

3.4 Comments for Other OGD Disciplines

Discipline	Comment
	None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078730

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time.

We acknowledge that you will perform dissolution testing using the following dissolution method and specifications for your Lansoprazole Delayed Release Orally Disintegrating Tablets:

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Specifications:	Acid stage: NMT (b) (4) % in 60 minutes Buffer stage: NLT (b) (4) % (Q) in 30 minutes

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4 OUTCOME PAGE

ANDA: 78730

Completed Assignment for 78730 ID: 12114

Reviewer: Kaur, Paramjeet **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
12114	9/8/2010	Other	Study Amendment	1	1	Edit	Delete
12114	9/15/2010	Other	Study amendment new dissolution data	1	1		
				Bean Total:	2		

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment	
Study Amendment-deficiency comments-dated 9/8/2010	1
Study Amendment-deficiency comments-dated 9/15/2010	1
Total number of Complexity Points	2

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

/s/

PARAMJEET KAUR
09/22/2010

CHANDRA S CHAURASIA
09/22/2010

BARBARA M DAVIT
09/22/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-730

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

December 27, 2006

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS,
15mg and 30mg

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15mg and 30mg.

Enclosed are archival and review copies assembled in accord with the Office of Generic Drugs' February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of **11** volumes; **5** for the archival copy and **6** for the review copy.

The application contains a full report of 2 *in vivo* bioequivalence studies. These studies compared Lansoprazole Delayed-Release Orally Disintegrating Tablets, 30mg manufactured by TEVA Pharmaceutical Industries, Ltd. to the reference listed drug, PREVACID® Delayed-Release Orally Disintegrating Tablets, 30mg under both fasting and post-prandial conditions.

Two separately bound copies of the drug substance and finished product analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/ds
Enclosures

78730

Authorized to use Fax of Martin Shimer 11 January 2007

TEVA FACSIMILE

TEVA PHARMACEUTICALS USA
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454
Phone: (215) 591-3000

FAX: (215) 591-8812

TO: Martin Shimer	DATE: January 3, 2007
COMPANY: FDA	
FAX NUMBER: 301-827-5911	FROM: Jill Pastore, R.Ph.
NO. OF PAGES: 1	DIRECT LINE: 215-591-3150

LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg
RECEIPT OF NOTICE UNDER SECTION 505(j)(2)(B)(I) and 21 CFR 314.95

Dear Mr. Shimer:

TEVA Pharmaceuticals USA submitted an ANDA for the above-referenced product on December 27, 2006. Therefore, TEVA will be providing Notices of Certification for U.S. Patents #4,628,098; #5,026,560; #5,045,321; #5,093,132; #5,433,959; #5,464,632; and #6,328,994 to TAP Pharmaceuticals as the holder of NDA #021428 for PREVACID® Delayed-Release Orally Disintegrating Tablets, and to the patent assignees, in accord with 21 CFR 314.95(b).

The purpose of this communication is to inform you of our intent to utilize Federal Express Tracking Documentation as evidence of receipt of Notice of Certification by the NDA holder and patent assignees in lieu of a United States Postal Service return receipt, in accord with 21 CFR 314.95(e).

Response to this correspondence may be made to my attention by telephone at (215) 591-3150 or via facsimile at (215) 591-8812.

Sincerely,

Jill Pastore

Jill Pastore, R.Ph.
Director, Regulatory Affairs

78-730
Please file in ANDA 78-730

PROMPT DELIVERY IS APPRECIATED

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 78-730 **FIRM NAME Teva Pharmaceuticals USA**

DRUG NAME **Lansoprazole Delayed-Release Orally Disintegrating Tablets**

DOSAGE FORM Disintegrating Tablets, 15 mg and 30 mg
SUBJ: Request for examination of: Bioequivalence Study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☒	**Waiver meets statutory requirements N/A**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Zakaria Wahba
Reviewer

_____ Date: _____
Chandra Chaurasia
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			Two BE studies (under fasting and fed conditions)on the 30 mg strength.
Assay Methodology	☒	☐			
Procedure SOP	☒	☐			
Methods Validation	☒	☐			
Study Results Ln/Lin	☒	☐			
Adverse Events	☒	☐			
IRB Approval	☒	☐			
Dissolution Data	☒	☐			
Pre-screening of Patients	☒	☐			
Chromatograms	☒	☐			
Consent Forms	☒	☐			
Composition	☒	☐			
Summary of Study	☒	☐			
Individual Data & Graphs, Linear & Ln	☒	☐			
PK/PD Data Disk Submitted)	☒	☐			Electronic data submitted.
Randomization Schedule	☒	☐			
Protocol Deviations	☒	☐			
Clinical Site	☒	☐			
Analytical Site	☒	☐			

Study Investigators	☒	☐			
Medical Records	☒	☐			
Clinical Raw Data	☒	☐			
Test Article Inventory	☒	☐			
BIO Batch Size	☐	☒			Not provided in the submission
Assay of Active Content Drug	☒	☐			
Content Uniformity	☒	☐			
Date of Manufacture	☒	☐			
Exp. Date of RLD	☒	☐			
BioStudy Lot Numbers	☒	☐			
Statistics	☒	☐			
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			
Waiver requests for other strengths / supporting data	☒	☐			15 mg strength

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. This application is submitted in an electronic format.
2. The RLD is PREVACID (LANSOPRAZOLE TABLET, DELAYED RELEASE, ORALLY DISINTEGRATING; 30 gm) by TAP PHARM; NDA #21428, approved date: 08/30/02.
3. The application contains two BE studies (Fasted and Fed) one the 30 mg strength.
4. The information on the bio batch size is not provided in the ANDA volumes related to BE submission.

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

/s/

Chandra S. Chaurasia
3/7/2007 06:41:50 AM

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 78-730 **FIRM NAME**: TEVA PHARMACEUTICALS USA

RELATED APPLICATION(S): SEE 77-255 FOR LANSOPRAZOLE DELAYED-RELEASE CAPSULES USP, 15 MG AND 30 MG FROM TEVA PHARMACEUTICALS PN 12/15/06 (RLD PREVACID) A 1.1 WITH F. FANG

First Generic Product Received? YES

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☐ **Micro Review (No)**
☐ **BST**	☒ **BDI**	

DRUG NAME: LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING
DOSAGE FORM: TABLETS, 15 MG AND 30 MG

Random Queue: 7
Chem Team Leader: M. Scott Furness PM: TBD Labeling Reviewer: Koung Lee

Letter Date: DECEMBER 27, 2006	**Received Date**: DECEMBER 27, 2006
Comments: EC - 2 YES **On Cards:** YES **Therapeutic Code:** 8030700 ANTI-ULCER	
Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)** **Review copy**: YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) **YES** (Required for Non-USP drugs) YES	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST Rebekah Granger **Date 03/26/2007**	**Recommendation:** ☐ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

ADDITIONAL COMMENTS REGARDING THE ANDA:
Based on the Handbook of Pharmaceutical Excipients – page 346, [redacted] (b) (4) is also known as [redacted] (b) (4) [redacted] (b) (4). [redacted] (b) (4) is an alternative to [redacted] (b) (4). Look at comments on Section VI.4, page 150.

Top 200 Drug Product:

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☒
Sec. II	**Basis for Submission** **NDA# : 21-428** Ref Listed Drug: PREVACID Firm: TAP PHARMACEUTICALS ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒

Sec. III

Patent Certification

1. Paragraph: IV YES Page 10
2. Expiration of Patent: 5/17/2019

A. Pediatric Exclusivity Submitted?

B. Pediatric Exclusivity Tracking System checked?

Exclusivity Statement: YES

Patent and Exclusivity Search Results from query on Appl No 021428 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021428	002	4628098	MAY 10,2009			
021428	002	5013743	FEB 12,2010			U-452
021428	002	5026560	JUN 25,2008			
021428	002	5045321	SEP 03,2008			
021428	002	5093132	SEP 03,2008			
021428	002	5433959	SEP 03,2008			
021428	002	5464632	NOV 07,2012			
021428	002	6123962	FEB 13,2007			
021428	002	6328994	MAY 17,2019			
021428	002	6749864	FEB 13,2007		Y	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021428	002	NPP	JUN 17,2007

Patent Use Codes

This page defines the patent use codes.

Code	Definition
U-452	USE OF LANSOPRAZOLE FOR COMBATTING DISEASES CAUSED BY THE GENUS CAMPYLOBACTER (C.PYLORI=H.PYLORI)

Exclusivity Codes

This page defines the exclusivity codes.

Code	Definition
NPP	NEW PATIENT POPULATION

Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Route of administration SAME 4. Dosage Form SAME 5. Strength SAME	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL YES 2. 1 RLD label and 1 RLD container label YES	☒
Sec. VI		☒
Study Type		☒

Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg *Abbreviated New Drug Application*

Table 2. Statistical Summary of the Comparative Bioavailability Data

Lansoprazole Dose (1 x 30 mg) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No. 2006-1270)				
A vs. C				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt	1682.81	1561.35	107.78	100.11 - 116.03
AUCinf	1715.59	1587.38	108.08	100.33 - 116.42
Cmax	421.73	369.64	114.09	103.25 - 126.07
B vs. C				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt	1655.25	1561.35	106.01	98.47 - 114.13
AUCinf	1689.20	1587.38	106.41	98.75 - 114.67
Cmax	415.51	369.64	112.41	101.73 - 124.21
Fasting Bioequivalence Study (Study No. 2006-1287)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt	2167.17	2218.12	97.70	93.27 - 102.35
AUCinf	2205.13	2256.89	97.71	93.33 - 102.28
Cmax	876.55	955.10	91.77	85.13 - 98.94

Table 2. Statistical Summary of the Comparative Bioavailability Data

Lansoprazole Dose (1 x 30 mg) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No. 2006-1270)				
A vs. C				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt	1682.81	1561.35	107.78	100.11 - 116.03
AUCinf	1715.59	1587.38	108.08	100.33 - 116.42
Cmax	421.73	369.64	114.09	103.25 - 126.07
B vs. C				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt	1655.25	1561.35	106.01	98.47 - 114.13
AUCinf	1689.20	1587.38	106.41	98.75 - 114.67
Cmax	415.51	369.64	112.41	101.73 - 124.21
Fasting Bioequivalence Study (Study No. 2006-1287)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt	2167.17	2218.12	97.70	93.27 - 102.35
AUCinf	2205.13	2256.89	97.71	93.33 - 102.28
Cmax	876.55	955.10	91.77	85.13 - 98.94

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. Adhesion Study c. Skin Irritation/Sensitization Study	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation YES 2. Inactive ingredients as appropriate YES	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers YES b. Type II DMF authorization letters or synthesis YES – DMF #17551 c. COA(s) specifications and test results from drug substance mfgr(s) YES d. Applicant certificate of analysis YES e. Testing specifications and data from drug product manufacturer(s) YES f. Spectra and chromatograms for reference standards and test samples YES g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified YES b. Testing specifications (including identification and characterization) YES c. Suppliers' COA (specifications and test results) YES d. Applicant certificate of analysis YES	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address YES 2. Functions YES 3. CGMP Certification/GLP YES 4. CFN numbers YES	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3.If sterile product: Aseptic fill / Terminal sterilization 4.Filter validation (if aseptic fill) 5. Reprocessing Statement YES – Page 815 **<u>PROPOSED COMMERCIAL BATCH SIZE</u>** 15 mg – (b) (4) Tablets 30 mg – (b) (4) Tablets	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES 2. In-process Controls - Specifications and data YES LOT #K-36985 (15 mg) LOT #K-36986 (30 mg) 15 mg / 30 mg Theoretical Yield: (b) (4) Tablets / (b) (4) ablets Made: Tablets / Tablets Packaged: Tablets / Tablets	☒

Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data (Type III DMF References) YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing N/A 5. Source of supply and suppliers address YES	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data YES 2. Certificate of Analysis for Finished Dosage Form YES	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted YES 2. Post Approval Commitments YES 3. Expiration Dating Period YES – 24 Months 4. Stability Data Submitted YES a. 3 month accelerated stability data YES b. Batch numbers on stability records the same as the test batch YES	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance YES 2. Finished Dosage Form YES 3. Same lot numbers - Not Mentioned	☒
Sec. XVII	**Environmental Impact Analysis Statement** YES	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature): YES – Page 1532 3. List of Convictions statement (original signature)	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe

Active Ingredient Search - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Search Favorites The My Web Search Bar has been improved !

Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/doc Go Links

021428	No	LANSOPRAZOLE	TABLET, DELAYED RELEASE, ORALLY DISINTEGRATING; ORAL	15MG	PREVACID
021428	Yes	LANSOPRAZOLE	TABLET, DELAYED RELEASE, ORALLY DISINTEGRATING; ORAL	30MG	PREVACID
021507	Yes	LANSOPRAZOLE; NAPROXEN	CAPSULE, DELAYED REL PELLETS, TABLET; ORAL	15MG,N/A;N/A,500MG	PREVACID NAPRAPAC 500 (COPACKAGED

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Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/doc Go Links

Search results from the "OB_Rx" table for query on "021428."

Active Ingredient:	LANSOPRAZOLE
Dosage Form;Route:	TABLET, DELAYED RELEASE, ORALLY DISINTEGRATING; ORAL
Proprietary Name:	PREVACID
Applicant:	TAP PHARM
Strength:	15MG
Application Number:	021428
Product Number:	001
Approval Date:	Aug 30, 2002
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	LANSOPRAZOLE
Dosage Form;Route:	TABLET, DELAYED RELEASE, ORALLY DISINTEGRATING; ORAL
Proprietary Name:	PREVACID

Done Local intranet

Orange Boook Detail Record Search - Microsoft Internet Explorer

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Active Ingredient:	LANSOPRAZOLE
Dosage Form;Route:	TABLET, DELAYED RELEASE, ORALLY DISINTEGRATING; ORAL
Proprietary Name:	PREVACID
Applicant:	TAP PHARM
Strength:	30MG
Application Number:	021428
Product Number:	002
Approval Date:	Aug 30, 2002
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs

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Patent and Exclusivity Search Results from query on Appl No 021428 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021428	001	4628098	MAY 10,2009			
021428	001	5013743	FEB 12,2010			U-452
021428	001	5026560	JUN 25,2008			
021428	001	5045321	SEP 03,2008			
021428	001	5093132	SEP 03,2008			
021428	001	5433959	SEP 03,2008			
021428	001	5464632	NOV 07,2012			
021428	001	6123962	FEB 13,2007			
021428	001	6328994	MAY 17,2019			
021428	001	6749864	FEB 13,2007		Y	

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Patent and Exclusivity Search Results - Microsoft Internet Explorer

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Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/doc Go Links

Patent and Exclusivity Search Results from query on Appl No 021428 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021428	002	4628098	MAY 10,2009			
021428	002	5013743	FEB 12,2010			U-452
021428	002	5026560	JUN 25,2008			
021428	002	5045321	SEP 03,2008			
021428	002	5093132	SEP 03,2008			
021428	002	5433959	SEP 03,2008			
021428	002	5464632	NOV 07,2012			
021428	002	6123962	FEB 13,2007			
021428	002	6328994	MAY 17,2019			
021428	002	6749864	FEB 13,2007		Y	

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Following this page, 4 pages withheld in full - (b)(4)

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

/s/

Martin Shimer
3/29/2007 07:25:40 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-730

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg

DATE OF APPLICATION: December 27, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 27, 2006

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this

information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Timothy W Ames
Project Manager
301-827-0492

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
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/

Martin Shimer
3/29/2007 07:24:27 AM
Signing for Wm Peter Rickman

TAP PHARMACEUTICAL PRODUCTS INC.

675 North Field Drive
Lake Forest, IL 60045

May 25, 2007

MC

Gary J. Buehler, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, Maryland 20855

RE: Takeda Pharmaceutical Company, Ltd. and TAP Pharmaceutical Products Inc. v. TEVA Pharmaceuticals USA (Case No. 07-331, U.S.D.C., D. Del.) and TEVA Pharmaceuticals USA's ANDA 78-730

Dear Mr. Buehler:

ANDA 78-730 filed by TEVA Pharmaceuticals USA ("TEVA") contains certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), asserting that U.S. Patent Nos. 4,628,098, 5,026,560, 5,045,321, 5,093,132, 5,433,959, 5,464,632, and 6,328,994 are invalid, unenforceable, or will not be infringed by the manufacture, use or sale of TEVA's Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg*. Takeda Pharmaceutical Company, Ltd. ("Takeda") and TAP Pharmaceutical Products Inc. ("TAP") own and/or are the exclusive licensees these patents. TAP received TEVA's paragraph IV certifications on April 13, 2007.

The purpose of this letter is to advise FDA that on May 25, 2007, TAP and Takeda filed a lawsuit against TEVA in the United States District Court for the District of Delaware, Case No. 07-331, alleging the infringement of the above referenced patents. A copy of the lawsuit is enclosed.

Because TAP and Takeda have filed this lawsuit within 45 days of receipt of notice of TEVA's paragraph IV certifications, pursuant to 21 U.S.C. §355(j)(5)(B)(iii), the agency cannot approve ANDA 78-730 until "the expiration of the thirty-month period beginning on the date of the receipt of the notice…or such shorter or longer period as the court may order…."

* These are generic versions of TAP's Prevacid SoluTab® 15 mg and 30 mg. orally disintegrating tablets, respectively.

Should you have any questions concerning this matter, please feel free to contact me directly.

Sincerely,

Binit Kwankin for

Donna Helms
TAP PHARMACEUTICAL PRODUCTS INC.
Director, Regulatory Affairs
Phone: 847-582-4922
Fax: 847-582-2880

Enclosures:
Civil Cover Sheet
Complaint: Case No. 07-331

MINOR AMENDMENT

ANDA 78-730

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: TEVA Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Theresa Liu PROJECT MANAGER: (301) 827-5791

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 27, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lansoprazole Delayed-Release Orally Disintegrating Tablets.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__3__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

See attached chemistry comments.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-730 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

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B. Comments:

1. The labeling and bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

2. Please provide updated stability data for the exhibit batch.

3. Please provide representative packaged samples of the RLD and your own drug product to assist in our evaluation of the ANDA. The samples should be sent separately to:

Theresa Liu, Project Manager, Team 7
Division of Chemistry II
Office of Generic Drugs
7500 Standish Place
Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
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/

Michael S Furness
6/7/2007 02:43:24 PM

BIOEQUIVALENCY AMENDMENT

ANDA 78-730

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: TEVA Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Keri Suh PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 27, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __two__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCY

ANDA: 78-730 APPLICANT: Teva

DRUG PRODUCT: Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiency has been identified:

1. Please conduct and submit dissolution testing on all strengths of the test and reference products (12 units each) using the following FDA-recommended method:

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Sampling Times:	60 minutes for acid stage and 5, 10, 15, 20, 30, and 45 minutes, and until at least 80% of the labeled content is dissolved for buffer stage

2. The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in the ANDA submission.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
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/

Barbara Davit
6/26/2007 05:35:57 PM
Signing for Dale P Conner

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

October 12, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCY AMENDMENT
(CONTAINS CMC INFORMATION)

ORIG AMENDMENT
10/AB

ANDA #78-730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15mg and 30mg
BIOEQUIVALENCY AMENDMENT – RESPONSE TO JUNE 27, 2007 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a Bioequivalency Amendment to the above-referenced pending ANDA in response to a review letter from the Division of Bioequivalence dated June 27, 2007. For ease of review, please find a copy of this letter provided in **Attachment 1**. Your comments are addressed in the order in which they were presented in the review letter.

1. As requested, dissolution testing was conducted using the parameters outlined below:

Medium:	500 mL of 0.1N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5mM SDS (second hour)
Temperature:	37°C ±0.5°C
Apparatus:	USP Apparatus 2 (Paddle)
Rotation:	75 rpm
Sampling Times:	60 minutes for acid stage and 5, 10, 15, 20, 30 and 45 minutes, and until at least 80% of the labeled amount is dissolved, for buffer stage.

Please find dissolution profiles, obtained using the method outlined above,comparing Teva's Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 and 30mg to TAP Pharmaceuticals PREVACID® SoluTab™ (Lansoprazole) Delayed-Release Orally Disintegrating Tablets, 15 and 30mg provided in **Attachment 2.**

2. Please find a disc containing the requested bioequivalence summary tables provided in both MS-Word and PDF formats in **Attachment 3**.

Please note, during review of the data for the above referenced summary tablet, it was noted the certificate of analysis and comparative dissolution profile of TAP Pharmaceuticals PREVACID® SoluTab™, lot number 330269P22 (Reference product for Study 2006-1287) was inadvertently omitted from our original application. The certificate of analysis and comparative dissolution profile are provided in **Attachment 4** for completeness of file.

This information is submitted toward the continued review and approval of our pending application. Should there be any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ds
Enclosures

LD 11/15/07 & SD 11/16/07
Notice of certification to RLD holder + Patent Assignees on 4/12/07. RR dated 4/13 & 4/16/07
Notice of Litigation filed 5/25/07
RG 1/9/08

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
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philip.erickson@tevausa.com

November 15, 2007

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

XP

ANDA # 78-730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg
PATENT AMENDMENT – RECEIPT OF NOTICE OF CERTIFICATION/ END OF 45-DAY CLOCK/ LEGAL STATUS

Dear Mr. Buehler:

TEVA Pharmaceuticals USA hereby certifies that Notice of Certification for U.S. Patent Nos. 4,628,098, 5,026,560, 5,045,321, 5,093,132, 5,433,959, 5,464,632 and 6,328,994 was provided to TAP Pharmaceutical Products Inc., as the holder of NDA # 21-428 for Prevacid® SoluTab™ and to Takeda Pharmaceuticals Company, Limited, Ethypharm SA and Ethypharm, Societe Anonyme as assignees of the patents. Please be informed that the Notice, dated April 12, 2007, contained the information required under 21 CFR 314.95(c).

In accord with requirements set forth in the Medicare Prescription Drug & Modernization Act of 2003, Notice was sent to the necessary parties within twenty days of the postmark date of FDA's correspondence acknowledging filing of TEVA's ANDA for Lansoprazole Delayed-Release Orally Disintegrating Tablets. Documentation of the date of acknowledgement, which was received via facsimile on March 29, 2007, is provided in **Attachment 1** for your reference.

In accord with 21 CFR 314.95(e), TEVA Pharmaceuticals USA is hereby providing documentation in **Attachment 2** of the receipt of the above-referenced April 12, 2007 Notice. As evidenced by the enclosed documentation, Notice was received by TAP Pharmaceutical Products Inc., on April 13, 2007 and by Takeda Pharmaceuticals Company Ltd., Ethypharm SA and Ethypharm, Societe Anonyme on April 16, 2007. In

accord with 21 CFR 314.95(f), the 45-day period provided for in Section 505(j)(4)(B)(iii) of the Act started on April 17, 2007 and ended on May 31, 2007.

Please note that on January 5, 2007, Teva received approval from the Regulatory Support Branch to use Federal Express delivery documentation in lieu of U.S. Postal Service certified delivery in accord with 21 CFR 314.95(e). Therefore, the documentation of receipt of Notice provided herein is in the form of Federal Express delivery tracking.

We hereby inform the Agency of a suit filed by Takeda Pharmaceutical Company Limited, TAP Pharmaceutical Products, Inc., and Ethypharm, SA against TEVA Pharmaceuticals USA and TEVA Pharmaceutical Industries Ltd., concerning U.S. Patent Nos. 5,464,632, 4,628,098, 5,045,321, 6,328,994. The suit, Civil Action No. 07-331 was filed on May 25, 2007 in the United States District Court for the District of Delaware. The aforementioned suit was filed within the 45-day period. Teva hereby commits to provide the Agency notification of the outcome of this suit in an appropriate submission to this application. A copy of the complaint is provided in **Attachment 3** for your records.

No suit was brought against TEVA regarding U.S. Patent Nos. 5,026,560, 5,093,132 and 5,433,959 within the 45 day period. Resultant from the failure of the NDA holder and patent assignees to undertake legal action within the 45-day period, they have waived their right to pursue future legal action under the scope of Waxman-Hatch with respect to these patents.

This information is submitted for your continued review of ANDA 78-730. If there are any questions on the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/dl
Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDAs (See Attached List)

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

This letter is in reference to the Abbreviated New Drug Applications (ANDAs), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for (as noted in the attached list).

We refer you to our "Not Approvable" letters (See Attached List), which detailed the deficiencies identified during our reviews of your ANDAs. The Agency may consider an ANDA applicant's failure to respond to a "Not Approvable" letter within 180 days to be a request by the applicant to withdraw the ANDA under 314.120(b). Your amendments to the applications are overdue. You must amend your applications within 10 days of receipt of this letter. Otherwise, an action to withdraw these applications will be initiated per 21 CFR 314.99.

If you do not wish to pursue approval of these applications at this time, you should request withdrawal in accord with 21 CFR 314.65. A decision to withdraw these applications would be without prejudice to refiling.

If you have further questions you may contact Saundra Middleton, Project Manager, Regulatory Support Branch, at (240) 276-8421.

Please send all correspondence to the following address:

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

TEVA Pharmaceuticals USA

ANDA Number	Name	Non-approvable Date
76-337	Norethindrone and Ethinyl Estradiol Tablets USP, 1 mg/0.035 mg (28 day)	9/14/2005
76-338	Norethindrone and Ethinyl Estradiol Tablets USP, 0.5 mg/0.035 mg, 0.75 mg/0.035 mg and 1 mg/0.035 mg (28 day)	9/14/2005
(b) (4)		
78-407	Fluvastatin Capsules, 20 mg and 40 mg	3/13/2007
(b) (4)		
78-730	Lansoprazole Delayed-release Orally Disintegrating Tablets, 15 mg and 30 mg	6/07/2007
76-999	Clopidogrel Bisulfate Tablets, 75 mg	6/19/2007
(b) (4)		
78-704	Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution, 2%/0.5%	9/04/2007
(b) (4)		

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

/s/

Saundra Middleton
7/24/2008 11:55:28 AM
Signing for Wm Peter Rickman

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

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Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

NDS - Scanned 8/12/08

August 6, 2008

N-000-(HC)

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RECEIVED
AUG 07 2008
OGD

Dear Mr. Buehler:

This letter is in response to your correspondence received by TEVA on July 28, 2008 in which several TEVA pending ANDAs were identified as requiring amendments. A copy of your letter is provided herein for reference.

The following table provides dates by which we intend to amend or withdraw the applications noted in the July 28, 2008 correspondence.

ANDA	Product	Non-approvable Date	Target Response Date/Comments
76-337	Norethindrone & Ethinyl Estradiol Tablets USP, 1 mg/0.035 mg (28 day)	9/14/05	*
76-338	Norethindrone & Ethinyl Estradiol Tablets USP, 0.5 mg/0.035 mg, 0.75 mg/0.035 mg and 1 mg/0.035 mg (28 day)	9/14/05	*
[redacted]			(b) (4)

ANDA	Product	Non-approvable Date	Target Response Date/Comments
[redacted]			(b) (4)
78-407	Fluvastatin Capsules, 20 mg and 40 mg	3/13/07	11/30/08
[redacted]			(b) (4)
78-730	Lansoprazole Delayed Release Orally Dsintegrating Tablets, 15 mg and 30 mg	6/7/07	9/30/08
76-999	Clopidogrel Bisulfate Tablets, 75 mg	6/19/07	11/30/08
[redacted]			(b) (4)
78-704	Dorzolamide HCl and Timolol Maleate Ophthalmic Solution, 2%/0.5%	9/4/07	11/30/08
[redacted]			(b) (4)

* For the [redacted] (b) (4) ANDAs noted in the table above, the sole comment in each of the stated non-approvable letters relates to site inspection issues at the manufacturing location ([redacted] (b) (4) [redacted] (b) (4) manufacturing facility). It is our belief that the site inspection issues have been resolved, however we have been unable to get official confirmation of the status of the facility in question. We have attempted to get this information for each of these three ANDAs, but have been told that the Office of Compliance still lists the [redacted] (b) (4) facility as being out of compliance. We will amend these three files just as soon as we receive notification that the facility has been found acceptable.

Please be assured that we are working on each of the above responses and will submit amendments as soon as possible. If, due to unforeseen circumstances, any of the amendments above should be significantly delayed beyond the target dates specified herein, we will notify you of such change. Should you have any questions on the information provided herein, please do not hesitate to contact me at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Crenshaw for

PE/jbp
Enclosure

cc: Saundra Middleton, OGD via facsimile

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

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philip.erickson@tevausa.com

September 10, 2008

MINOR AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AM

ANDA #78-730
LANSOPRAZOLE DELAYED RELEASE ORALLY DISINTEGRATING TABLETS
MINOR AMENDMENT – RESPONSE TO REVIEW LETTER DATED JUNE 7, 2007

Dear Mr. Buehler:

We submit herewith a minor amendment to the above referenced pending ANDA in response to a review letter dated June 7, 2007. Reference is also made to the July 24, 2008 "Amend or Withdraw" letter, and Teva's commitment in a letter dated August 6, 2008 to respond by September 30, 2008. For ease of review, a copy of the aforementioned letters are provided in **Attachment 1**.

Please note that new exhibit batches have been manufactured and the supporting data for these batches are included herein. Your comments are addressed in the order in which they were presented. The following minor changes were made to the formula of the [redacted] (b) (4) [redacted] (b) (4) of Lansoprazole D.R. Orally Disintegrating Tablets 15 mg and 30 mg:

- The amount of [redacted] (b) (4) (used [redacted] (b) (4) in the formulation) was revised as follows:
  15 mg strength: [redacted] (b) (4) tablet.
  30 mg strength: [redacted] (b) (4) tablet.
- The amount of [redacted] (b) (4) (used [redacted] (b) (4) in the formulation) was revised as follows:
  15 mg strength: [redacted] (b) (4) tablet.
  30 mg strength: [redacted] (b) (4) tablet.

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SEP 11 2008
OGD

Following this page, 5 pages withheld in full - (b)(4)

Due to the recent implementation of USP general chapter <467> Residual Solvents, we have performed an assessment of our product and formulated ingredients and conclude the product is in compliance with USP <467> Option 1. A report summarizing the formulated ingredients and the corresponding maximum residual solvent levels due to each ingredient is provided in **Attachment 22**. As (b) (4) used in manufacture of the drug product, testing of the finished dosage form is required. Appropriate controls have been established and are provided within this amendment in response to comment 7.

It is our belief that the above constitutes a complete response to the review letter dated June 7, 2007. We look forward to your continued review and approval of ANDA #78-730. Should you have any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ds
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

September 15, 2008

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT

ORIG AMENDMENT
N-AA

ANDA #78-730
LANSOPRAZOLE DELAYED RELEASE ORALLY DISINTEGRATING TABLETS
UNSOLICITED AMENDMENT – ADDITIONAL SITE OF DRUG PRODUCT MANUFACTURE

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above-referenced, pending ANDA to provide for the following:

- Additional site of manufacture for the final mixing and tabletting of the drug product
- Additional site of packaging for the drug product
- Additional sites of analytical testing

The original and proposed drug product manufacturing sites are as follows:

Original Site:	Proposed Additional Site:
TEVA Pharmaceutical Industries, Ltd.	TEVA Pharmaceuticals USA
Hashikma Street Industrial Zone	650 Cathill Road
P.O. Box 353	Sellersville, PA 18960
Kfar-Saba 44102-Israel	USA
Site Reg. No.: 3002721084	Site Reg. No.: 2517175

The proposed site will also serve as an additional analytical testing facility. This facility may be used for the testing of raw materials, packaging components, and finished products (in-process, release, and stability). The contact person for the proposed site is [redacted] (b) (6) (Phone No: [redacted] (b) (6)).

RECEIVED
SEP 15 2008
OGD

Following this page, 3 pages withheld in full - (b)(4)

Additionally, in conjunction with the addition of analytical testing at the Sellersville facility, we propose the use of (b) (4) for (b) (4) testing of (b) (4) (b) (4). The change is due to the fact that the (b) (4) instrumentation used in the Kfar-Saba facility is unavailable in Sellersville. Due to the differences in (b) (4) (b) (4) methodologies between the (b) (4) and (b) (4) instruments, the (b) (4) (b) (4) specification has been revised as follows:

Specification Using (b) (4) Instrumentation (Kfar-Saba Site)	Specification Using (b) (4) Instrumentation (Sellersville Site)
(b) (4)	(b) (4)

In support of the above, provided in **Attachment 12**, please find a cross validation report for the (b) (4). This validation report demonstrates that the (b) (4) (b) (4) is suitable for the (b) (4) testing of (b) (4). Also included in **Attachment 12** are (b) (4) testing results by (b) (4) methods for 10 lots of (b) (4).

This information is submitted for your review and approval. If there are any questions, please do not hesitate to contact me by telephone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/KR

PE/ds/jls
Enclosures

COMPLETE RESPONSE -- MINOR

ANDA 78-730

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Theresa Liu FDA CONTACT PHONE: (240) 276-8555

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 27, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lansoprazole Orally Disintegrating Delayed-release Tablets, 15 mg and 30 mg.

Reference is also made to your amendments dated September 10 and 15, 2008.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (__**3**__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

ANDA: 78-730 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

1.

2.

3.

4.

5.

6. [redacted] (b) (4)

B. Comments:

1. Please provide updated stability data for the exhibit batches.

2. Please provide representative packaged samples (about 20 tablets each) of the drug product batches made with the revised formulation K-39662 (15 mg) and K-39663 (30 mg) and the batches manufactured at the alternate site 2621-014 (15 mg) and 2621-015 (30 mg) to assist in our evaluation of the ANDA. The samples should be sent separately to:

   Theresa Liu, Project Manager, Team 7
   Division of Chemistry II
   Office of Generic Drugs
   7500 Standish Place
   Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
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/

Damaris Maldonado
2/20/2009 10:32:57 AM

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

March 27, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT – CMC AND BIOEQUIVALENCE (DISSOLUTION)

N/AM
N/AB

ANDA #78-730
LANSOPRAZOLE DELAYED RELEASE ORALLY DISINTEGRATING TABLETS
MINOR AMENDMENT – RESPONSE TO REVIEW LETTER DATED FEBRUARY 20, 2009

Dear Mr. Buehler:

We submit herewith a minor amendment to the above referenced pending ANDA in response to a review letter dated February 20, 2009. For ease of review, a copy of the aforementioned letter is provided in **Attachment 1**.

A. Deficiencies:

1. (b) (4)

2.

Following this page, 1 page withheld in full - (b)(4)

(b) (4)

6.

B. Comments:

1. Updated stability data are provided in **Attachment 11** for the following exhibit batches:
   Lansoprazole DR ODT 15mg, Batch K-36985, through 24-mos CRT
   Lansoprazole DR ODT 30mg, Batch K-36986, through 24-mos CRT
   Lansoprazole DR ODT 15mg, Batch K-39662, through 12-mos CRT
   Lansoprazole DR ODT 30mg, Batch K-39663, through 12-mos CRT
   Lansoprazole DR ODT 15mg, Batch 2621-014, through 9-mos CRT
   Lansoprazole DR ODT 30mg, Batch 2621-015, through 9-mos CRT

   In addition, accelerated stability summary reports for the batches manufactured in the Sellersville facility have been revised in accord with the dissolution method and are provided herein.

2. As requested, samples of the exhibit batches manufactured at both the Kfar Saba and Sellersville facilities have been provided to the Division of Chemistry II. A copy of the letter which accompanied the samples is provided in **Attachment 12**.

It is our belief that the above constitutes a complete response to the review letter dated February 20, 2009. We look forward to your continued review and approval of ANDA #78-730. Should you have any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ds
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
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philip.erickson@tevausa.com

March 31, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ADDENDUM TO MINOR AMENDMENT DATED MARCH 27, 2009

ORIG AMENDMENT
N-AM

ANDA #78-730
LANSOPRAZOLE DELAYED RELEASE ORALLY DISINTEGRATING TABLETS
ADDENDUM TO MINOR AMENDMENT DATED MARCH 27, 2009

Dear Mr. Buehler:

We submit herewith an addendum to the minor amendment, dated March 27, 2009, which was submitted to the above referenced pending ANDA. For reference, a copy of the cover letter of the minor amendment is provided herein.

On page 3 of the letter, the proposed [redacted] (b) (4) specification presented in response to item #A.6 incorrectly stated a limit of [redacted] (b) (4) However, the proposed [redacted] (b) (4) specification for release and stability testing of the drug product is [redacted] (b) (4). The [redacted] (b) (4) specification that was provided within the body of data contained in the amendment states the correct drug product specification of [redacted] (b) (4).

We apologize for any inconvenience this may have caused. We look forward to your continued review and approval of ANDA #78-730. Should you have any questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/ds

PE/ds
Enclosures

APR 0 1 2009

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

June 11, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED LABELING AMENDMENT – UPDATED LABELING AND EXCLUSIVITY STATEMENT

ANDA #78-730
LANSOPRAZOLE DELAYED RELEASE ORALLY DISINTEGRATING TABLETS, 15mg and 30mg
UNSOLICITED LABELING AMENDMENT – UPDATED LABELING AND EXCLUSIVITY STATEMENT

Dear Mr. Buehler:

We submit herewith an unsolicited labeling amendment to the above-referenced pending ANDA for the purpose of providing an update to our draft labeling and to provide an updated exclusivity statement.

Provided in **Attachment 1**, please find a disk containing our proposed draft labeling. Teva's package insert [Iss 6-2009 (IS)] has been updated in accord with the most current labeling for the reference listed drug, Prevacid® Orally Disintegrating Tablets, approved on October 28, 2008, and is provided in Word and PDF formats. The change to the RLD package insert includes a change to PLR format. Therefore, a comparison of Teva's draft package insert to the approved RLD package insert [(Iss 6-2009 (IS) to RLD Approved 10-28-08)] is provided in PDF format.

Teva's draft blister labeling [(BC) Iss 12-2008(IS)] has been updated due to minor format changes and is provided in Word and PDF formats. A comparison to the last submitted version [10-2006 IS] is provided in PDF format. The draft carton labeling [(CR) A 1-2009 (15mg 3x10 & 30mg 5x6) (IS)] has been updated to include statements regarding child resistance and additional patient information. The draft carton labeling is provided in Word and PDF formats. A comparison to the last submitted version [9-2006 IS] is provided in PDF format.

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

Please note that an additional site of drug product manufacturing (Sellersville, PA) was proposed for this ANDA in an amendment dated September 15, 2008. Therefore, also provided on the disk in **Attachment 1** are the draft package insert [Iss 6-2009 (PA)]; draft blister labeling [(BC) Iss 12-2008 (PA)]; and draft carton labeling [(CR) A 1-2009 (15mg 3x10 & 30mg 5x6) (PA)] in Word and PDF formats which reflect the Sellersville, PA, site of manufacture. Comparisons of the draft package insert, blister labeling, and carton labeling for the Sellersville, PA site to the Kfar Saba, Israel site are provided in PDF format to demonstrate that the only difference is the statement of site of manufacture.

Teva's exclusivity statement has been updated to reflect the expiration of new patient population exclusivity (NPP), as well as to acknowledge the addition of exclusivity M-85 and pediatric exclusivity (PED) associated with M-85. The updated Exclusivity statement is provided in **Attachment 2**, along with printouts of the current electronic Orange Book listings for the reference drug product.

Further, we wish to clarify that there are two patents that now appear in the electronic Orange Book for which certification has not been provided. Specifically, U.S. Patents 7,399,485 and 7,431,942 listed in the Electronic Orange Book subsequent to Teva's ANDA submission, but beyond 30 days from their date of issuance by the Patent and Trademark Office (PTO).

U.S. Patent 7,399,485 issued by the PTO on July 15, 2008 and first appeared in the electronic Orange Book on November 18, 2008. U.S. Patent 7,431,942 issued by the PTO on October 7, 2008 and first appeared in the electronic Orange Book on January 29, 2009. As these patents are deemed late-listed, Teva has not provided certification to these patents.

This information is submitted for your continued review and tentative approval of ANDA #78-730. Should you have any questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Ericksen/jp

PE/ds
Enclosures

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

June 16, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT – RESPONSE TO JUNE 15, 2009 REQUEST

ORIG AMENDMENT
N-000-AM

ANDA #78-730
LANSOPRAZOLE DELAYED RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg
TELEPHONE AMENDMENT – RESPONSE TO JUNE 15, 2009 REQUEST

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith a telephone amendment to the above-referenced pending ANDA in response to a June 15, 2009 request made by Shahnaz Read of your office. Specifically, it was requested that the same information provided via a telephone amendment on June 11, 2009 to our ANDA 77-255 for Lansoprazole Delayed-Release Capsules be provided to this application.

1) (b) (4)

determination. Results are presented in the following table:

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JUN 17 2009
OGD

Following this page, 2 pages withheld in full - (b)(4)

(b) (4)

are provided in **Attachment 6**.

Please note that the above responses provide identical information to that submitted in TEVA's June 11, 2009 telephone amendment to ANDA 77-255 (Lansoprazole Delayed Release Capsules), with the exception of the drug product information discussed above in response #4 (and the drug product report provided in Attachment 4).

Finally, subsequent to submission of TEVA's March 27, 2009 minor amendment, a typographical error was noticed in the cover letter of that submission. The same typo also appeared in Attachment #2 (Formula Composition Comparison document located on page 8) of the amendment. Specifically, the amount of (b) (4) stated for the 30 mg strength was noted as (b) (4). The correct amount of (b) (4) in the 30 mg tablet is (b) (4). A corrected Formula Composition Comparison document is provided herein **Attachment 7**. We apologize for any confusion this may have caused.

We look forward to your continued review and tentative approval of ANDA #78-730. Should you have any questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Ericson /jp

PE/ds
Enclosures

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

June 23, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT – RESPONSE TO JUNE 23, 2009 REQUEST

ORIG AMENDMENT
N-000-AM

ANDA #78-730
LANSOPRAZOLE DELAYED RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg
TELEPHONE AMENDMENT – RESPONSE TO JUNE 23, 2009 REQUEST

Dear Mr. Buehler:

Teva Pharmaceuticals USA submits herewith a telephone amendment to the above-referenced pending ANDA in response to two separate telephone discussions with Bob West and Scott Vehovic of your Office on June 23, 2009.

Based on our conversation with Bob West, TEVA Pharmaceuticals USA hereby requests that (b) (4) (b) (4) be withdrawn from our application.

Scott Vehovic requested (b) (4) of the dissolution specification for the buffer stage as follows:

Previously Proposed:	Sampling Time: 45 minutes Tolerance NLT (b) (4) %(Q)
Proposed:	Sampling Time: **30 minutes** Tolerance NLT (b) (4) %(Q)

Further, it was communicated that the specification of NMT (b) (4) % in 60 minutes for the acid stage is to remain as previously proposed in our minor amendment dated March 27, 2009. Teva Pharmaceuticals USA herewith commits to provide the revised product specification reflecting this change in our request for final approval.

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JUN 24 2009
OGD

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Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
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We look forward to your continued review and tentative approval of ANDA #78-730. Should you have any questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ds
Enclosures

COMPLETE RESPONSE -- MINOR

ANDA 78-730

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Theresa Liu FDA CONTACT PHONE: (240) 276-8555

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 27, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lansoprazole Orally Disintegrating Delayed-release Tablets, 15 mg and 30 mg.

Reference is also made to your amendments dated March 27 and 31, and June 16 and 23, 2009.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

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

/s/

THERESA C LIU
07/30/2009

DAMARIS C MALDONADO
07/30/2009

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

August 27, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

RECEIVED
AUG 28 2009
OGD

SD #14

ANDA #78-730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS,
15 mg and 30 mg
MINOR AMENDMENT – RESPONSE TO REVIEW LETTER DATED JULY 30, 2009

Dear Mr. Buehler:

We submit herewith a minor amendment to the above referenced pending ANDA in response to a review letter dated July 30, 2009. For ease of review, a copy of the aforementioned letter is provided in **Attachment 1**. Your comments are addressed in the order in which they were presented.

A. Deficiencies:

1. (b) (4)

Following this page, 8 pages withheld in full - (b)(4)

9. [redacted] (b) (4)

With reference to our amendment dated March 27, 2009, we have commited to provide the [redacted] (b) (4) [redacted] (b) (4) method and validation information for the excipient [redacted] (b) (4). Provided in **Attachment 13**, please find the following:

- Specification for [redacted] (b) (4) revised to include a test for [redacted] (b) (4) with a specification of [redacted] (b) (4).
- Analytical methods QEX0002866 (Version 7.0) and QGM 0001009 (Version 3.0) revised to include the test for [redacted] (b) (4)
- Method validation report QGM0001012 (Version 2.0) and an amendment to the validation report QGM0001016 (Version 1.0) detailing the studies conducted and test results for the analysis of [redacted] (b) (4).

It is our belief that the above constitutes a complete response to the review letter dated July 30, 2009. We look forward to your continued review and approval of ANDA #78-730. Should you have any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson for

PE/ds/lf
Enclosures

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

October 5, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED LABELING AMENDMENT
(ELECTRONIC FORMAT)

ANDA #78-730
LANSOPRAZOLE DELAYED RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg
UNSOLICITED LABELING AMENDMENT – FINAL PRINT LABELING

Dear Mr. Buehler:

Teva Pharmaceuticals USA submits herewith an unsolicited labeling amendment to the above-referenced pending ANDA for the purpose of providing final print labeling. Specifically, Teva's insert has been updated in accord with labeling approved on July 31, 2009 for the reference drug product, Prevacid® Orally Disintegrating Tablets. Further, Teva's blister labels and carton labeling are provided in final print format, for completeness of the application.

Please note that this ANDA contains two drug product manufacturing sites, and final print labeling is provided to support product manufactured at each site. As such, labeling pieces are distinguished parenthetically with (IS) referring to drug product manufactured at our Kfar Saba, Israel site, and (PA) referring to drug product manufactured at our Sellersville, PA site. The only difference in labeling between the Kfar Saba site and the Sellersville site is the "manufactured by" information.

Contained in the labeling folder herein are the following:

Blister Card Labeling: 15 mg (10s) and 30 mg (6s)

- Final print blister labels are provided in PDF format (Iss. 12-2008).
- No changes have been made to the blister labeling since it was last submitted in draft format in a June 11, 2009 labeling amendment.

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Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

Carton Labeling: 15 mg (3 x 10) and 30 mg (5 x 6)

- Final print carton labels are provided in PDF format (Rev. A 1-2009).
- No changes have been made to the carton labeling since it was last submitted in draft format in a June 11, 2009 labeling amendment.

Insert Labeling:

- Teva's final print package insert, revised in accord with the most current insert approved for the RLD, is provided in Word and PDF formats (Iss. 8-2009).
- A document in PDF format comparing the current insert to that which was last submitted (Iss. 8-2009 (IS) to 6-2009 (IS)) is provided to delineate changes made to the Kfar Saba version of Teva's insert.
- In addition, for ease of review, a document comparing the insert for Teva's Sellersville facility versus the insert for Teva's Kfar Saba facility (Iss. 8-2009 (PA) to Iss. 8-2009 (IS)) is provided in PDF format.

In accord with 21 CFR 11.2 (b)(2), this entire submission is presented electronically on the enclosed disk. For ease of navigation, on overall table of contents containing hyperlinks is provided (**Table of Contents.pdf**). Please note that an originally signed paper certification or declaration accompanies this submission wherever an original handwritten signature is currently provided. The electronic amendment is provided on one CDROM comprised of approximately 2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted for your continued review and final approval of ANDA #78-730. Please note that we anticipate final approval of this application upon patent expiry on November 10, 2009. Should you have any questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ds
Enclosure

QUALITY DEFICIENCY - MINOR

ANDA 078730

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Theresa Liu FDA CONTACT PHONE: (240) 276-8555

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 27, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lansoprazole Orally Disintegrating Delayed-release Tablets, 15 mg and 30 mg.

Reference is also made to your amendment dated August 27, 2009.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **__3__** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

DAMARIS C MALDONADO
11/02/2009

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

November 12, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

QUALITY MINOR AMENDMENT – RESPONSE TO INFORMATION REQUEST

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg
QUALITY MINOR AMENDMENT – RESPONSE TO INFORMATION REQUEST DATED NOVEMBER 2, 2009

Dear Mr. Buehler:

We submit herewith a quality minor amendment to the above referenced pending ANDA in response to a review letter dated November 2, 2009. For ease of review, a copy of the aforementioned letter is provided in **Attachment 1**. Your comments are addressed in the order in which they were presented.

1) (b) (4)

2)

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We believe the documentation presented herein demonstrates Teva's manufacturing process to be robust, reproducible, and indicative of our ability to consistently produce product that is qualitatively similar to the batches contained in the original ANDA which demonstrated bioequivalence to the innovator product. We commit to continue to gather data in the post-approval period, and to propose limits for the requested in-process controls discussed above in a timely fashion.

This entire submission is presented electronically on the enclosed disk. For ease of navigation, on overall table of contents containing hyperlinks is provided (**Table of Contents.pdf**). Please note that an originally signed paper certification or declaration accompanies this submission wherever an original handwritten signature is currently provided. The electronic amendment is provided on one CDROM comprised of approximately 8 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not also need to provide a copy to the ORA District Office. As District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room, TEVA Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic amendment has been submitted to CDER for this application.

It is our belief that the above constitutes a complete response to the review letter dated November 2, 2009. We look forward to your continued review and approval of ANDA #078730. Should you have any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson Jr

PE/ds
Enclosures

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

November 25, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

QUALITY AMENDMENT – RESPONSE TO INFORMATION REQUESTS

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg
RESPONSE TO NOVEMBER 18, 2009 INFORMATION REQUESTS

Dear Mr. Buehler:

We submit herewith additional information concerning the commercial manufacture of the above referenced product in response to requests from Dr. Read received on November 18, 2009 related to pending ANDA 078730. Dr. Read's questions are addressed in the order in which they were presented.

(b) (4)

same as the current commercial batch size.

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The current manufacturing procedures for [redacted] (b) (4) operations for Lansoprazole DR ODT, 15mg and 30mg are provided in **Attachment 9**.

The following additional request was made by Dr. Read on November 18, 2009:

Could you also let us know in your response when we can expect in-process data for each [redacted] (b) (4) *for the two additional batches?*

Please be advised that manufacture of the two additional [redacted] (b) (4) batches is currently ongoing. We expect results of these batches to be available within one month.

This entire submission is presented electronically on the enclosed disk. For ease of navigation, an overall table of contents containing hyperlinks is provided (**Table of Contents.pdf**). Please note that an originally signed paper certification or declaration accompanies this submission wherever an original handwritten signature is currently provided. The electronic amendment is provided on one CDROM comprised of approximately **45** megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not also need to provide a copy to the ORA District Office. As District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room, TEVA Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic amendment has been submitted to CDER for this application.

It is our belief that the above constitutes a complete response to the November 18, 2009 information request. We look forward to your continued review and approval of ANDA #078730. Should you have any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ds
Enclosures

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

December 28, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

QUALITY TELEPHONE AMENDMENT – RESPONSE TO INFORMATION REQUEST

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS,
15 mg and 30 mg
TELEPHONE AMENDMENT - RESPONSE TO DECEMBER 23, 2009 INFORMATION REQUEST

Dear Mr. Buehler:

Teva Pharmaceuticals USA submits herewith a telephone amendment response to requests received from Dr. Shanaz Read via email on December 23, 2009 related to pending ANDA #078730. Dr. Read's questions are reproduced below and addressed in the order in which they were presented.

(1) Why are the results for batches L60011, L60012 and L60013 not included in the finished product analysis in Attachment 8 [of Teva's November 25, 2009 amendment]?

Drug product batches L60011, L60012 and L60013 were manufactured from the (b) (4) Thus, they were excluded from the analysis in Attachment 8 of our November 25th amendment.

(2) Since the batch size of the (b) (4) (b) (4) ***Since the batch size for the 30 mg tablets is*** (b) (4)

Following this page, 4 pages withheld in full - (b)(4)

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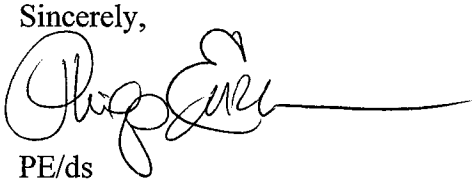
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

It is our belief that the above constitutes a complete response to the December 23, 2009 information request. We look forward to your final approval of ANDA #078730. Should you have any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/ds
Enclosures

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

January 8, 2010

TELEPHONE AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS,
15 mg and 30 mg
TELEPHONE AMENDMENT - RESPONSE TO JANUARY 8, 2010 REQUEST

Dear Mr. Buehler:

Teva Pharmaceuticals USA submits herewith a telephone amendment in response to a request received from Dr. Shanaz Read via email on January 8, 2010 related to pending ANDA #078730.

Teva Pharmaceuticals USA commits to implement the following controls for testing of the finished drug product:

(1) Content Uniformity samples will be withdrawn at (b) (4) (b) (4).

(2) Finished product dissolution testing will be performed on 12 tablets.

This entire submission is presented electronically on the enclosed disk. For ease of navigation, an overall table of contents containing hyperlinks is provided (**Table of Contents.pdf**). Please note that an originally signed paper certification or declaration accompanies this submission wherever an original handwritten signature is currently provided. The electronic amendment is provided on one CDROM comprised of approximately 1.2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not also need to provide a copy to the ORA District Office. As District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room, TEVA Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic amendment has been submitted to CDER for this application.

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Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

It is our belief that the above constitutes a complete response to the January 8, 2010 request. We look forward to your final approval of ANDA #078730. Should you have any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/PE

PE/ds
Enclosures

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

January 14, 2010

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS,
15 mg and 30 mg
PATENT AMENDMENT - RESPONSE TO JANUARY 14, 2010 REQUEST

Dear Mr. Buehler:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced, pending ANDA in response to a request from Martin Shimer of the Office of Generic Drugs to provide status of litigation with respect to this application. Please note that Teva prevailed in Civil Action 07-331 with respect to U.S. Patent 5,464,632. A copy of the November 9, 2009 district court decision is provided for your reference. As noted within this document, suit related to U.S. Patent 6,328,994 was previously dismissed.

Please note that the NDA holder, Takeda Pharmaceuticals, filed an appeal of the November 9, 2009 decision. The appellate court has not yet rendered a decision in this action.

This entire submission is presented electronically on the enclosed disk. For ease of navigation, an overall table of contents containing hyperlinks is provided (**Table of Contents.pdf**). Please note that an originally signed paper certification or declaration accompanies this submission wherever an original handwritten signature is currently provided. The electronic amendment is provided on one CDROM comprised of approximately 1.2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our belief that the above constitutes a complete response to Martin Shimer's request. We look forward to your final approval of ANDA #078730. Should you have any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp

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Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

QUALITY DEFICIENCY - MINOR

ANDA 078730

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Teva Pharmaceuticals USA

TEL: (215) 591-3141

ATTN: Philip Erickson

FAX: (215) 591-8812

FROM: Theresa Liu

FDA CONTACT PHONE: (240) 276-8555

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 27, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lansoprazole Orally Disintegrating Delayed-release Tablets, 15 mg and 30 mg.

Reference is also made to your amendments dated November 12, 25, and December 28, 2009; January 8, 2010.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/*

Following this page, 1 page withheld in full - (b)(4)

11. Please provide a summary Pharmaceutical development report listing any changes since filing with rationale, since the ANDA has undergone significant changes with respect to formulation, process, and site change activities.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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/s/

RADHIKA RAJAGOPALAN
03/19/2010

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

March 22, 2010

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15mg and 30mg

Dear Mr. Buehler:

Teva Pharmaceuticals USA submits herewith a Quality Minor Amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated March 19, 2010. For ease of review, a copy of the aforementioned letter is enclosed in **Attachment 1**. We have addressed your comments in the order in which they were presented.

1. The manufacturing site of Lansoprazole DR ODT, 15 mg batches (L61001, L61002, L61003) and Lansoprazole DR ODT, 30 mg batches (L60002 through L60010 and L60014 through L60029) is:

   TEVA Pharmaceutical Industries
   Hashikma Street,
   Industrial Zone,
   Kfar-Saba 44102
   ISRAEL
   Registration no. 3002721084
   DUNS no. 533065814

   (b) (4)

   .

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

Following this page, 2 pages withheld in full - (b)(4)

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 11 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that letters have been forwarded to the applicable offices of the FDA certifying that an electronic sequence has been submitted to CDER.

It is Teva Pharmaceuticals USA's belief that the information provided herein represents a complete response to the comments presented in the March 19, 2010 correspondence. This information is submitted toward the continued review and final approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

PE/ds
Enclosures

Philip Erickson /JP
Philip Erickson
Senior Director, Regulatory Affairs

3/22/10
Date

BIOEQUIVALENCE AMENDMENT

ANDA 078730

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Teva Pharmaceuticals USA

TEL: (215) 591-3141

ATTN: Philip Erickson

FAX: (215) 591-8812

FROM: Diane Nhu

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on September 15, 2008, March 27, 2009, and June 23, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lansoprazole Orally Disintegrating Delayed Release Tablets, 15 mg and 30 mg.

The Division of Bioequivalence has completed its review of the submissions referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Missing Information not Included in Original
Bioequivalence Long Term Stability
Bioequivalence Other
Bioequivalence SOPs
Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 078730

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg

The Division of Bioequivalence (DBE) has completed its review and has identified the following deficiencies:

1. The dissolution testings of your test product Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg exhibit mean dissolution release of less than (b)(4)% compared to the reference listed drug (RLD) Prevacid® SoluTab™ (Lansoprazole) Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg (mean dissolution release more than (b)(4)%) at 30- and 45-minutes. Please provide reasons for incomplete release of the drug from the test products Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg.

2. Please provide the dissolution data obtained from Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg batches kept on accelerated and long-term storage stability conditions.

3. The approved labeling for the RLD states that the product may be administered via an oral syringe. The RLD labeling also states that the product may be administered by nasogastric tube. Therefore, we request that you perform the following in vitro tests to compare the performance of your product to that of the RLD under these conditions of use.

    a. Please conduct comparative dispersibility testing using 20 units of the test and reference 15 mg and 30 mg tablets in oral syringe using 4 mL and 10 mL of water, respectively.

    b. Please conduct comparative acid resistance stability testing using 12 units of all strengths of the test and reference products. The stability studies should be conducted using the dispersed tablets with acid resistance as the stability indicator using the following method:

- Disperse the tablets into water in oral syringe for 15 minutes. Use 4 mL of water for 15 mg tablets and 10 mL for 30 mg tablets.

- Transfer the contents of syringe into dissolution vessel containing 500 mL of 0.1 N HCl maintained at 37 °C ±0.5 °C.

- Refill the syringe with 2 mL of water for 15 mg tablets and 5 mL for 30 mg tablets, shake gently and transfer any remaining contents into the dissolution media mentioned above.

- Acid resistance testing should be conducted using USP Apparatus II at 75 rpm.

- Analyze the amount of lansoprazole released at 60 minutes.

- Repeat the acid resistance stability testing using combination of a syringe and nasogastric (8 FR) tube.

c. Please conduct the comparative recovery studies of the dispersed tablets from oral syringe and from a combination of oral syringe and 8 French nasogastric tube using 20 units of all strengths of the test and reference listed products using 4 mL of water for 15 mg tablets and 10 mL for 30 mg tablets.

4. Please submit standard operating procedures for dispersibility, stability and recovery testing, individual data, mean values, standard deviations, coefficient of variation (CV%), and plots of percent release of lansoprazole in stability testing in acid medium test.

5. Please note if you want to retain the option of using Kfar-Saba, Israel location as alternate manufacturing site, please provide the data for the tests mentioned in # 1-4 above from the batches manufactured at this site as well.

6. Comments related to the chemistry, manufacturing and controls section will be sent by the chemistry review team.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

BARBARA M DAVIT
03/23/2010

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

May 7, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE MISSING INFORMATION NOT INCLUDED IN ORIGINAL
BIOEQUIVALENCE LONG TERM STABILITY
BIOEQUIVALENCE OTHER
BIOEQUIVALENCE SOPs
BIOEQUIVALENCE RESPONSE TO INFORMATION REQUEST

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a Bioequivalence Amendment to the above-referenced, pending Abbreviated New Drug Application in response to a March 23, 2010 review letter from the Division of Bioequivalence II. For ease of review, a copy of the aforementioned letter is enclosed in **Attachment 1**. We have addressed your comments in the order in which they were presented.

1. Regarding drug product dissolution, we refer you to the dissolution data provided to the Chemistry division in a March 22, 2010 minor amendment. These data were obtained from ten recent commercial scale batches manufactured at Teva's Kfar Saba, Israel facility. These data demonstrate that Teva's product not only consistently meets the FDA-recommended dissolution specification, with mean dissolution release values of approximately (b)(4)% at 30 and 45 minutes, but also demonstrate comparability to the values presented for the brand product within our original ANDA. The data from the more recent batches are re-provided in **Attachment 2** for ease of reference.

   As Teva's product has been demonstrated to be bioequivalent to the brand product in the *in-vivo* studies supportive of this ANDA, we feel the slight variations observed between the two during the buffer stage of dissolution testing to be inconsequential. It is our belief that these slight variations can be attributed to differences in the products' manufacturing technologies.

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

2. Provided in **Attachment 3**, please find accelerated and CRT stability reports for Teva's Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg which include the requested dissolution data. Please note, the buffer stage dissolution specifications listed in the accelerated stability study reports reflect the 45-minute Q time which was in effect at the time the batches were manufactured and tested. These stability data support the quality of Teva's drug product throughout the proposed two-year shelf life.

3. As requested, the following *in-vitro* testing was conducted to compare the performance of Teva's drug product to that of the RLD product under the specified conditions of use. Data reports are provided in **Attachment 5** which serve to demonstrate the comparability of the two products.

   a. Comparative dispersibility testing was conducted using 20 units of each strength of both the test and reference products. The 15 mg tablets were dispersed using 4mL of water, and the 30 mg tablets were dispersed using 10mL of water, in an oral syringe.

   b. Comparative acid resistance stability testing was conducted using 12 units of each strength of both the test and reference products. The dispersed tablets were introduced to the dissolution vessel using 1) the oral syringe and 2) a combination of the oral syringe with a nasogastric tube (8 FR). In accord with your request, acid resistance was used as the stability indicator.

   c. Comparative recovery studies of the dispersed tablets was conducted using 20 units of each strength of both the test and reference products. The 15 mg tablets were dispersed using 4mL of water, and the 30 mg tablets were dispersed using 10mL of water. The recovery was measured from 1) the oral syringe and 2) a combination of the oral syringe with the nasogastric tube (8 FR).

4. Provided in **Attachment 4**, please find the procedure manual describing the sample preparation and analytical procedures used for performing the dispersibility, stability, and recovery testing. As noted above, a report detailing the results of the requested comparative *in-vitro* studies is provided in **Attachment 5**.

5. The batches used for the comparative in vitro testing were manufactured at Teva's Kfar Saba, Israel location. Please note that Kfar Saba, Israel is the only intended site of commercial manufacture for Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg and 30 mg. The Sellersville, PA site, proposed in September 2008 as an additional site of manufacture, was later withdrawn via a Quality Minor Amendment dated March 22, 2010.

6. Teva has responded to all comments related to the chemistry, manufacturing and controls section of this ANDA received to date from the chemistry review team.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is Teva Pharmaceuticals USA's belief that the information provided herein represents a complete response to the comments presented in the March 23, 2010 review letter. This information is submitted toward the final approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

PE/ds
Enclosures

Philip Erickson /JMD

Philip Erickson
Senior Director, Regulatory Affairs

5/7/10
Date

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

May 18, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a labeling amendment to provide updated final print labeling in accord with the most current labeling for the reference-listed drug product, Prevacid Delayed-Release Orally Disintegrating Tablets, approved on May 12, 2010.

Provided in **Attachment 1**, please find Teva's final print package insert (Iss. 05/2010) in Word and PDF formats, and a comparison to the last submitted package insert (Iss. 08/2009) in PDF format. Please note that in preparation for drug listing and SPL requirements, additional formatting revisions have been made. Specifically, the product description was clarified to include "round, artificial strawberry flavored" in Sections 3 and 16; and the sugar sphere composition is further defined as being comprised of sucrose and corn starch in Section 11. This additional labeling text is included for clarity and to comply with elements of drug listing only. No changes have been made to the qualitative or quantitative product formulation as submitted in the ANDA.

In addition, Teva Pharmaceuticals USA commits to provide the Agency labeling in SPL format within 14 days of receiving final approval of this application.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted toward the final approval of this ANDA. If there are any questions,

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

PE/ds
Enclosures

Philip Erickson

Philip Erickson
Senior Director, Regulatory Affairs

5/18/10
Date

Record of Telephone Conversation

After internal discussion, TEVA was contacted for the following question:

The drug product is not 100% dissolved, we would like to know where is the rest of the drug.

Two lots were given as examples: L-61010 and L-61009.

Possible reasons for not reaching 100%: analytical methods, degradation, or it just never dissolved.

TEVA is requested to respond to this question as a telephone amendment to the office.

Date:
6/4/10

ANDA Number:
078730

Product Name:
Lansoprazole DR ODT

Firm Name:
TEVA

Firm Representative:
Philip Erickson

Phone Number:
215-591-3141

FDA Representatives:
Lawrence Yu
Barbara Davit
Chaurasia Chandra
Robert Lionberger
Wenlei Jiang
Glen Smith
Radhika Rajagopalan
Theresa Liu

Endorsements:

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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/s/

THERESA C LIU
06/14/2010

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

June 11, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT – RESPONSE TO JUNE 4, 2010 REQUEST

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a telephone amendment to the above-referenced, pending Abbreviated New Drug Application in response to a June 4, 2010 request made by Dr. Lawrence Yu. Referring to data submitted in our March 22, 2010 quality minor amendment, Dr. Yu requested an explanation for, what appears to be, overall low dissolution results obtained during testing of the drug product in the buffer stage. Ultimately, the Agency is concerned as to why we do not achieve higher results indicative of full drug release from the finished product. In response to the Agency's concern, Teva Pharmaceuticals USA provides the following information and data for your review and consideration.

It is Teva's position that the dissolution conditions are less than optimal for use with this particular drug substance and dosage form. Often dissolution methods are able to produce seemingly large differences in results for relatively minor differences in formulae. When this occurs, one traditionally sees a disparity in release rates between the generic or test formulation in comparison to the RLD product. However, as can be observed in the comparative dissolution profile data provided as **Attachment 1**, both Teva's product and the RLD have overall low dissolution results. Provided are profiles comparing Teva's original ANDA batches to the RLD as well as profiles comparing the original ANDA batches to the reformulated batches submitted via an amendment to the file. Due to the consistent observation, one is led to question if the method and/or dissolution conditions are ideally suited to the drug itself.

The first point considered was the appropriateness of the dissolution media employed. In support of a related file submitted by Teva to the Canadian health authorities, a study was performed to justify the use of a pH 6.8 phosphate buffer as the dissolution media. This report is provided as **Attachment 2**. Within this study it was concluded that the stability of lansoprazole

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Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
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is, in fact, pH dependent. This dependency is such that, in aqueous solutions, the rate of degradation of the lansoprazole increases with a decrease in pH. The degradation half life of lansoprazole in an aqueous solution at 25 °C was found to be approximately 0.5 hours at pH 5.0, while at pH 7.0 the observed half life was approximately 18 hours. Considering this lack of stability, one can certainly question the overall dissolution values considering the product experiences 1 hour in the aqueous acid media followed by an additional 30 minutes at pH 6.8. Any drug released during this 90 minutes time frame would be subjected to a less than optimal environment for its stability. The stability of the lansoprazole in the FDA designated media is further questioned by the results of an acid resistance test that had been requested by the Agency's Division of Bioequivalence (provided herein as **Attachment 3**). Acid resistance of both the test and reference product were studied by comparing the assay results (b) (4) before and after being exposed to the aqueous acid media for 1 hour. This comparison showed as much as a 6 to 7% decrease in assay (b) (4) after the 1 hour exposure to the acid media. This suggests that the drug product formulations may release some amount of drug in the acid stage, albeit less than the (b) (4) upper limit allowed for this stage of dissolution testing. However, based on the stability study referenced earlier in **Attachment 2**, any drug so released in the acid stage would be expected to rapidly degrade and therefore, would not be included in the overall dissolution value obtained. Additionally, it is suggested that drug that may be in solution during the 30 minute pH 6.8 buffer stage could also experience degradation, albeit to a lesser extent.

Additionally, the influence of the dissolution vessel and potential interaction with the drug product was questioned. To determine if the vessel itself could be affecting the overall dissolution results by decreasing or preventing adequate flow of media about the drug product, a preliminary test was performed. In this trial, the dissolution test was run using all existing conditions and parameters with the exception that the USP vessel was replaced with a peak vessel. Results of this comparison are provided as **Attachment 4**. While the difference in overall dissolution was not drastic, a consistent increase in overall dissolution was observed for both Teva's product and the RLD. Further study would be needed to confirm these observations and determine the extent to which this may be a contributing factor.

In order to assure that the dissolution results in question are not indicative of either an assay or uniformity issue, Teva reviewed the data available on the two batches mentioned by Dr. Yu, specifically Lots L61010 and L61009. It should be noted here that, the assay and impurity sample preparations are performed at pH 10 which is a far more stable environment for this drug substance. Provided as **Attachment 5**, please find the finished product certificates of analysis which establish that the drug product potency and uniformity results are acceptable and around 100%. Additionally in-process data obtained on the delayed release coated (b) (4) lot LAP015 (which was used to manufacture the two finished drug product lots mentioned above), was reviewed. These data may be found in **Attachment 6**. All data obtained (b) (4) was very consistent and well within specification. Therefore the product quality, potency and uniformity has been confirmed. This consistency in both the in-process and finished product uniformity data is not consistent with the few lower than typical dissolution results that have been observed which would again lead one to question if the dissolution test is optimal. Please note that the individual values referenced still meet the USP L2 testing criteria of Q-15% and are therefore, fully USP compliant.

Given the potential issues noted with respect to the dissolution method, one must determine the use of the resultant data. The method and its corresponding limit of NMT (b)(4)%(Q) in 30 minutes for the buffer stage can be adequate for the routine QC release testing of the drug product as it accurately reflects the release profile under the given test conditions. However, since the overall value is considered to be low, one must ask what this low value really means in relation to the product itself. If one assumes that the profile is indicative of in-vivo performance, the results are consistent with the bioequivalence study in which Teva's product was shown to be bioequivalent to the RLD. Alternatively, if the results are falsely low and thereby not mimicking the in-vivo performance of the drug product, again we are seeing similar behavior by both the Teva and RLD formulations. Following this assumption, the lack of evidence of in-vivo behavior is mitigated by the comparability to the performance of the reference listed drug. In light of the Agency's recent comments and in consideration of the discussions herein, Teva hereby commits to investigate this observed behavior and will provide the results of this investigation and any corrective actions via a CBE-30 supplement to this ANDA.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry, Manufacturing, and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic submission has been submitted to CDER.

It is Teva Pharmaceuticals USA's belief that the information provided herein represents a complete response to the June 4, 2010 request. This information is submitted toward the continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

PE/
Enclosures

Philip Erickson
Senior Director, Regulatory Affairs

June 11, 2010
Date

BIOEQUIVALENCE AMENDMENT

ANDA 078730

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Teva Pharmaceuticals USA

TEL: (215) 591 - 3141

ATTN: Philip Erickson

FAX: (215) 591 - 8812

FROM: Diane (Duong) Nhu

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on December 27, 2006, October 12, 2007, September 15, 2008, March 27, 2009, June 23, 2009, May 07, 2010, and June 11, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lansoprazole Delayed Release Orally Disintegrating Tablet, 15 mg and 30 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgement
Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response. Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.**

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/*

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 078730

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Lansoprazole Delayed Release Orally Disintegrating Tablets, 15 mg and 30 mg

The Division of Bioequivalence (DBE) has completed its review and has identified the following deficiencies:

1. The DBE acknowledges your submission of dissolution data using PEAK Vessels. We concluded that we do not recommend the use of the PEAK Vessel for dissolution testing of Lansoprazole Delayed Release Orally Disintegrating Tablets. [redacted] (b) (4) the use of PEAK Vessels for dissolution testing for Lansoprazole Delayed Release Orally Disintegrating Tablets.

2. Your application is incomplete pending your acceptance of following FDA-recommended interim dissolution method and specifications:

Medium:	500 mL of 0.1 N HCl for the first hour followed by 900 mL phosphate buffer pH 6.8 with 5 mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75 rpm
Specifications:	Acid stage: NMT (b) (4) % in 60 minutes Buffer stage: NLT (b) (4) % (Q) in 30 minutes

Please indicate whether you accept the above interim dissolution method and specifications.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

BARBARA M DAVIT
07/28/2010

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

August 12, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT
LABELING AMENDMENT

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a patent and labeling amendment to the above-referenced, pending Abbreviated New Drug Application to provide an updated patent certification and updated final print labeling.

Specifically, the patent certification has been revised due to the expiration of U.S. Patent 5013743, and also reflects that U.S. Patents: 4628098, 4689333, 5026560, 5045321, 5093132, 5433959, 6123962 and 674986, are also expired. Please find the updated patent certification provided in **Attachment 1**.

U.S. Patent #5,013,743, now expired, was associated with use code U-452, defined as "use of Lansoprazole for combating diseases caused by the genus campylobacter (C. Pylori = H. Pylori)". Due to the expiry of this patent, the product labeling now includes the indication previously protected by this use code. Provided in **Attachment 2**, please find Teva's final print package insert (Iss. 07/2010) in Word and PDF formats, and a comparison to the last submitted package insert (Iss. 05/2010) in PDF format.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

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This information is submitted toward the continued review and approval of this ANDA. If there are any questions, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/ds
Enclosures

Jean W. Zwicker
Senior Director, Regulatory Affairs

8/12/2010
Date

Record of a Telephone Conversation

Subject:	Teva is requesting clarification of the review letter received on July 28, 2010.
Meeting Type:	Teleconference between FDA and Teva
ANDA:	078730
Product Name:	Lansoprazole Delayed Release Orally Dispersible Tablet, 15 mg and 30 mg
Firm:	Teva Pharmaceuticals, USA
Date:	August 26, 2010, 12:30 pm – 2:00 pm

Attendees:

OGD:
Barbara Davit
Chandra Chaurasia
Glen Smith
Ethan Stier (on the phone)
Radhika Rajagopalan (on the phone)
Paramjeet Kaur
Om Anand
Diane Nhu

Teva representatives:
Rob Vincent
Philip Erickson
Jill Pastore
Dee Sawickij

Background

Teva is requesting clarification of the review letter received on July 28, 2010. Specifically item #2 requests that we adopt a dissolution specification for the buffer stage of NLT (b)(4)% (Q) in 30 minutes. Teva claims that the recommended specification does not take into account the dissolution data obtained at release of the batch used to establish bioequivalence to the RLD. Teva states that it is well-known that modified release dosage forms often are approved with dissolution specifications that are specific to a given drug product. Additionally, the specification that is currently proposed in Teva's application, (i.e. NLT (b)(4)%(Q) in 30 minutes) had been provided to Teva from the Division of Bioequivalence via a telephone request on June 23, 2009 to which an amendment was provided on the same date.

Teva would like the opportunity to discuss this matter so that they may understand the basis for this revised specification. There may be other means by which Teva is capable of addressing your underlying concerns.

Summary discussion before teleconference from 12:30 pm to 1:00 pm

Om Anand conducted extensive additional research on Lansoprozole DR ODT dissolution and found that the rate of degradation of the compound in aqueous solution increases with decreasing pH. The degradation half-life of the drug substance in aqueous solution at 25C is approximately 0.5 hour at pH 5.0 approximately 18 hours at pH 7.0 (PDR).

Dissolution data of the RLD submitted by different firms ((b) (4) and Takida – although the names were not mentioned during the subsequent t-con) demonstrate a complete release of lansoprazole from the RLD using the FDA recommended method. The only firm that could not achieve this complete dissolution of the RLD was Teva.

When comparing Teva's dissolution profiles for 15 mg and 30 mg strengths, it is noted that Teva's lansoprazole dissolution shows a plateau (b) (4) and then the amount of lansoprazole dissolved in the media declines. Teva's dissolution testing also shows high variation and incomplete dissolution, this could be due to degradation or precipitation.

Teva's dissolution method at the buffer stage is to add to each vessel of the acid stage dissolution 420 mL of heated buffer solution (buffer solution pH 6.8 is obtained) and immediately operate the apparatus. The method of adding the buffer phase is not as per USP 711 Method A, which states that the media should be added with the apparatus operating at the rate specified. Om thinks that the firm may not be adjusting the pH appropriately. If pH decreases with mixing of the acid the drug may degrade.

Regarding to the analytical method used by Teva, there are no recovery data provided. The accuracy was performed between two methods (assay and dissolution method). So it is not clear how much lansoprazole the method is capable of recovering.

Barbara states that the bottom line is that we are not changing our specification. We have in-house dissolution data showing that it is possible to achieve 100 % dissolution of the RLD. Teva is the only firm that did not achieve this same dissolution of the RLD. It appears to us that Teva may be doing something wrong.

Om requested that if Teva can provided us the pH value at different sampling time point, the recovery data, and to conduct dissolution testing in only pH 6.8 without acid phase.

Discussion from 1:00 pm – 1:40 pm

We began with a round of self-introductions by participants.

Teva states that looking at the deficiency letter and our request for the specification at the buffer stage:

1. It is different than what DBE2 asked last year and
2. Want clarification if the FDA takes into account the data were generated for our demonstration shown bioequivalence to the RLD.

Barbara: We do realize that there was a different specification that we tentatively considered last year. Since that time, we have taken a more careful look at the dissolution data with the entire review team. There are two issues with your product:

1. There seem to more variability in your product than we typically see for this product from data available to the FDA.

2. It appears that of all the various investigators that have generated dissolution data for the RLD using this method, Teva has the lowest dissolution and this is referring to the RLD not the test product.

We believe that it is possible to achieve nearly 100 % dissolution of the RLD by 30 minutes using the method that we recommended. And secondly, we are concerned about the variability of the product using this method and we want to use dissolution as a strong quality control tool. As a review team, we have all agreed that the specification in the buffer stage of NLT (b) (4) (Q) in 30 minutes is the most appropriate for this product.

Teva: The chemists have questions regarding dissolution

Barbara introduced Dr. Om Anand as DBE2's dissolution specialist and that Om has some ideas about how to optimize the dissolution method.

Teva: The approach that we usually used was using the acid dissolution media add buffer to that acid media and then adjust pH once we maintain the volume. Would that be the respective approach?

Om: Other investigators can achieve this method, so it is possible. For your method, while you are changing the dissolution media from acid phase to buffer phase you are stopping the paddle and then adding the buffer phase. Immediately after the adjustment of pH 6.8, you are starting the paddle again. Whereas USP states that the phase change should be done with the apparatus operating at the rate specified.
We would like to understand the dissolution method better and we would appreciate if you can provide us the following data:

1. pH value of the dissolution media at the end of the buffer phase and at different sampling time. Also, if you have optimized the rate of addition of the buffer phase to the acid phase. How slowly can it be done?

2. We reviewed the validation of the assay, we did not see the recovery data of the assay method of dissolution samples. Please provide these data to us.
3. Have you conducted the dissolution testing of the tablets only in pH 6.8 buffer without any acid phase? Please provide this information to us.

Teva: We do not have the data requested right now. We will work on it and send in the information as requested.

Barbara: There are two points that are of concern to us

1. Of all the different investigators that have used this method with the RLD, you are the only lab that has been unable to achieve nearly 100 % dissolution of the RLD
2. Considering the relative variability of the dissolution of your product, we are wondering if we have missed something about the manufacturing specification.

Glen: For complex dosage form, we are asking for samples to be sent to us of the RLD and your product to the FDA.

Barbara: The objective of this request is to have our lab do the dissolution testing. We would like to see what our lab generates using this method. It is mystifying to us because of all the different labs that ran this dissolution method, Teva is the only one that is achieving relatively low dissolution.

Teva: Regarding the variability on the test product, if it turns out if there were some issues of how we were performing the test, would that add to the variability?

Barbara: It is entirely possible. You can try the different steps that Dr Anand has outline for you. Also, we will have our lab try this method. That could help answer the question whether it is the product or whether the way the method is being run.

Radhika: We can achieve the buffer phase dissolution at different test from acid resistance that would mean to conduct two sets of dissolution and we can avoid the entire method of how buffer is added and how the change in the pH is affecting the dissolution data. Teva can do the acid resistance test and then do a separate set of dissolution testing using buffer media alone.

Teva: That is certainly something we could attempt.

Om: We would want to see dissolution data of 12 units instead of 6 units. Please provide us the data on 12 units in acid and 12 units in buffer.

Teva: If we remove the acid resistance testing from the finished product evaluation, does that ultimately have an impact on the Q time? Do we still expect to be 30 minutes?

Barbara: Yes, we still expect to be 30 minutes. If there is any question that the way in which the buffer is being added to the acid is causing the degradation of the acid ingredient and that responsible for the low concentration, that would answer the question.

Glen: At this point, we want you to provide us with data before we can speculate whether the Q time is going to have to change. Please provide us the data and we review what you have.

Barbara: Several investigators can achieve 100 % dissolution of the RLD using this dissolution method, and Teva is the only one that can not. We want to know why.

Teva: We will gather some data and share that with the FDA. Would you prefer a teleconference or a formal submission?

Barbara: We would prefer a formal submission. If you accept our tentative dissolution method and specification, we can certainly move forward with this application for approval.

Teva: If our chemists still have questions, can we set up another telephone conference?

Barbara: Yes, definitely. Please contact Diane and set up another teleconference with Dr. Anand since he is our dissolution specialist. If you are discussing about methodology, I do not necessary have to be there.

Conclusion:
The firm will gather data that we requested and submit to us as a formal submission.

Action Items:
1. The firm will provide us:
    1. pH value of the dissolution media at the end of the buffer phase and at different sampling time.
    2. The recovery data of the assay method of dissolution samples.
    3. The dissolution testing of the tablets only in pH 6.8 buffer without any acid phase.

2. The firm will attempt to do the acid resistance test and then do a separate set of dissolution testing using buffer media alone.

3. The firm will contact Diane Nhu to set up another telephone conference with Om Anand if they have questions about the dissolution method.

CC: ANDA 078730

V:\FIRMSAZ\Teva\TELECONS\078730.doc
Drafted: Diane Nhu, 08/27/2010
Comments: Om Anand, 08/30/2010, Barbara Davit, 08/30/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78730	ORIG-1	TEVA PHARMACEUTICALS USA	LANSOPRAZOLE

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

/s/

DUONG NHU
08/30/2010

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 8, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
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BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT
BIOEQUIVALENCE RESPONSE TO INFORMATION REQUEST

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a Bioequivalence Amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter from the Division of Bioequivalence II dated July 28, 2010. For ease of review, a copy of the aforementioned letter is enclosed in **Attachment 1**. We have addressed your comments in the order in which they were presented.

1. Please be advised that Teva does not propose the use of PEAK vessels for routine testing of the drug product. The data obtained using PEAK dissolution vessels was presented as additional information for the purpose of investigating the cause of low dissolution values obtained while testing the drug product with the recommended dissolution method.

2. We hereby accept the recommended interim dissolution method and specification as follows:

Medium:	500mL of 0.1N HCl for the first hour followed by 900mL phosphate buffer pH 6.8 with 5mM SDS (second hour)
Temperature:	37°C
Apparatus:	USP II (paddles)
Rotation:	75rpm
Specifications:	Acid Stage: NMT (b) (4) in 60 minutes Buffer Stage: NLT % (Q) in 30 minutes

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The product specifications have been revised to reflect the recommended method and specification. Please find the product specification for the enteric coated (b) (4) provided in **Attachment 2**, and the product specification for the finished drug product provided in **Attachment 3**.

With reference to a teleconference between FDA and Teva Pharmaceuticals USA held on August 26, 2010, Teva has conducted additional dissolution studies to further investigate the low dissolution values obtained during testing of both our product and the RLD product, using the recommended dissolution method.

The discussion focused on the performance of both the test and reference product during the buffer stage of the dissolution. It was noted that Teva has consistently observed low dissolution values and relatively high variability at the 30 minute sampling time point. During the teleconference, a number of points were discussed specific to the procedure employed for dissolution testing in an effort to gain further understanding of the dissolution methodology and a cause for the apparently low results obtained while testing the drug products in our laboratories. At the conclusion of the teleconference, Teva agreed to provide additional information as described below:

A. Do we stop the paddle rotation when changing from acid stage to buffer stage?

In performing the method as originally proposed, the dissolution apparatus was stopped during the addition of the buffer phase. The method has been revised to specify the paddles continue to rotate while the buffer is added to the acid phase.

B. What is the pH of the buffer media at the beginning, and throughout the buffer stage? Additionally, it was requested that Teva provide data related to the pH of the buffer media at each sampling time point

To determine if the pH of the individual vessels were influenced over time, two sets of 6-unit dissolution tests were performed to monitor the dissolution medium pH of each dissolution vessel at each time point after addition of the buffer medium. The following pH results were obtained:

15mg Batch L-61001				30mg Batch L-60002			
Buffer stage-Time (min.)				Buffer stage-Time (min.)			
0	10	20	30	0	10	20	30
(b) (4)							

The pH of the dissolution medium, after addition of the buffer, is stable over the duration of the dissolution test.

C. Have we studied the effect of the rate of buffer addition to the acid media?

The addition of buffer solution to the acid media occurs in less than a minute. As such, further studies related to addition rate were deemed unnecessary.

D. Provide data where the acid stage and the buffer stage dissolutions are run as stand-alone tests. The test results should be provided on 12 units of both Teva's product and the RLD product.

Twelve-unit dissolution profiles were conducted on both the Teva product and the RLD product using new tablets for the buffer stage test. The resulting dissolution profiles demonstrated comparability between the two products, but did not achieve significant improvement in the buffer stage. Individual data is provided in **Attachment 4** and is summarized as follows:

	Acid Stage	**Buffer Stage**		
	60 min	**30 min**	**45 min**	**60 min**
15 mg Teva Average	0%	88	90	90
15 mg Prevacid Average	0%	93	92	90
30 mg Teva Average	0%	85	90	90
30 mg Prevacid Average	0%	92	93	91

E. Please provide data for the accuracy of the dissolution method.

The original accuracy studies were conducted by comparison of dissolution results obtained using 2 different HPLC methods. Additional accuracy studies were conducted by spiking placebo samples with known levels of Lansoprazole. The results of the recovery study revealed a negative bias of approximately 10% when using an HPLC method for analysis of dissolution samples.

The following table summarizes the findings of the recovery study using the HPLC method:

Spiked concentration (% labeled amount)	50%	100%	120%
% Recovery	93%	90%	93%

As a result of these findings, a new analytical method utilizing UV detection was developed for this product. The method is based on the analytical method specified in the USP monograph for Lansoprazole Delayed-Release Capsules. A recovery study was performed using the UV method, with the following values obtained:

Spiked concentration (% labeled amount)	50%	100%	120%
% Recovery	103%	99%	99%

The analytical method has been subsequently validated. The validation report is provided in **Attachment 5**.

F. Samples of both the RLD and Teva's product should be sent to FDA for evaluation.

The requested samples are currently in transit from our site in Israel, and will be provided to your attention under separate cover, as soon as they are available.

In summary, Teva has determined the root cause for the low dissolution values obtained during drug product dissolution testing is due to a bias in the analytical method used for testing the dissolution samples. In an effort to improve the overall repeatability of the dissolution method, the procedure has been modified to specify that paddle rotation is maintained while the buffer solution is added to the acid media, and a more accurate UV method is proposed for analysis of the dissolution samples.

Provided in **Attachment 6**, please find the revised method for testing the enteric coated (b) (4) The revised method for testing the final drug product is provided in **Attachment 7**.

Comparative dissolution profile studies are currently being conducted to compare Teva's Lansoprazole Delayed-Release Orally Disintegrating Tablets 15mg and 30mg to the reference listed product, using the methods proposed herein. The data will be provided as soon as they are available.

Please be advised that multiple drug product batches have already been manufactured and tested in accord with the dissolution method in effect at the time of batch manufacture. Teva herewith commits to perform dissolution testing of each intended commercial batch of Lansoprazole Delayed-Release Orally Disintegrating Tablets, using the revised dissolution test procedure for finished drug product, as provided herein, prior to distribution to establish conformance to the FDA recommended acceptance criteria agreed to herein.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 1

megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry, Manufacturing, and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic submission has been submitted to CDER.

It is Teva Pharmaceuticals USA's belief that the information provided herein represents a complete response to the comments presented in the July 28, 2010 review letter. This information is submitted toward the continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/ds
Enclosures

Jean W. Zwicker

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/8/2010
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 14, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
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Rockville, MD 20855

LABELING AMENDMENT – REVISED LABELING DUE TO RLD INSERT UPDATE

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS, 15 mg and 30 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a labeling amendment to provide revised final print labeling in accord with the most current labeling for the reference-listed drug product, Prevacid® Delayed-Release Orally Disintegrating Tablets, approved on September 3, 2010. Specifically the labeling has been revised to include new warnings and precautions information, and to add a patient package insert.

Provided in **Attachment 1**, please find the following:

- Teva's final print package insert (Iss. 09/2010) in Word and PDF formats, and a comparison to the last submitted package insert (Iss. 07/2010) in PDF format

- Teva's patient package insert (Iss. 09/2010) in Word and PDF formats, and a comparison to the RLD patient package insert in PDF format.

It is our intent to provide one patient package insert with each carton of 30 tablets. Further, Teva Pharmaceuticals USA commits to provide the Agency labeling in SPL format within 14 days of receiving final approval of this application.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

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This information is submitted toward the continued review and final approval of this ANDA. If there are any questions, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/ds
Enclosures

Jean Zwicker

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/14/10
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 15, 2010

Keith Webber, Ph.D., Acting Director
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BIOEQUIVALENCE AMENDMENT – ADDENDUM TO AMENDMENT DATED SEPTEMBER 8, 2010

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ODT, 15 mg and 30 mg

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an addendum to a Bioequivalence Amendment dated September 8, 2010 for the above-referenced, pending Abbreviated New Drug Application. The purpose of this addendum is to fulfill a commitment to submit comparative dissolution data, per Teva's September 8, 2010 Bioequivalence Amendment.

Dissolution profile testing comparing 12 units of each strength of Teva's product to the RLD product, using the revised method presented in our September 8, 2010 amendment, has been completed. Provided in **Attachment 1**, please find bioequivalence summary table 5 reflecting the results of this testing. The comparative dissolution profile report is provided in **Attachment 2**.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted toward the continued review and final approval of this ANDA. Please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812 should you have any questions on the information contained herein.

Sincerely,
{see appended signature page}

JWZ/ds
Enclosures

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Jean Zwicker/JS
Jean W. Zwicker
Senior Director, Regulatory Affairs

9/15/10
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 15, 2010

Florence Fang
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Rockville, MD 20855

BIOEQUIVALENCE AMENDMENT – SUBMISSION OF REQUESTED SAMPLES

ANDA #078730
LANSOPRAZOLE DELAYED-RELEASE ODT, 15 mg and 30 mg

Dear Dr. Fang:

Teva Pharmaceuticals USA submits herewith correspondence to the above-referenced, pending Abbreviated New Drug Application to provide drug product samples which were requested by the Agency during a teleconference call with Teva on August 26, 2010. As such, please find enclosed the following representative samples:

- Teva's Lansoprazole Delayed-Release ODT, 15mg Batch L61001 (60 tablets)
- Teva's Lansoprazole Delayed-Release ODT, 30mg Batch L60002 (60 tablets)
- Prevacid® SoluTab™ Delayed-Release ODT, 15mg Lot 856662E21 (30 tablets)
- Prevacid® SoluTab™ Delayed-Release ODT, 30mg Lot 811472E23 (30 tablets)

Certificates of Analysis for the above-noted lots of Teva product are provided in **Attachment 1**.

The submission which accompanies the requested samples is presented in electronic format, while those documents with a handwritten signature are also provided in paper. The electronic submission is provided on one CDROM comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted toward the continued review and final approval of this ANDA. Please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812 should you have any questions on the information contained herein.

Sincerely,
{see appended signature page}

JWZ/ds
Enclosures

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Jean Zwicker / gp

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/15/10
Date

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-730 Applicant TEVA Pharmaceuticals USA
Drug Lansoprazole Delayed-release ODT Strength(s) 15 mg and 30 mg

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 14 January 2010 Initials MHS	Date 10/14/10 Initials rlw/for

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = Prevacid NDA# 21-428
Date Checked Granted
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.

Comments: ANDA submitted on 12/27/2006, BOS=Prevacid ODT NDA 21-428, PIV to '098, '560, '321, '132, '959, '632, and '994 patents, PIII to the '962 and '864 patents, MOU to the '743(U-452). ANDA ack for filing with PIV on 12/27/2006 (LO dated 3/29/2007). Firm authorized to use FedEx on 1/5/2007. Correspondence submitted by TAP Pharmaceuticals on 5/29/2007-TAP acknowledges receiving notice on 4/13/2007, CA 07-331 filed in the D of Del on 5/25/2007 for infringement of the '098, '321, '632, '994. Patent Amendment submitted by TEVA on 11/16/2007-FedEx notice provided to Takeda in Osaka Japan on 4/16/2007, to Tap in Lake Forest IL on 4/13/2007, to EthyPharm SA in Saint Cloud FR on 4/16/2007, and Ethypharm in Houdan FR on 4/16/2007. 30 month stay of approval=10/16/2009, TEVA was not sued on the '560, '132 and '959 patents. On 6/12/2009 the sponsor provided a revised exclusivity statement which addressed the M-85 exclusivity. The 6/12/09 amendment also asserted that the '485 and '942 patents are late listed with respect to TEVAs ANDA and therefore TEVA need not certify to them.

The '485 and '942 patents were issued by the PTO on 7/15/2008 and 10/7/2008 respectively. According to patent files retained by the OB, the '485 patent was submitted for listing on 11/18/2008 and the '942 was submitted on 1/21/2009. Since it is clear that each of these patents was submitted for listing well after 30 days of issuance and TEVAs ANDA had been pending with the Agency since 12/27/2006 both of these patents are late listed with respect to this ANDA. Therefore no certification is required.

TEVA was the first applicant to submit an ANDA for this drug product which contained a PIV certification to a listed patent. However, in order to retain eligibility for 180 day exclusivity TEVA needed to secure Tentative Approval by NLT 6/27/2009. TA was not issued by this date therefore TEVA has forfeited eligibility for 180 day exclusivity.

Final Recommendation: ANDA is eligible for Full Approval but no longer remains eligible for 180 day exclusivity.

UPdate 10/12/2010: On this date Marty called Jean Zwicker and asked for the following:

1. Copy of the dismissal order regarding the '994 patent
2. update on the disposition of the appeal of the DC decision finding that TEVA did not infringe the '632(DC opinion was from August of 2009)

Update 10/13/2010-e mail rec'd from Jill Pastore of TEVA containing copies of the Stipulation and Order of Partial Dismissal for the '994 patent. This Dismissal was entered by the Court on 10/24/2008. Takeda also granted TEVA a covenant not to sue with respect to the '994 patent. TEVA also provided a copy of the Mandate which was issued on 3/1/2010 affirming the DC decision that TEVA does not infringe the '632 patent. The DC decision that was affirmed by the CAFC can be located in the 1/14/2010 patent amendment in DARRTs.

Final Patent Disposition:
'098-now expired
'743-now expired
'632-TEVA won in DC with decision affirmed by CAFC
'994-suit dismissed with respect to this patent
'485-late listed

'942-late listed, TEVA also granted covenant not to sue as this patent is a continuation of the '994 patent.

Final recommendation is the same as mentioned above--ANDA is eligible for Full Approval but they are no longer eligible for 180 day exclusivity.

2. Project Manager, Theresa Liu Team 7 Date6/23/09 Date1/11/10
Review Support Branch Initialstcl Initialstcl

Original Rec'd date12/27/06
Date Acceptable for Filing12/27/06
Patent Certification (type)pIV
Date Patent/Exclus.expires11/17/2019
Citizens' Petition/Legal Case Yes☒ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver Yes ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 6/24/09
Date of Office Bio Review 6/24/09
Date of Labeling Approv. Sum 6/26/09
Labeling Acceptable Email Rec'd Yes ☒ No ☐
Labeling Acceptable Email filed Yes ☒ No ☐
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer:
Date_____
Name/Initials_____

Labeling Team Leader:
Date10/15/10
Name/Initials rlw/for

Comments:
Final-printed labeling (FPL) found acceptable for approval 10/14/10. REMS is not required.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 13Oct10
OGD Regulatory Counsel, Post-MMA Language Included ☐ InitialsDTR
Comments:Changes to AP ltr saved to V drive.

5. Div. Dir./Deputy Dir. Date10/7/10
Chemistry Div. II InitialsFF

Comments:Dissolution spec. upgraded. cmc ok.

6. Frank Holcombe **First Generics Only** Date 10/14/10
Assoc. Dir. For Chemistry Initialsrlw/for
Comments: (First generic drug review)
With her endorsement of this approval, the chemistry division director has determined that there are no precedent setting issues associated with the review and approval of this drug product. Thus, no further CMC review is required.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Prevacid SoluTab Delayed-release Orally Disintegrating Tablets, 15 and 30 mg
Takeda Pharmaceuticals north America, Inc. NDA 21-428

8. Peter Rickman Date 10/15/10
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐
Comments: Bioequivalence studies (fasting and non-fasting) on the 30 mg tablet strength found acceptable. In-vitro dissolution data for both tablet strengths also found acceptable. Data for alternate drug product manufacturing site (Kfar-Saba, Israel to Sellersville, PA) and minor firmulation changes reviewed - Dissolution data (multipoint) and single-dose fasting bioequivalence study comparing relative bioequivalence (rate and extent of absorption) - Sellersville vs. RLD. Waiver granted to the 15 mg strength under 21 CFR 320.24(b)(6). Additional dissolution data requested by DBE on 3/23/10. Office-level bio endorsed 12/21/07, 6/24/09, 5/25/10, 7/27/10 and 9/22/10.

Final-printed labeling (FPL) found acceptable for approval 10/30/09 as updated 10/13/10.

CMC found acceptable for approval (Chemistry Review #6)

OR

8. Robert L. West Date 10/15/10
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 6/24/09 (Verified 10/14/10). No "OAI" Alerts noted.

Refer to the regulatory assessment above by M.Shimer for the regulatory/legal basis for the approval of this ANDA.

This ANDA is recommended for approval.

9. Gary Buehler Date 10/15/10
Director, OGD Initials rlw/for
Comments: for Keith Webber, Ph.D.
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Theresa Liu Team 7 Date10/15/10
Review Support Branch Initials fjn
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
10/15/10Time notified of approval by phone 10/15/10Time approval letter faxed

FDA Notification:
10/15/10Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
n/aDate Approval letter copied to \\CDS014\DRUGAPP\ directory.

ORANGE BOOK PRINT OFF:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 021428 Product 002 in the OB_Rx list.

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Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021428	002	4628098*PED	Nov 10, 2009				
N021428	002	5013743	Feb 12, 2010			U - 452	
N021428	002	5013743*PED	Aug 12, 2010				
N021428	002	5464632	Nov 7, 2012				
N021428	002	5464632*PED	May 7, 2013				
N021428	002	6328994	May 17, 2019				
N021428	002	6328994*PED	Nov 17, 2019				
N021428	002	7399485	May 26, 2018		Y		
N021428	002	7399485*PED	Nov 26, 2018				
N021428	002	7431942	May 17, 2019		Y		
N021428	002	7431942*PED	Nov 17, 2019				

<>

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021428	002	PED	Apr 28, 2012
N021428	002	M - 85	Oct 28, 2011

Additional information:

1. **Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).**
2. **Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.**
3. ****** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.**

View a list of all patent use codes
View a list of all exclusivity codes
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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through September, 2010
Patent and Generic Drug Product Data Last Updated: October 14, 2010

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/s/

FRANK J NICE
10/15/2010