# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

***APPLICATION NUMBER:***

# ANDA 78003

**Name:** Esomeprazole Magnesium Delayed-release Capsules USP, 20 mg and 40 mg

**Sponsor:** IVAX Pharmaceuticals, Inc.
(an indirect and wholly owned subsidiary of Teva Pharmaceuticals, USA)

**Approval Date:** January 26, 2015

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 78003

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 78003

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 078003

**APPROVAL**

IVAX Pharmaceuticals, Inc.
(An indirect and wholly owned subsidiary of Teva Pharmaceuticals USA)
425 Privet Road
Horsham, PA 19044

Attention: Rich Leone
Senior Director, Regulatory Affairs, U.S. Generics

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated November 25, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Esomeprazole Magnesium Delayed-release Capsules USP, 20 mg and 40 mg.

Reference is also made to the complete response letter issued by this office on July 11, 2014, and to your amendments dated August 22, October 29, and December 12, 2014; and January 5, 2015.

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.[1] The Division of Bioequivalence has determined your Esomeprazole Magnesium Delayed-release Capsules USP, 20 mg and 40 mg, to be bioequivalent and, therefore, therapeutically equivalent to the RLD, Nexium Delayed-release Capsules, 20 mg and 40 mg, of AstraZeneca Pharmaceuticals LP (AstraZeneca).

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 using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |

[1] The agency has determined that the applicant who was first to file a substantially complete ANDA with a paragraph IV certification to one or more of the patents listed for the reference listed drug (RLD) has forfeited its eligibility for 180-day generic drug exclusivity under section 505(j)(5)(B)(iv) of the Act.

| **Specifications** | Acid stage: NMT (b)(4)% in 120 minutes<br>Buffer stage: NLT (b)(4)% in 30 minutes |
|---|---|

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement – Changes Being Effected when there are no revisions to the "interim" specifications or when 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, AstraZeneca's Nexium Delayed-release Capsules, 20 mg and 40 mg, is subject to periods of patent protection. The following unexpired patents and expiration dates (with pediatric exclusivity added) are currently listed[2] in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

| U.S. Patent No. | Expiration Date |
|---|---|
| 5,714,504 (the '504 patent) | August 3, 2015 |
| 5,900,424 (the '424 patent) | November 4, 2016 |
| 6,147,103 (the '103 patent) | April 9, 2019 |
| 6,166,213 (the '213 patent) | April 9, 2019 |
| 6,191,148 (the '148 patent) | April 9, 2019 |
| 6,369,085 (the '085 patent) | November 25, 2018 |
| 6,428,810 (the '810 patent) | May 3, 2020 |
| 7,411,070 (the '070 patent) | November 25, 2018 |
| 8,466,175 (the '175 patent) | November 25, 2018 |

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Esomeprazole Magnesium Delayed-release Capsules USP, 20 mg and 40 mg, under this ANDA. You have notified the agency that IVAX Pharmaceuticals, Inc., an indirect and wholly owned subsidiary of Teva Pharmaceuticals USA (Teva), complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Teva for infringement of the '504, '810, and '085 patents within the statutory 45-day period in the United States District Court for the District of New Jersey [AstraZeneca AB, Aktiebolaget Hässle, AstraZeneca LP, KBI Inc., and KBI-E Inc. v. Ivax Corporation, Ivax Pharmaceuticals, Inc., Zenith Laboratories, Inc., Teva Pharmaceutical Industries Ltd., and Teva Pharmaceuticals USA., Civil Action No. 06 CV 1057] and that in the same court, litigation was initiated against Teva for infringement of the '070 patent within the statutory 45-day period [AstraZeneca AB, Aktiebolaget Hässle, AstraZeneca LP, KBI Inc., and KBI-E Inc. v. Ivax Corporation, Ivax Pharmaceuticals, Inc., Ivax Pharmaceuticals NV, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., and Cipla, Ltd., Civil Action No. 08 CV 4993]. You also notified the agency of the dismissal of these cases.

[2] Also listed is U.S. Patent No. 5,690,960 (the '960 patent) which expired on November 25, 2014. A pediatric exclusivity period associated with the '960 patent expires on May 25, 2015.

With respect to the pediatric exclusivity period scheduled to expire on May 25, 2015 that is associated with the '960 patent, you have provided a copy of a letter from AstraZeneca that waives this exclusivity period, effective from December 15, 2014. This ANDA is therefore eligible for approval.

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
Office of Prescription Drug Promotion
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 Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

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/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

William P. Rickman -S

Digitally signed by William P. Rickman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300043242, cn=William P. Rickman -S
Date: 2015.01.26 12:19:11 -05'00'

For Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 78003

# OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 078003

**COMPLETE RESPONSE**

IVAX Pharmaceuticals, Inc.
An indirect and wholly owned subsidiary of Teva Pharmaceuticals USA
Attention: Scott D. Tomsky
Vice President, Regulatory Affairs, NA Generics
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated November 23, 2005, received November 25, 2005, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Magnesium Delayed-release Capsules USP, 20 mg and 40 mg.

We acknowledge receipt of your amendments dated March 31, and May 16, 2014. The March 31, 2014 submission constituted a complete response to our February 10, 2014, action letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

## PRODUCT QUALITY

The deficiencies presented below represent minor deficiencies.

1. DMF 18821 for esomeprazole magnesium is currently inadequate and the DMF holder, Cipla Limited, was notified of any deficiencies on June 30, 2014 and they have responded. Please consult the DMF holder regarding the drug substance (b) (4)

## BIOEQUIVALENCE

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns 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.

The Division of Bioequivalence II (DB II) has completed its review of your submissions. The following deficiencies have been identified:

**Deficiencies related to your In vitro test for Nasogastric (NG) Tube administration:**

1. We acknowledge that you conducted particle size distribution study after delivery through syringe and NG tube using water with different pH (5.4, 5.9 and 6.4) and different soak times (0, 15, 30 and 60 minutes). However, your particle size distribution analysis using microscopy may not be suitable to determine particle size distribution (D10, D50 and D90), therefore it is not acceptable.

   In addition, since a tap water with pH varying between 6.5 to 8.5 may be possibly used to deliver the medicine to hospitably patients, please determine the comparative particle size of granule dispersion using 12 units each strength of the test and the reference products **in pH 7.5 water with soak times of 0 and 15 minutes**. Please follow the procedure described in the deficiency letter (deficiency #2) issued by the DB II on 9/26/2012.

   Please provide the particle size data at the **D10, D50**, and **D90** levels **using laser diffraction method**. Please also provide validation reports for particle size distribution study.

2. We acknowledge that you have conducted acid resistance stability testing for both 20 mg and 40 mg strengths after recovery through a combination of oral syringe and 8 French NG tube in water with different pH (5.4, 5.9, and 6.4) at 0, 15, 30 and 60 minutes. For the same reason mentioned above in deficiency 1, please repeat comparative acid resistance stability testing for both strengths using 12 units of the test and the reference products **in pH 7.5 water at 0 minute and 15 minutes.** Please follow the procedure described in the deficiency letter (deficiency #4) issued by the DB II on 9/26/2012.

3. We acknowledge that you had conducted comparative recovery testing in your previous amendment dated 04/25/2013, where the pH of water used in the recovery test was not defined. To ensure that the test product has the same recovery as that of the RLD using different pH of water (5.5, 6.5 and 7.5), please repeat the comparative recovery studies of the dispersed granules for both 20 mg and 40 mg strengths using the 8 French nasogastric tubes in 50 ml water **with different pH (5.5, 6.5, and 7.5) at 0 minute and 15 minutes**. Please use 12 units of the test and the reference products and follow the procedure described in previous deficiency letter (deficiency #3) issued by the DB II on 9/26/2012.

4. Please provide the expiration date for the reference listed product (20 mg: batch #J014509; 40 mg: batch# J012025) and testing dates for your particle size distribution study and acid resistance testing submitted in your current amendment dated 3/31/2014.

## LABELING

1. CONTAINER
    a. Reduce the prominence of the company logo. Please ensure that the prominence of the company logo be less prominent than that of the drug product name and strength.
    b. Please use title case for the drug product name for better recognition of the drug name.
    c. Include the expiration date rather than the issue date.

2. INSERT
    a. Replace the term "Nexium" (without the dosage form associated) with "esomeprazole magnesium" rather than "esomeprazole" throughout the text.
    b. Upon further review, we note that the information for the age group of less than 1 year is specifically associated with the oral suspension only. For this reason, we ask that you the remove any information associated with the age group of less than 1 year old from you labeling throughout the text.

3. MEDICATION GUIDE
    See comment under INSERT.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

## FACILITY INSPECTIONS

We have not yet completed inspection(s)/compliance evaluation of your manufacturing facility(s) named or referenced in this ANDA. We must perform a complete evaluation of the information associated with the inspection before determining that the site(s) are satisfactory and this ANDA may be approved.

## OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**RESUBMISSION**
**MINOR**
**COMPLETE RESPONSE AMENDMENT**
**CHEMISTRY / BIOEQUIVALENCE / LABELING**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, contact Heidi Lee, Regulatory Project Manager, at heidi.lee@fda.hhs.gov or 240-402-8989.

Sincerely yours,

*{See appended electronic signature page}*

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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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.**

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/s/

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WILLIAM P RICKMAN
07/11/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 078003

**COMPLETE RESPONSE**

IVAX Pharmaceuticals, Inc.
An indirect and wholly owned subsidiary of Teva Pharmaceuticals USA
Attention: Scott D. Tomsky
Vice President, US Generics Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated November 23, 2005, received November 25, 2005, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Magnesium Delayed-Release Capsules USP, 20 mg and 40 mg.

We acknowledge receipt of your amendments dated November 13, 2006; March 4, May 29, and September 12, 2008; September 22, 2009; August 19, 2011; August 8, 2012; April 25 and September 20, 2013.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

## PRODUCT QUALITY

The deficiencies presented below represent MINOR deficiencies.

1. The amendment for the DMF 18821 has been reviewed and found inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has responded to the deficiencies.

2. (b) (4)

3.

4.

5.

6.

(b) (4)

**BIOEQUIVALENCE**

The Division of Bioequivalence II (DB II) has completed its review of your submissions acknowledged on the cover sheet. The following deficiencies have been identified:

**Deficiencies related to your In vitro test for Nasogastric (NG) Tube administration:**

1. Your sample preparation for particle size analysis by laser diffraction method is incorrect. Your test procedure states that, "*take out 10 ml of the dispersion and proceed for particle size test at 0 minutes/15 minutes as mentioned in section D for particle size test.*" However, due to rapid sedimentation, there is absence of particles remaining in solution per your observation. Instead of taking out 10 mL of sample from the dispersion, you should collect the pellets in the container in order to determine the particle size distribution of the pellets.

   Please determine the comparative particle size of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, before (in syringe) and after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 and 15 min. **Please collect the pellets** in the container to determine the particle size distribution of the pellets.

   Please provide all particle size data at the D10, D50, and D90 levels. Please visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all the observations and supporting photographs. Please take photos at different stages (syringe with capsule's content, attaching syringe to the NG tube, injecting water with pellets into the NG tube, flushing NG tube etc.).

2. Please provide validation reports for your particle size distribution study.

3. Please provide information of the nasogastric tube and syringe (e.g. material, brand, size, etc.) and type and pH of the water used in your in vitro NG tube study (e.g. sedimentation, particle size, recovery and acid resistance).

4. Since your test product is designed in such a way that enteric coating starts dissolving above pH 5.5, and the pH of the water may vary between 6.5 to 8.5, there is a concern that the process of dispersing capsule in water, soaking for a certain time, and dispensing through an oral syringe with an NG tube might adversely impact the integrity of the enteric coating. Please demonstrate the stability of the dispersed granules in different pH of water with different soak time prior to performing the acid resistance testing.

   Please repeat acid resistance stability testing using 12 units of both strengths of the test and the reference products as follows:

   a. Prepare the granule dispersion in 50 mL water (soak for 15 min), and collect the contents of granule dispersion at the tube exit. **Please measure the initial pH of water and pH of the water after the dispersed granules are delivered through the combination of syringe and NG tube.**

   b. Transfer the contents of granule dispersion into dissolution vessel containing 300 mL of 0.1 N HCl maintained at 37 ±0.5°C.

   c. Flush the nasogastric tube with additional water and transfer any remaining contents into the dissolution media mentioned above.

   d. Acid resistance testing should be conducted using USP Apparatus II at 100 rpm. Analyze the amount of esomeprazole released at 120 minutes.

   **Please repeat the above steps using different pH of water (e.g. pH 6, 7 and 8) with different soak times in syringe (e.g. 15 min, 30 min and 60 min).**

## LABELING

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. It appears that you submitted all labeling pieces in draft. You are required to submit the labeling in final printed format for full approval.

   b. Please be advised that your drug product is now the subject of a USP monograph. We recommend that you include the designation “USP” in association with the drug product name on all labeling pieces. However, we encourage the inclusion of "USP" in association with your drug product name in the following sections only in the insert labeling: the

TITLE, INDICATIONS AND USAGE, DESCRIPTION and HOW SUPPLIED/STORAGE AND HANDLING.

2. CONTAINER – 30s, 90s, and 1000s

   a. See GENRAL COMMENTS above.

   b. Although it is not required to include the bar code on the container label for the drug product which is directly dispensed to the patients, we encourage the inclusion of the bar code or/and comment.

   c. Please note that the patient information leaflet for the Nexium® Delayed-Release Capsules was replaced with medication guide on September 28, 2012. Please revise the pharmacist directive accordingly.

   d. 1000s

      We recommend that you include the statement "This package is not intended for household use."

3. (b) (4)

4.

5. INSERT

   a. GENRAL

      i. See GENERAL COMMENTS above.

      ii. Please note that updated Nexium® labeling was approved on October 9, 2012. Please revise your labeling accordingly. Please ensure that the highlight sections and the entire insert of the final printed labeling can easily be read and that the type size not be smaller than 6 points. We refer you to 21 CFR 201.56(d) regarding PLR format for further guidance.

   b. DESCRIPTIONS

      We note that you revised the text "…either 20 mg or 40 mg of esomeprazole (present as (b) (4) mg esomeprazole magnesium dehydrate" to read "…either 20 mg or 40 mg of esomeprazole (present as

21.69 mg or 43.38 mg esomeprazole magnesium dehydrate)". Please justify this revision and/or comment.

6. MEDICATION GUIDE

a. See GENRAL COMMENTS above.

Please note that the patient information leaflet for the Nexium® Capsules was replaced with medication guide September 28, 2012. Please submit your proposal for the medication guide.

b. Please describe your plan for supplying the medication guide with your product. (e.g., how many medication guides will you supply for each container size and how will these medication guides be supplied.)

c. Please be advised that the final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 points.

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

## FACILITY INSPECTIONS

We have not yet completed inspection(s)/compliance evaluation of your manufacturing facility(s) named or referenced in this ANDA. We must perform a complete evaluation of the information associated with the inspection before determining that the site(s) are satisfactory and this ANDA may be approved.

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A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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**RESUBMISSION**
**MINOR**
**COMPLETE RESPONSE AMENDMENT**
**CHEMISTRY / BIOEQUIVALENCE / LABELING**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, contact Heidi Lee, Regulatory Project Manager, at heidi.lee@fda.hhs.gov or (240) 276-9717.

Sincerely yours,

*{See appended electronic signature page}*

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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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.**

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/s/

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WILLIAM P RICKMAN
02/10/2014

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 78003

# LABELING

NDC 0093-6450-56

# ESOMEPRAZOLE MAGNESIUM

## Delayed-Release Capsules USP

## 20 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

**30 CAPSULES**

TEVA

*Each delayed-release capsule contains 20 mg esomeprazole (present as 21.69 mg of esomeprazole magnesium dihydrate).

**Usual Dosage:** See package insert for full prescribing information.

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

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

**KEEP CONTAINER TIGHTLY CLOSED**

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

M.L.NO. PD/46

Manufactured In India By:
CIPLA LTD., Kurkumbh, India

Manufactured For:
TEVA PHARMACEUTICALS USA, INC.
North Wales, PA 19454

KE46 B

Rev. A 7/2014

N
3 0093-6450-56 7

NDC 0093-6450-98

# ESOMEPRAZOLE MAGNESIUM

## Delayed-Release Capsules USP

## 20 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

**90 CAPSULES**

TEVA

*Each delayed-release capsule contains 20 mg esomeprazole (present as 21.59 mg of esomeprazole magnesium dihydrate).

**Usual Dosage:** See package insert for full prescribing information.

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

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

**KEEP CONTAINER TIGHTLY CLOSED**

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

M.L.NO. PD/46

Manufactured In India By:
CIPLA LTD., Kurkumbh, India

Manufactured For:
TEVA PHARMACEUTICALS USA, INC.
North Wales, PA 19454

KE47 B

Rev. A 7/2014

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3 0093-6450-98 7

NDC 0093-6450-10

# ESOMEPRAZOLE MAGNESIUM

## Delayed-Release Capsules USP

## 20 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

1000 CAPSULES

TEVA

*Each delayed-release capsule contains 20 mg esomeprazole (present as 21.69 mg of esomeprazole magnesium dihydrate).

**Usual Dosage:** See package insert for full prescribing information.

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

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

**KEEP CONTAINER TIGHTLY CLOSED**

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

This package is not intended for household use.

M.L.NO. PD/46

Manufactured In India By:
CIPLA LTD.
Kurkumbh, India
Manufactured For:
TEVA PHARMACEUTICALS USA, INC.
North Wales, PA 19454

Rev. A 7/2014

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N 3 0093-6450-10 9

NDC 0093-6451-56

# ESOMEPRAZOLE MAGNESIUM

## Delayed-Release Capsules USP

## 40 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

30 CAPSULES

TEVA

*Each delayed-release capsule contains 40 mg esomeprazole (present as 43.38 mg of esomeprazole magnesium dihydrate).

**Usual Dosage:** See package insert for full prescribing information.

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

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

**KEEP CONTAINER TIGHTLY CLOSED**

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

M.L.NO. PD/46

Manufactured In India By:
CIPLA LTD., Kurkumbh, India

Manufactured For:
TEVA PHARMACEUTICALS USA, INC.
North Wales, PA 19454

KE49 B

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NDC 0093-6451-98

# ESOMEPRAZOLE MAGNESIUM

## Delayed-Release Capsules USP

## 40 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

**90 CAPSULES**

TEVA

*Each delayed-release capsule contains 40 mg esomeprazole (present as 43.38 mg of esomeprazole magnesium dihydrate).

**Usual Dosage:** See package insert for full prescribing information.

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

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

**KEEP CONTAINER TIGHTLY CLOSED**

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

M.L.NO. PD/46

Manufactured In India By:
CIPLA LTD., Kurkumbh, India

Manufactured For:
TEVA PHARMACEUTICALS USA, INC.
North Wales, PA 19454

KE50 B

Rev. A 7/2014

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3 0093-6451-98 4

NDC 0093-**6451**-10

# ESOMEPRAZOLE MAGNESIUM

## Delayed-Release Capsules USP

## 40 mg*

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

**1000 CAPSULES**

TEVA

*Each delayed-release capsule contains 40 mg esomeprazole (present as 43.38 mg of esomeprazole magnesium dihydrate).

**Usual Dosage:** See package insert for full prescribing information.

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

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

**KEEP CONTAINER TIGHTLY CLOSED**

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

This package is not intended for household use.

M.L.NO. PD/46

Manufactured In India By:
CIPLA LTD.
Kurkumbh, India

Manufactured For:
TEVA PHARMACEUTICALS USA, INC.
North Wales, PA 19454

N 0093-6451-10 3 6

KE51 B

Rev. A 7/2014

ESOMEPRAZOLE MAGNESIUM DELAYED-RELEASE CAPSULES USP

6450
6451

℞ only

Rev. B 1/2015

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use esomeprazole magnesium delayed-release capsules USP safely and effectively. See full prescribing information for esomeprazole magnesium delayed-release capsules USP.**

**ESOMEPRAZOLE MAGNESIUM delayed-release capsules USP, for oral use**

**Initial U.S. Approval: 1989 (omeprazole)**

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

| | |
|---|---|
| Warnings and Precautions, Interactions with Diagnostic Investigations for Neuroendocrine Tumors (5.10) | 03/2014 |
| Contraindications (4) | 12/2014 |
| Warnings and Precautions, Acute Interstitial Nephritis (5.3) | 12/2014 |
| Warnings and Precautions, Cyanocobalamin (vitamin B-12) Deficiency (5.4) | 12/2014 |

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

Esomeprazole Magnesium Delayed-Release Capsules USP are a proton pump inhibitor indicated for the following:

- Treatment of gastroesophageal reflux disease (GERD) (1.1)
- Risk reduction of NSAID-associated gastric ulcer (1.2)
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (1.3)
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome (1.4)

**-----DOSAGE AND ADMINISTRATION-----**

| Indication | Dose | Frequency |
|---|---|---|
| **Gastroesophageal Reflux Disease (GERD)** | | |
| Adults | 20 mg or 40 mg | Once daily for 4 to 8 weeks |
| 12 to 17 years | 20 mg or 40 mg | Once daily for up to 8 weeks |
| 1 to 11 years | 10 mg or 20 mg | Once daily for up to 8 weeks |
| **Risk Reduction of NSAID-Associated Gastric Ulcer** | | |
| | 20 mg or 40 mg | Once daily for up to 6 months |
| ***H. pylori* Eradication** *(Triple Therapy):* | | |
| Esomeprazole Magnesium Delayed-Release Capsules | 40 mg | Once daily for 10 days |
| Amoxicillin | 1000 mg | Twice daily for 10 days |
| Clarithromycin | 500 mg | Twice daily for 10 days |
| **Pathological Hypersecretory Conditions** | | |
| | 40 mg | Twice daily |

See full prescribing information for administration options (2)

Patients with severe liver impairment-do not exceed dose of 20 mg (2)

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

Esomeprazole Magnesium Delayed-Release Capsules: 20 mg and 40 mg (3)

**--------CONTRAINDICATIONS--------**

Patients with known hypersensitivity to proton pump inhibitors (PPIs) (angioedema and anaphylaxis have occurred). (4)

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

- Symptomatic response does not preclude the presence of gastric malignancy (5.1)
- Atrophic gastritis has been noted with long-term omeprazole therapy. (5.2)
- Acute interstitial nephritis has been observed in patients taking PPIs. (5.3)
- Cyanocobalamin (vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.4)
- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea. (5.5)
- Avoid concomitant use of esomeprazole magnesium with clopidogrel. (5.6)
- 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. (5.7)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs. (5.8)
- Avoid concomitant use of esomeprazole magnesium with St. John's Wort or rifampin due to the potential reduction in esomeprazole levels (5.9, 7.3)
- Interactions with diagnostic investigations for neuroendocrine tumors: Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors. (5.10, 12.2)

**--------ADVERSE REACTIONS--------**

Most common adverse reactions (6.1):

- Adults (≥ 18 years) (incidence ≥ 1%) are headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth
- Pediatric (1 to 17 years) (incidence ≥ 2%) are headache, diarrhea, abdominal pain, nausea, and somnolence

**To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-866-832-8537 or drug.safety@tevapharm.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**--------DRUG INTERACTIONS--------**

- May affect plasma levels of antiretroviral drugs – use with atazanavir and nelfinavir is not recommended; if saquinavir is used with esomeprazole magnesium, monitor for toxicity and consider saquinavir dose reduction. (7.1)
- May interfere with drugs for which gastric pH affects bioavailability (e.g., ketoconazole, iron salts, erlotinib, digoxin and mycophenolate mofetil). Patients treated with esomeprazole magnesium and digoxin may need to be monitored for digoxin toxicity. (7.2)
- Combined inhibitor of CYP 2C19 and 3A4 may raise esomeprazole levels. (7.3)
- Clopidogrel: esomeprazole magnesium decreases exposure to the active metabolite of clopidogrel. (7.3)
- May increase systemic exposure of cilostazol and an active metabolite. Consider dose reduction. (7.3)
- Tacrolimus: esomeprazole magnesium may increase serum levels of tacrolimus (7.5)
- Methotrexate: esomeprazole magnesium may increase serum levels of methotrexate. (7.7)

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

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Revised: 1/2015**

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

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

### 1.1 Treatment of Gastroesophageal Reflux Disease (GERD)

*Healing of Erosive Esophagitis*

Esomeprazole Magnesium Delayed-Release Capsules USP are indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8 week course of Esomeprazole Magnesium Delayed-Release Capsules USP may be considered.

*Maintenance of Healing of Erosive Esophagitis*

Esomeprazole Magnesium Delayed-Release Capsules USP are indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.

*Symptomatic Gastroesophageal Reflux Disease*

Esomeprazole Magnesium Delayed-Release Capsules USP are indicated for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults and children 1 year or older.

### 1.2 Risk Reduction of NSAID-Associated Gastric Ulcer

Esomeprazole Magnesium Delayed-Release Capsules USP are indicated for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers. Patients are considered to be at risk due to their age (≥ 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months.

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

Triple Therapy (Esomeprazole Magnesium Delayed-Release Capsules USP plus amoxicillin and clarithromycin): Esomeprazole Magnesium Delayed-Release Capsules USP, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence *[see Dosage and Administration (2) and Clinical Studies (14)]*.

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted [*see Clinical Pharmacology (12.4) and the prescribing information for clarithromycin*].

### 1.4 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

Esomeprazole Magnesium Delayed-Release Capsules USP are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

## 2 DOSAGE AND ADMINISTRATION

Esomeprazole Magnesium Delayed-Release Capsules are supplied as delayed-release capsules for oral administration. The recommended dosages are outlined in **Table 1**. Esomeprazole Magnesium Delayed-Release Capsules should be taken at least one hour before meals.

The duration of proton pump inhibitor administration should be based on available safety and efficacy data specific to the defined indication and dosing frequency, as described in the prescribing information, and individual patient medical needs. Proton pump inhibitor treatment should only be initiated and continued if the benefits outweigh the risks of treatment.

**Table 1: Recommended Dosage Schedule of Esomeprazole Magnesium Delayed-Release Capsules**

| Indication | Dose | Frequency |
|---|---|---|
| **Gastroesophageal Reflux Disease (GERD)** | | |
| Healing of Erosive Esophagitis | 20 mg or 40 mg | Once Daily for 4 to 8 weeks* |
| Maintenance of Healing of Erosive Esophagitis | 20 mg | Once Daily** |
| Symptomatic Gastroesophageal Reflux Disease | 20 mg | Once Daily for 4 Weeks*** |
| **Pediatric GERD** | | |
| **12 to 17 Year Olds** | | |
| Healing of Erosive Esophagitis | 20 mg or 40 mg | Once Daily for 4 to 8 Weeks |
| Symptomatic GERD | 20 mg | Once Daily for 4 Weeks |
| **1 to 11 Year Olds**+ | | |
| Short-term Treatment of Symptomatic GERD | 10 mg | Once Daily for up to 8 Weeks |
| Healing of Erosive Esophagitis | | |
| weight < 20 kg | 10 mg | Once Daily for 8 Weeks |
| weight ≥ 20 kg | 10 mg or 20 mg | Once Daily for 8 Weeks |
| **Risk Reduction of NSAID-Associated Gastric Ulcer** | 20 mg or 40 mg | Once Daily for up to 6 months** |
| ***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence** | | |
| *Triple Therapy:* | | |
| Esomeprazole magnesium delayed-release capsules | 40 mg | Once Daily for 10 Days |
| Amoxicillin | 1000 mg | Twice Daily for 10 Days |
| Clarithromycin | 500 mg | Twice Daily for 10 Days |
| **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome** | 40mg † | ‡Twice Daily |

* [*See Clinical Studies (14.1).*] The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4 to 8 weeks, an additional 4 to 8 weeks of treatment may be considered.

** Controlled studies did not extend beyond six months.

*** If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.

+ Doses over 1 mg/kg/day have not been studied.

† The dosage of esomeprazole magnesium delayed-release capsules in patients with pathological hypersecretory conditions varies with the individual patient. Dosage regimens should be adjusted to individual patient needs.

‡ Doses up to 240 mg daily have been administered [*see Drug Interactions (7)*].

Please refer to amoxicillin and clarithromycin prescribing information for Contraindications, Warnings, and dosing in elderly and renally-impaired patients.

**Special Populations**

*Hepatic Insufficiency*

In patients with mild to moderate liver impairment (Child Pugh Classes A and B), no dosage adjustment is necessary. For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg of esomeprazole magnesium delayed-release capsules should not be exceeded [*see Clinical Pharmacology (12.3)*].

Directions for use specific to the route and available methods of administration for each of these dosage forms are presented in **Table 2**.

**Table 2: Administration Options**

| Administration Options (See text following table for additional instructions.) | | |
|---|---|---|
| **Dosage Form** | **Route** | **Options** |
| | | |
| Delayed-Release Capsules | Oral | Capsule can be swallowed whole.<br>-or-<br>Capsule can be opened and mixed with applesauce. |
| | | |
| Delayed-Release Capsules | Nasogastric Tube | Capsule can be opened and the intact granules emptied into a syringe and delivered through the nasogastric tube. |

Esomeprazole magnesium delayed-release capsules should be swallowed whole.

Alternatively, for patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the esomeprazole magnesium delayed-release capsule can be opened, and the granules inside the capsule carefully emptied onto the applesauce. The granules should be mixed with the applesauce and then swallowed immediately: do not store for future use. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The granules should not be chewed or crushed. If the granules/applesauce mixture is not used in its entirety, the remaining mixture should be discarded immediately.

For patients who have a nasogastric tube in place, esomeprazole magnesium delayed-release capsules can be opened and the intact granules emptied into a 60 mL catheter tipped syringe and mixed with 50 mL of water. It is important to only use a catheter tipped syringe when administering esomeprazole magnesium through a nasogastric tube. Replace the plunger and shake the syringe vigorously for 15 seconds. Hold the syringe with the tip up and check for granules remaining in the tip. Attach the syringe to a nasogastric tube and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the granules, the nasogastric tube should be flushed with additional water. Do not administer the granules if they have dissolved or disintegrated.

The mixture must be used immediately after preparation.

## 3 DOSAGE FORMS AND STRENGTHS

Esomeprazole magnesium delayed-release capsules, 20 mg, are available as off-white to pale yellow granule-filled, light turquoise blue, opaque, hard-gelatin capsules, spin-printed "Ꝣ" and "6450" on the cap and "20 mg" on the body in gold ink containing 20 mg esomeprazole packaged in bottles of 30, 90, and 1000 capsules.

Esomeprazole magnesium delayed-release capsules, 40 mg, are available as off-white to pale yellow granule-filled, light turquoise blue, opaque, hard-gelatin capsules, spin-printed "Ꝣ" and "6451" on the cap and "40 mg" on the body in gold ink containing 40 mg esomeprazole packaged in bottles of 30, 90, and 1000 capsules.

## 4 CONTRAINDICATIONS

Esomeprazole magnesium is contraindicated in patients with known hypersensitivity to substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria [*see Adverse Reactions (6)*].

For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with esomeprazole magnesium, refer to the CONTRAINDICATIONS section of their package inserts.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Concurrent Gastric Malignancy

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

### 5.2 Atrophic Gastritis

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole is an enantiomer.

### 5.3 Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including esomeprazole magnesium. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue esomeprazole magnesium if acute interstitial nephritis develops [*see Contraindications (4)*].

### 5.4 Cyanocobalamin (vitamin B-12) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo-or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

### 5.5 *Clostridium difficile* Associated Diarrhea

Published observational studies suggest that PPI therapy like esomeprazole magnesium may be associated with an increased risk of C*lostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [*see Adverse Reactions (6.2)*].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with esomeprazole magnesium, refer to WARNINGS and PRECAUTIONS sections of those package inserts.

### 5.6 Interaction With Clopidogrel

Avoid concomitant use of esomeprazole magnesium with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using esomeprazole magnesium consider alternative anti-platelet therapy [*see Drug Interactions (7.3) and Pharmacokinetics (12.3)*].

### 5.7 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)*].

### 5.8 Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [*see Adverse Reactions (6.2)*].

### 5.9 Concomitant Use of Esomeprazole Magnesium With St. John's Wort or Rifampin

Drugs which induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease esomeprazole concentrations [*see Drug Interactions (7.3)*]. Avoid concomitant use of esomeprazole magnesium with St. John's Wort or rifampin.

### 5.10 Interactions With Diagnostic Investigations for Neuroendocrine Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary. [*see Clinical Pharmacology (12.2)*].

### 5.11 Concomitant Use of Esomeprazole Magnesium With Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients [*see Drug Interactions (7.7)*].

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

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 practice.

**Adults**

The safety of esomeprazole magnesium was evaluated in over 15,000 patients (aged 18 to 84 years) in clinical trials worldwide including over 8,500 patients in the United States and over 6,500 patients in Europe and Canada. Over 2,900 patients were treated in long-term studies for up to 6 to 12 months. In general, esomeprazole magnesium was well tolerated in both short and long-term clinical trials.

The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1,240 patients on esomeprazole magnesium 20 mg, 2,434 patients on esomeprazole magnesium 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse reactions (≥ 1%) in all three groups were headache (5.5, 5, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking esomeprazole magnesium or omeprazole.

Additional adverse reactions that were reported as possibly or probably related to esomeprazole magnesium with an incidence < 1% are listed below by body system:

*Body as a Whole:* abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, substernal chest pain, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors.

*Cardiovascular:* flushing, hypertension, tachycardia.

*Endocrine:* goiter.

*Gastrointestinal:* bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting.

*Hearing:* earache, tinnitus.

*Hematologic:* anemia, anemia hypochromic, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia.

*Hepatic:* bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased.

*Metabolic/Nutritional:* glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease.

*Musculoskeletal:* arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica.

*Nervous System/Psychiatric:* anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect.

*Reproductive:* dysmenorrhea, menstrual disorder, vaginitis.

*Respiratory:* asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis.

*Skin and Appendages:* acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculopapular, skin inflammation, sweating increased, urticaria.

*Special Senses:* otitis media, parosmia, taste loss, taste perversion.

*Urogenital:* abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria.

*Visual:* conjunctivitis, vision abnormal.

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to esomeprazole magnesium, were reported in ≤ 1% of patients: increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone [see *Clinical Pharmacology (12)*]. Decreases were seen in hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroxine.

Endoscopic findings that were reported as adverse reactions include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration.

The incidence of treatment-related adverse reactions during 6 month maintenance treatment was similar to placebo. There were no differences in types of related adverse reactions seen during maintenance treatment up to 12 months compared to short-term treatment.

Two placebo-controlled studies were conducted in 710 patients for the treatment of symptomatic gastroesophageal reflux disease. The most common adverse reactions that were reported as possibly or probably related to esomeprazole magnesium were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

**Pediatrics**

The safety of esomeprazole magnesium was evaluated in 316 pediatric and adolescent patients aged 1 to 17 years in four clinical trials for the treatment of symptomatic GERD [*see Clinical Studies (14.2)*]. In 109 pediatric patients aged 1 to 11 years, the most frequently reported (at least 1%) treatment-related adverse reactions in these patients were diarrhea (2.8%), headache (1.9%) and somnolence (1.9%). In 149 pediatric patients aged 12 to 17 years the most frequently reported (at least 2%) treatment-related adverse reactions in these patients were headache (8.1%), abdominal pain (2.7%), diarrhea (2%), and nausea (2%).

No new safety concerns were identified in pediatric patients.

**Combination Treatment With Amoxicillin and Clarithromycin**

In clinical trials using combination therapy with esomeprazole magnesium plus amoxicillin and clarithromycin, no additional adverse reactions specific to these drug combinations were observed. Adverse reactions that occurred were limited to those observed when using esomeprazole magnesium, amoxicillin, or clarithromycin alone.

The most frequently reported drug-related adverse reactions for patients who received triple therapy for 10 days were diarrhea (9.2%), taste perversion (6.6%), and abdominal pain (3.7%). No treatment-emergent adverse reactions were observed at higher rates with triple therapy than were observed with esomeprazole magnesium alone.

For more information on adverse reactions with amoxicillin or clarithromycin, refer to their package inserts, Adverse Reactions sections.

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

For more information on laboratory changes with amoxicillin or clarithromycin, refer to their package inserts, Adverse Reactions section.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of esomeprazole magnesium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system:

*Blood And Lymphatic:* agranulocytosis, pancytopenia.

*Eye:* blurred vision.

*Gastrointestinal:* pancreatitis, stomatitis, microscopic colitis.

*Hepatobiliary:* hepatic failure, hepatitis with or without jaundice.

*Immune System:* anaphylactic reaction/shock.

*Infections and Infestations:* GI candidiasis, *Clostridium difficile* associated diarrhea.

*Metabolism and Nutritional Disorders:* hypomagnesemia, with or without hypocalcemia and/or hypokalemia.

*Musculoskeletal and Connective Tissue:* muscular weakness, myalgia, bone fracture.

*Nervous System:* hepatic encephalopathy, taste disturbance.

*Psychiatric:* aggression, agitation, depression, hallucination.

*Renal and Urinary:* interstitial nephritis.

*Reproductive System and Breast:* gynecomastia.

*Respiratory, Thoracic, and Mediastinal:* bronchospasm.

*Skin and Subcutaneous Tissue:* alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

## 7 DRUG INTERACTIONS

### 7.1 Interference With Antiretroviral Therapy

Concomitant use of atazanavir and nelfinavir with proton pump inhibitors is not recommended. Coadministration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance. Coadministration of saquinavir with proton pump inhibitors is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction.

Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19.

*Reduced concentrations of atazanavir and nelfinavir*

For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg daily), AUC was decreased by 36% and 92%, $C_{max}$ by 37% and 89% and $C_{min}$ by 39% and 75% respectively for nelfinavir and M8. Following multiple doses of atazanavir (400 mg, daily) and omeprazole (40 mg, daily, 2 hr before atazanavir), AUC was decreased by 94%, $C_{max}$ by 96%, and $C_{min}$ by 95%. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended.

*Increased concentrations of saquinavir*

For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported, with an increase in AUC by 82%, in $C_{max}$ by 75%, and in $C_{min}$ by 106%, following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg daily coadministered days 11 to 15. Therefore, clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with esomeprazole magnesium. Dose reduction of saquinavir should be considered from the safety perspective for individual patients.

There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

### 7.2 Drugs for Which Gastric pH Can Affect Bioavailability

Due to its effects on gastric acid secretion, esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Esomeprazole is an enantiomer of omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Coadministration of digoxin with esomeprazole magnesium is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with esomeprazole magnesium.

Coadministration of omeprazole in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving esomeprazole magnesium and MMF. Use esomeprazole magnesium with caution in transplant patients receiving MMF [*see Clinical Pharmacology (12.3)*].

### 7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. *In vitro* and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin.

However, postmarketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam.

*Clopidogrel*

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of esomeprazole 40 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant administration of esomeprazole magnesium with clopidogrel. When using esomeprazole magnesium, consider use of alternative anti-platelet therapy [*see Pharmacokinetics (12.3)*].

Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased $C_{max}$ and AUC of cilostazol by 18% and 26% respectively. $C_{max}$ and AUC of one of its active metabolites, 3,4-dihydro-cilostazol, which has 4 to 7 times the activity of cilostazol, were increased by 29% and 69% respectively. Coadministration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its above mentioned active metabolite. Therefore a dose reduction of cilostazol from 100 mg twice daily to 50 mg twice daily should be considered.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. However, in patients with Zollinger-Ellison's Syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's Wort an inducer of CYP3A4. In a cross-over study in 12 healthy male subjects, St. John's Wort (300 mg three times daily for 14 days) significantly decreased the systemic exposure of omeprazole in CYP2C19 poor metabolizers ($C_{max}$ and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolizers ($C_{max}$ and AUC decreased by 49.6% and 43.9%, respectively). Avoid concomitant use of St. John's Wort or rifampin with esomeprazole magnesium.

### 7.4 Interactions With Investigations of Neuroendocrine Tumors

Drug-induced decrease in gastric acidity results in enterochromaffin-like cell hyperplasia and increased Chromogranin A levels which may interfere with investigations for neuroendocrine tumors [*see Warnings and Precautions (5.10) and Clinical Pharmacology (12.2)*].

### 7.5 Tacrolimus

Concomitant administration of esomeprazole and tacrolimus may increase the serum levels of tacrolimus.

### 7.6 Combination Therapy With Clarithromycin

Coadministration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin [*see Clinical Pharmacology (12.4)*].

Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions [*see Warnings and Precautions in prescribing information for clarithromycin*]. Because of these drug interactions, clarithromycin is contraindicated for coadministration with certain drugs [*see Contraindications in prescribing information for clarithromycin*].

### 7.7 Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted [*see Warnings and Precautions (5.11)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

***Teratogenic Effects***

Pregnancy Category C

*Risk Summary*

There are no adequate and well-controlled studies with esomeprazole magnesium in pregnant women. Esomeprazole is the S-isomer of omeprazole. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use.

Teratogenicity was not observed in animal reproduction studies with administration of oral esomeprazole magnesium in rats and rabbits with doses about 68 times and 42 times, respectively, an oral human dose of 40 mg (based on a body surface area basis for a 60 kg person). However, changes in bone morphology were observed in offspring of rats dosed through most of pregnancy and lactation at doses equal to or greater than approximately 34 times an oral human dose of 40 mg *(see Animal Data)*. Because of the observed effect at high doses of esomeprazole magnesium on developing bone in rat studies, esomeprazole magnesium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Human Data*

Esomeprazole is the S-isomer of omeprazole. Four epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to $H_2$-receptor antagonists or other controls.

A population based retrospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, from 1995 to 99, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. The number of infants exposed *in utero* to omeprazole that had any malformation, low birth weight, low Apgar score, or hospitalization was similar to the number observed in this population. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole-exposed infants than the expected number in this population.

A population-based retrospective cohort study covering all live births in Denmark from 1996 to 2009, reported on 1,800 live births whose mothers used omeprazole during the first trimester of pregnancy and 837,317 live births whose mothers did not use any proton pump inhibitor. The overall rate of birth defects in infants born to mothers with first trimester exposure to omeprazole was 2.9% and 2.6% in infants born to mothers not exposed to any proton pump inhibitor during the first trimester.

A retrospective cohort study reported on 689 pregnant women exposed to either $H_2$-blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,572 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an $H_2$-blocker, or were unexposed was 3.6%, 5.5%, and 4.1% respectively.

A small prospective observational cohort study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rate of major congenital malformations was 4% in the omeprazole group, 2% in controls exposed to non-teratogens, and 2.8% in disease paired controls. Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight were similar among the groups.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

*Animal Data*

Reproduction studies have been performed with esomeprazole magnesium in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 41 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole magnesium.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with esomeprazole magnesium at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg on a body surface area basis). Neonatal/early postnatal (birth to weaning) survival was decreased at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis). Body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg/kg/day (about 17 times an oral human dose of 40 mg on a body surface area basis). In addition, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at doses equal to or greater than 14 mg/kg/day (about 3.4 times an oral human dose of 40 mg on a body surface area basis). Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole magnesium at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis).

Effects on maternal bone were observed in pregnant and lactating rats in a pre- and postnatal toxicity study when esomeprazole magnesium was administered at oral doses of 14 to 280 mg/kg/day (about 3.4 to 68 times an oral human dose of 40 mg on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis).

A pre- and postnatal development study in rats with esomeprazole strontium (using equimolar doses compared to esomeprazole magnesium study) produced similar results in dams and pups as described above.

### 8.3 Nursing Mothers

Esomeprazole is likely present in human milk. Esomeprazole is the S-isomer of omeprazole and limited data indicate that maternal doses of omeprazole 20 mg daily produce low levels in human milk. Caution should be exercised when esomeprazole magnesium is administered to a nursing woman.

### 8.4 Pediatric Use

The safety and effectiveness of esomeprazole magnesium have been established in pediatric patients 1 to 17 years of age for short-term treatment (up to eight weeks) of GERD.

*1 to 17 years of age*

Use of esomeprazole magnesium in pediatric and adolescent patients 1 to 17 years of age for short-term treatment (up to eight weeks) of GERD is supported by extrapolation of results from adequate and well-controlled studies for adults and safety and pharmacokinetic studies performed in pediatric and adolescent patients [*see Dosage and Administration (2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies, (14.3)*]. The safety and effectiveness of esomeprazole magnesium for other pediatric uses have not been established.

*Juvenile Animal Data*

In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses about 34 to 68 times a daily human dose of 40 mg based on body surface area. Increases in death were seen at the high dose, and at all doses of esomeprazole, there were decreases in body weight, body weight gain, femur weight and femur length, and decreases in overall growth *[see Nonclinical Toxicology (13.2)]*.

### 8.5 Geriatric Use

Of the total number of patients who received esomeprazole magnesium in clinical trials, 1459 were 65 to 74 years of age and 354 patients were ≥ 75 years of age.

No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

## 10 OVERDOSAGE

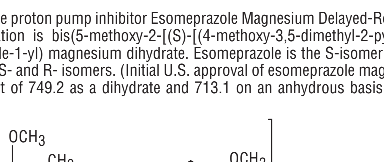
A single oral dose of esomeprazole at 510 mg/kg (about 124 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions.

The symptoms described in connection with deliberate esomeprazole magnesium overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - *Adverse Reactions*). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose contact a Poison Control Center at 1–800–222–1222.

## 11 DESCRIPTION

The active ingredient in the proton pump inhibitor Esomeprazole Magnesium Delayed-Release Capsules USP for oral administration is bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1*H*-benzimidazole-1-yl) magnesium dihydrate. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. (Initial U.S. approval of esomeprazole magnesium: 2001.) It has a molecular weight of 749.2 as a dihydrate and 713.1 on an anhydrous basis. The structural formula is:




$(C_{17}H_{18}N_3O_3S)_2$ Mg • 2 $H_2O$     M.W. 749.2

The magnesium salt is an off-white to pale yellow colored crystalline powder. It contains 2 moles of water of solvation and is slightly soluble in water. The stability of esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25°C and about 8 hours at 37°C.

Each Esomeprazole Magnesium Delayed-Release Capsule USP contains either 20 mg or 40 mg of esomeprazole (present as 21.69 mg or 43.38 mg esomeprazole magnesium dihydrate) in the form of enteric-coated granules. In addition, each delayed-release capsule contains the following inactive ingredients: FD&C blue #1, gelatin, hypromellose, methacrylic acid copolymer dispersion, polysorbate 80, propylene glycol, shellac, sugar spheres, talc, titanium dioxide, triethyl citrate, and yellow iron oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the $H^+/K^+$-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

### 12.2 Pharmacodynamics

*Antisecretory Activity*

The effect of esomeprazole magnesium on intragastric pH was determined in patients with symptomatic gastroesophageal reflux disease in two separate studies. In the first study of 36 patients, esomeprazole magnesium 40 mg and 20 mg capsules were administered over 5 days. The results are shown in **Table 3:**

**Table 3: Effect on Intragastric pH on Day 5 (N = 36)**

| Parameter | Esomeprazole Magnesium 40 mg | Esomeprazole Magnesium 20 mg |
|---|---|---|
| % Time Gastric pH > 4† (Hours) | 70%* (16.8 h) | 53% (12.7 h) |
| Coefficient of variation | 26% | 37% |
| Median 24 Hour pH | 4.9* | 4.1 |
| Coefficient of variation | 16% | 27% |

† Gastric pH was measured over a 24 hour period

*p < 0.01 esomeprazole magnesium 40 mg vs. esomeprazole magnesium 20 mg

In a second study, the effect on intragastric pH of esomeprazole magnesium 40 mg administered once daily over a five day period was similar to the first study, (% time with pH > 4 was 68% or 16.3 hours).

*Serum Gastrin Effects*

The effect of esomeprazole magnesium on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6 to 12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum Chromogranin A (CgA) levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

*Enterochromaffin-like (ECL) Cell Effects*

In 24 month carcinogenicity studies of omeprazole in rats, a dose-related significant occurrence of gastric ECL cell carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals [*see Nonclinical Toxicology (13.1)*]. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of $H_2$-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3,000 patients (both children and adults) treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients.

In over 1,000 patients treated with esomeprazole magnesium (10, 20 or 40 mg/day) up to 6 to 12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

*Endocrine Effects*

Esomeprazole magnesium had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of esomeprazole magnesium on the endocrine system were assessed using omeprazole studies. Omeprazole given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin, or secretin.

### 12.3 Pharmacokinetics

*Absorption*

Esomeprazole magnesium delayed-release capsules and esomeprazole magnesium for delayed-release oral suspension contain a bioequivalent enteric-coated granule formulation of esomeprazole magnesium. Bioequivalency is based on a single dose (40 mg) study in 94 healthy male and female volunteers under fasting condition. After oral administration peak plasma levels ($C_{max}$) occur at approximately 1.5 hours ($T_{max}$). The $C_{max}$ increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 micromol*hr/L on Day 1 to 11.2 micromol*hr/L on Day 5 after 40 mg once daily dosing.

The AUC after administration of a single 40 mg dose of esomeprazole magnesium is decreased by 43% to 53% after food intake compared to fasting conditions. Esomeprazole magnesium should be taken at least one hour before meals.

The pharmacokinetic profile of esomeprazole magnesium was determined in 36 patients with symptomatic gastroesophageal reflux disease following repeated once daily administration of 20 mg and 40 mg capsules of esomeprazole magnesium over a period of five days. The results are shown in **Table 4**:

**Table 4: Pharmacokinetic Parameters of Esomeprazole Magnesium on Day 5 Following Oral Dosing for 5 Days**

| Parameter* (CV) | Esomeprazole Magnesium 40 mg | Esomeprazole Magnesium 20 mg |
|---|---|---|
| AUC (micromol*h/L) | 12.6 (42%) | 4.2 (59%) |
| $C_{max}$ (micromol/L) | 4.7 (37%) | 2.1 (45%) |
| $T_{max}$ (h) | 1.6 | 1.6 |
| $t_{1/2}$ (h) | 1.5 | 1.2 |

* Values represent the geometric mean, except the $T_{max}$, which is the arithmetic mean; CV = Coefficient of variation

*Distribution*

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2 to 20 micromol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

*Metabolism*

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP 2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP 3A4 which forms the sulphone metabolite. CYP 2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack CYP 2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

*Excretion*

The plasma elimination half-life of esomeprazole is approximately 1 to 1.5 hours. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

*Pharmacokinetics: Combination Therapy With Antimicrobials*

Esomeprazole magnesium 40 mg once daily was given in combination with clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for 7 days to 17 healthy male and female subjects. The mean steady state AUC and $C_{max}$ of esomeprazole increased by 70% and 18%, respectively during triple combination therapy compared to treatment with esomeprazole alone. The observed increase in esomeprazole exposure during coadministration with clarithromycin and amoxicillin is not expected to produce significant safety concerns.

The pharmacokinetic parameters for clarithromycin and amoxicillin were similar during triple combination therapy and administration of each drug alone. However, the mean AUC and $C_{max}$ for 14-hydroxyclarithromycin increased by 19% and 22%, respectively, during triple combination therapy compared to treatment with clarithromycin alone. This increase in exposure to 14-hydroxyclarithromycin is not considered to be clinically significant.

**Concomitant Use with Clopidogrel**

Results from a crossover study in healthy subjects have shown a pharmacokinetic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. once daily) when coadministered for 30 days. Exposure to the active metabolite of clopidogrel was reduced by 35% to 40% over this time period. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation was related to the change in the exposure to clopidogrel active metabolite.

**Concomitant Use with Mycophenolate Mofetil**

Administration of omeprazole 20 mg twice daily for 4 days and a single 1000 mg dose of MMF approximately one hour after the last dose of omeprazole to 12 healthy subjects in a cross-over study resulted in a 52% reduction in the $C_{max}$ and 23% reduction in the AUC of MPA.

**Special Populations**

*Geriatric*

The AUC and $C_{max}$ values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

*1 to 11 Years of Age*

The pharmacokinetics of esomeprazole were studied in pediatric patients with GERD aged 1 to 11 years. Following once daily dosing for 5 days, the total exposure (AUC) for the 10 mg dose in patients aged 6 to 11 years was similar to that seen with the 20 mg dose in adults and adolescents aged 12 to 17 years. The total exposure for the 10 mg dose in patients aged 1 to 5 years was approximately 30% higher than the 10 mg dose in patients aged 6 to 11 years. The total exposure for the 20 mg dose in patients aged 6 to 11 years was higher than that observed with the 20 mg dose in 12 to 17 year-olds and adults, but lower than that observed with the 40 mg dose in 12 to 17 year-olds and adults. See **Table 6.**

**Table 6: Summary of PK Parameters in 1 to 11 Year Olds With GERD Following 5 Days of Once-Daily Oral Esomeprazole Treatment**

| | **1 to 5 Year Olds** | **6 to 11 Year Olds** | |
|---|---|---|---|
| **Parameter** | **10 mg (N = 8)** | **10 mg (N = 7)** | **20 mg (N = 6)** |
| AUC (micromol*h/L)* | 4.83 | 3.7 | 6.28 |
| $C_{max}$ (micromol/L)* | 2.98 | 1.77 | 3.73 |
| $t_{max}$ (h)† | 1.44 | 1.79 | 1.75 |
| $t_{1/2\lambda z}$ (h)* | 0.74 | 0.88 | 0.73 |
| Cl/F (L/h)* | 5.99 | 7.84 | 9.22 |

*Geometric mean; †arithmetic mean

*12 to 17 Years of Age*

The pharmacokinetics of esomeprazole magnesium were studied in 28 adolescent patients with GERD aged 12 to 17 years inclusive, in a single center study. Patients were randomized to receive esomeprazole magnesium 20 mg or 40 mg once daily for 8 days. Mean $C_{max}$ and AUC values of esomeprazole were not affected by body weight or age; and more than dose-proportional increases in mean $C_{max}$ and AUC values were observed between the two dose groups in the study. Overall, esomeprazole magnesium pharmacokinetics in adolescent patients aged 12 to 17 years were similar to those observed in adult patients with symptomatic GERD. See **Table 7**.

**Table 7: Comparison of PK Parameters in 12 to 17 Year Olds With GERD and Adults With Symptomatic GERD Following the Repeated Daily Oral Dose Administration of Esomeprazole***

| | **12 to 17 Year Olds (N = 28)** | | **Adults (N = 36)** | |
|---|---|---|---|---|
| | **20 mg** | **40 mg** | **20 mg** | **40 mg** |
| AUC (micromol*h/L) | 3.65 | 13.86 | 4.2 | 12.6 |
| $C_{max}$ (micromol/L) | 1.45 | 5.13 | 2.1 | 4.7 |
| $t_{max}$ (h) | 2 | 1.75 | 1.6 | 1.6 |
| $t_{1/2\lambda z}$ (h) | 0.82 | 1.22 | 1.2 | 1.5 |

Data presented are geometric means for AUC, $C_{max}$ and $t_{1/2\lambda z}$, and median value for $t_{max}$.

* Duration of treatment for 12 to 17 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

*Gender*

The AUC and $C_{max}$ values were slightly higher (13%) in females than in males at steady state. Dosage adjustment based on gender is not necessary.

*Hepatic Insufficiency*

The steady state pharmacokinetics of esomeprazole obtained after administration of 40 mg once daily to 4 patients each with mild (Child Pugh A), moderate (Child Pugh Class B), and severe (Child Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver function. In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded [*see Dosage and Administration (2)*].

*Renal Insufficiency*

The pharmacokinetics of esomeprazole magnesium in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of esomeprazole is excreted unchanged in urine.

*Other Pharmacokinetic Observations*

Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole.

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant changes in the pharmacokinetic profiles of esomeprazole or these NSAIDs.

### 12.4 Microbiology

Esomeprazole magnesium, amoxicillin, and clarithromycin triple therapy has been shown to be active against most strains of *Helicobacter pylori (H. pylori) in vitro* and in clinical infections [*see Indications and Usage (1) and Clinical Studies (14)]*.

*Helicobacter pylori:* Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin using agar dilution methodology, and minimum inhibitory concentrations (MICs) were determined.

*Pretreatment Resistance:* Clarithromycin pretreatment resistance rate (MIC ≥ 1 mcg/mL) to *H. pylori* was 15% (66/445) at baseline in all treatment groups combined. A total of > 99% (394/395) of patients had *H. pylori* isolates that were considered to be susceptible (MIC ≤ 0.25 mcg/mL) to amoxicillin at baseline. One patient had a baseline *H. pylori* isolate with an amoxicillin MIC = 0.5 mcg/mL.

*Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes:* The baseline *H. pylori* clarithromycin susceptibility results and the *H. pylori* eradication results at the Day 38 visit are shown in **Table 8:**

**Table 8: Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes[a] for Triple Therapy - (Esomeprazole magnesium 40 mg once daily/amoxicillin 1000 mg twice daily/clarithromycin 500 mg twice daily for 10 days)**

| Clarithromycin Pretreatment Results | | *H. pylori* negative (Eradicated) | *H. pylori* positive (Not Eradicated) Post-treatment susceptibility results | | | |
|---|---|---|---|---|---|---|
| | | | Sb | Ib | Rb | No MIC |
| Susceptible[b] | 182 | 162 | 4 | 0 | 2 | 14 |
| Intermediate[b] | 1 | 1 | 0 | 0 | 0 | 0 |
| Resistant[b] | 29 | 13 | 1 | 0 | 13 | 2 |

[a] Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results

[b] Susceptible (S) MIC ≤ 0.25 mcg/mL, Intermediate (I) MIC = 0.5 mcg/mL, Resistant (R) MIC ≥ 1 mcg/mL

Patients not eradicated of *H. pylori* following esomeprazole magnesium /amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, when possible. Patients with clarithromycin resistant *H. pylori* should not be re-treated with a clarithromycin-containing regimen.

*Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes:* In the esomeprazole magnesium/amoxicillin/clarithromycin clinical trials, 83% (176/212) of the patients in the esomeprazole magnesium/amoxicillin/clarithromycin treatment group who had pretreatment amoxicillin susceptible MICs (≤ 0.25 mcg/mL) were eradicated of *H. pylori*, and 17% (36/212) were not eradicated of *H. pylori*. Of the 36 patients who were not eradicated of *H. pylori* on triple therapy, 16 had no post-treatment susceptibility test results and 20 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Fifteen of the patients who were not eradicated of *H. pylori* on triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs. There were no patients with *H. pylori* isolates who developed treatment emergent resistance to amoxicillin.

*Susceptibility Test for Helicobacter pylori:* For susceptibility testing information about *Helicobacter pylori*, see Microbiology section in prescribing information for clarithromycin and amoxicillin.

*Effects on Gastrointestinal Microbial Ecology:* Decreased gastric acidity due to any means, including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly *Clostridium difficile* in hospitalized patients.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of esomeprazole magnesium was assessed using studies of omeprazole, of which esomeprazole is an enantiomer. In two 24 month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44, and 140.8 mg/kg/day (about 0.4 to 34 times the human dose of 40 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 3.4 times the human dose of 40 mg/day on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78 week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *In vitro* human lymphocyte chromosome aberration test. Omeprazole was positive in the *in vitro* human lymphocyte chromosome aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test.

The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 34 times the human dose of 40 mg/day on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

### 13.2 Animal Toxicology and/or Pharmacology

*Reproduction Studies*

Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole [*see Pregnancy, Animal Data (8.1)]*.

*Juvenile Animal Study*

A 28 day toxicity study with a 14 day recovery phase was conducted in juvenile rats with esomeprazole magnesium at doses of 70 to 280 mg/kg/day (about 17 to 68 times a daily oral human dose of 40 mg on a body surface area basis). An increase in the number of deaths at the high dose of 280 mg/kg/day was observed when juvenile rats were administered esomeprazole magnesium from postnatal day 7 through postnatal day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 34 times a daily oral human dose of 40 mg on a body surface area basis), produced treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length, and affected overall growth. Comparable findings described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

## 14 CLINICAL STUDIES

### 14.1 Healing of Erosive Esophagitis

The healing rates of esomeprazole magnesium 40 mg, esomeprazole magnesium 20 mg, and omeprazole 20 mg (the approved dose for this indication) were evaluated in patients with endoscopically diagnosed erosive esophagitis in four multicenter, double-blind, randomized studies. The healing rates at Weeks 4 and 8 were evaluated and are shown in **Table 9:**

**Table 9: Erosive Esophagitis Healing Rate (Lite-Table Analysis)**

| Study | No. of Patients | Treatment Groups | Week 4 | Week 8 | Significance Level* |
|---|---|---|---|---|---|
| 1 | 588 | Esomeprazole magnesium 20 mg | 68.7% | 90.6% | N.S. |
| | 588 | Omeprazole 20 mg | 69.5% | 88.3% | |
| 2 | 654 | Esomeprazole magnesium 40 mg | 75.9% | 94.1% | p < 0.001 |
| | 656 | Esomeprazole magnesium 20 mg | 70.5% | 89.9% | p < 0.05 |
| | 650 | Omeprazole 20 mg | 64.7% | 86.9% | |
| 3 | 576 | Esomeprazole magnesium 40 mg | 71.5% | 92.2% | N.S. |
| | 572 | Omeprazole 20 mg | 68.6% | 89.8% | |
| 4 | 1216 | Esomeprazole magnesium 40 mg | 81.7% | 93.7% | p < 0.001 |
| | 1209 | Omeprazole 20 mg | 68.7% | 84.2% | |

* log-rank test vs. omeprazole 20 mg

N.S. = not significant (p > 0.05).

In these same studies of patients with erosive esophagitis, sustained heartburn resolution and time to sustained heartburn resolution were evaluated and are shown in **Table 10:**

**Table 10: Sustained Resolution‡ of Heartburn (Erosive Esophagitis Patients)**

| | | | Cumulative Percent# with Sustained Resolution | | |
|---|---|---|---|---|---|
| Study | No. of Patients | Treatment Groups | Day 14 | Day 28 | Significance Level* |
| 1 | 573 | Esomeprazole magnesium 20 mg | 64.3% | 72.7% | N.S. |
| | 555 | Omeprazole 20 mg | 64.1% | 70.9% | |
| 2 | 621 | Esomeprazole magnesium 40 mg | 64.8% | 74.2% | p < 0.001 |
| | 620 | Esomeprazole magnesium 20 mg | 62.9% | 70.1% | N.S. |
| | 626 | Omeprazole 20 mg | 56.5% | 66.6% | |
| 3 | 568 | Esomeprazole magnesium 40 mg | 65.4% | 73.9% | N.S. |
| | 551 | Omeprazole 20 mg | 65.5% | 73.1% | |
| 4 | 1187 | Esomeprazole magnesium 40 mg | 67.6% | 75.1% | p < 0.001 |
| | 1188 | Omeprazole 20 mg | 62.5% | 70.8% | |

‡ Defined as 7 consecutive days with no heartburn reported in daily patient diary.

# Defined as the cumulative proportion of patients who have reached the start of sustained resolution

* log-rank test vs. omeprazole 20 mg

N.S. = not significant (p > 0.05)

In these four studies, the range of median days to the start of sustained resolution (defined as 7 consecutive days with no heartburn) was 5 days for esomeprazole magnesium 40 mg, 7 to 8 days for esomeprazole magnesium 20 mg and 7 to 9 days for omeprazole 20 mg.

There are no comparisons of 40 mg of esomeprazole magnesium with 40 mg of omeprazole in clinical trials assessing either healing or symptomatic relief of erosive esophagitis.

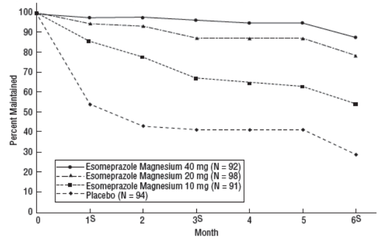
*Long-Term Maintenance of Healing of Erosive Esophagitis*

Two multicenter, randomized, double-blind placebo-controlled 4-arm trials were conducted in patients with endoscopically confirmed, healed erosive esophagitis to evaluate esomeprazole magnesium 40 mg (n = 174), 20 mg (n = 180), 10 mg (n = 168) or placebo (n = 171) once daily over six months of treatment.

No additional clinical benefit was seen with esomeprazole magnesium 40 mg over esomeprazole magnesium 20 mg.

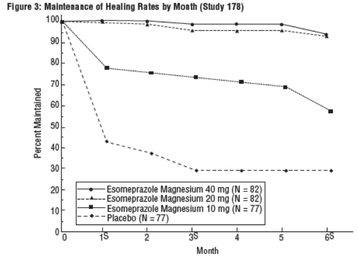
The percentages of patients that maintained healing of erosive esophagitis at the various time points are shown in **Figures 2** and **3:**

**Figure 2: Maintenance of Healing Rates by Month (Study 177)**




s = scheduled visit

**Figure 3: Maintenance of Healing Rates by Month (Study 178)**




s = scheduled visit

Patients remained in remission significantly longer and the number of recurrences of erosive esophagitis was significantly less in patients treated with esomeprazole magnesium compared to placebo.

In both studies, the proportion of patients on esomeprazole magnesium who remained in remission and were free of heartburn and other GERD symptoms was well differentiated from placebo.

In a third multicenter open label study of 808 patients treated for 12 months with esomeprazole magnesium 40 mg, the percentage of patients that maintained healing of erosive esophagitis was 93.7% for six months and 89.4% for one year.

### 14.2 Symptomatic Gastroesophageal Reflux Disease (GERD)

Two multicenter, randomized, double-blind, placebo-controlled studies were conducted in a total of 717 patients comparing four weeks of treatment with esomeprazole magnesium 20 mg or 40 mg once daily versus placebo for resolution of GERD symptoms. Patients had ≥ 6 month history of heartburn episodes, no erosive esophagitis by endoscopy, and heartburn on at least four of the seven days immediately preceding randomization.

The percentage of patients that were symptom-free of heartburn was significantly higher in the esomeprazole magnesium groups compared to placebo at all follow-up visits (Weeks 1, 2, and 4).

No additional clinical benefit was seen with esomeprazole magnesium 40 mg over esomeprazole magnesium 20 mg.

The percent of patients symptom-free of heartburn by day are shown in **Figures 4** and **5:**

**Figure 4: Percent of Patients Symptom-Free of Heartburn by Day (Study 225)**

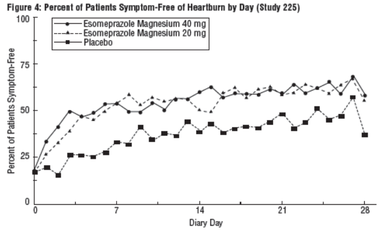
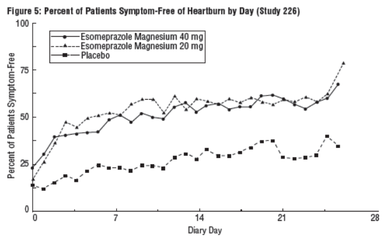



**Figure 5: Percent of Patients Symptom-Free of Heartburn by Day (Study 226)**




In three European symptomatic GERD trials, esomeprazole magnesium 20 mg and 40 mg and omeprazole 20 mg were evaluated. No significant treatment related differences were seen.

### 14.3 Pediatric Gastroesophageal Reflux Disease (GERD)

*1 to 11 Years of Age*

In a multicenter, parallel-group study, 109 pediatric patients with a history of endoscopically-proven GERD (1 to 11 years of age; 53 female; 89 Caucasian, 19 Black, 1 Other) were treated with esomeprazole magnesium once daily for up to 8 weeks to evaluate safety and tolerability. Dosing by patient weight was as follows:

weight < 20 kg: once daily treatment with esomeprazole magnesium 5 mg or 10 mg

weight ≥ 20 kg: once daily treatment with esomeprazole magnesium 10 mg or 20 mg

Patients were endoscopically characterized as to the presence or absence of erosive esophagitis.

Of the 109 patients, 53 had erosive esophagitis at baseline (51 had mild, 1 moderate, and 1 severe esophagitis). Although most of the patients who had a follow up endoscopy at the end of 8 weeks of treatment healed, spontaneous healing cannot be ruled out because these patients had low grade erosive esophagitis prior to treatment, and the trial did not include a concomitant control.

*12 to 17 Years of Age*

In a multicenter, randomized, double-blind, parallel-group study, 149 adolescent patients (12 to 17 years of age; 89 female; 124 Caucasian, 15 Black, 10 Other) with clinically diagnosed GERD were treated with either esomeprazole magnesium 20 mg or esomeprazole magnesium 40 mg once daily for up to 8 weeks to evaluate safety and tolerability. Patients were not endoscopically characterized as to the presence or absence of erosive esophagitis.

### 14.4 Risk Reduction of NSAID-Associated Gastric Ulcer

Two multicenter, double-blind, placebo-controlled studies were conducted in patients at risk of developing gastric and/or duodenal ulcers associated with continuous use of non-selective and COX-2 selective NSAIDs. A total of 1429 patients were randomized across the 2 studies. Patients ranged in age from 19 to 89 (median age 66 years) with 70.7% female, 29.3% male, 82.9% Caucasian, 5.5% Black, 3.7% Asian, and 8% Others. At baseline, the patients in these studies were endoscopically confirmed not to have ulcers but were determined to be at risk for ulcer occurrence due to their age (≥ 60 years) and/or history of a documented gastric or duodenal ulcer within the past 5 years. Patients receiving NSAIDs and treated with esomeprazole magnesium 20 mg or 40 mg once-a-day experienced significant reduction in gastric ulcer occurrences relative to placebo treatment at 26 weeks. See **Table 11**. No additional benefit was seen with esomeprazole magnesium 40 mg over esomeprazole magnesium 20 mg. These studies did not demonstrate significant reduction in the development of NSAID-associated duodenal ulcer due to the low incidence.

**Table 11: Cumulative Percentage of Patients Without Gastric Ulcers at 26 Weeks:**

| Study | No. of Patients | Treatment Group | % of Patients Remaining Gastric Ulcer Free[†] |
|---|---|---|---|
| 1 | 191 | Esomeprazole magnesium 20 mg | 95.4 |
| | 194 | Esomeprazole magnesium 40 mg | 96.7 |
| | 184 | Placebo | 88.2 |
| 2 | 267 | Esomeprazole magnesium 20 mg | 94.7 |
| | 271 | Esomeprazole magnesium 40 mg | 95.3 |
| | 257 | Placebo | 83.3 |

[†]⅓= Life Table Estimate. Significant difference from placebo (p < 0.01).

### 14.5 *Helicobacter pylori* (*H. pylori*) Eradication in Patients With Duodenal Ulcer Disease

*Triple Therapy (esomeprazole magnesium/amoxicillin/clarithromycin):* Two multicenter, randomized, double-blind studies were conducted using a 10 day treatment regimen. The first study (191) compared esomeprazole magnesium 40 mg once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily to esomeprazole magnesium 40 mg once daily plus clarithromycin 500 mg twice daily. The second study (193) compared esomeprazole magnesium 40 mg once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily to esomeprazole magnesium 40 mg once daily. *H. pylori* eradication rates, defined as at least two negative tests and no positive tests from CLOtest®, histology and/or culture, at 4 weeks post-therapy were significantly higher in the esomeprazole magnesium plus amoxicillin and clarithromycin group than in the esomeprazole magnesium plus clarithromycin or esomeprazole magnesium alone group. The results are shown in **Table 12:**

**Table 12: *H. pylori* Eradication Rates at 4 Weeks After 10 Day Treatment Regimen**
**% of Patients Cured**
**[95% Confidence Interval]**
**(Number of Patients)**

| Study | Treatment Group | Per-Protocol[†] | Intent-to-Treat[‡] |
|---|---|---|---|
| 191 | Esomeprazole magnesium plus amoxicillin and clarithromycin | 84%* [78, 89] (n = 196) | 77% [71, 82] (n = 233) |
| | Esomeprazole magnesium plus clarithromycin | 55% [48, 62] (n = 187) | 52% [45, 59] (n = 215) |
| 193 | Esomeprazole magnesium plus amoxicillin and clarithromycin | 85%** [74, 93] (n = 67) | 78%** [67, 87] (n = 74) |
| | Esomeprazole magnesium | 5% [0, 23] (n = 22) | 4% [0, 21] (n = 24) |

[†] Patients were included in the analysis if they had *H. pylori* infection documented at baseline, had at least one endoscopically verified duodenal ulcer ≥ 0.5 cm in diameter at baseline or had a documented history of duodenal ulcer disease within the past 5 years, and were not protocol violators. Patients who dropped out of the study due to an adverse reaction related to the study drug were included in the analysis as not *H. pylori* eradicated.

‡ Patients were included in the analysis if they had documented *H. pylori* infection at baseline, had at least one documented duodenal ulcer at baseline, or had a documented history of duodenal ulcer disease, and took at least one dose of study medication. All dropouts were included as not *H. pylori* eradicated.

* p < 0.05 compared to esomeprazole magnesium plus clarithromycin

** p < 0.05 compared to esomeprazole magnesium alone

The percentage of patients with a healed baseline duodenal ulcer by 4 weeks after the 10 day treatment regimen in the esomeprazole magnesium plus amoxicillin and clarithromycin group was 75% (n = 156) and 57% (n = 60) respectively, in the 191 and 193 studies (per-protocol analysis).

### 14.6 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

In a multicenter, open-label dose-escalation study of 21 patients (15 males and 6 females, 18 Caucasian and 3 Black, mean age of 55.5 years) with pathological hypersecretory conditions, such as Zollinger-Ellison Syndrome, esomeprazole magnesium significantly inhibited gastric acid secretion. Initial dose was 40 mg twice daily in 19/21 patients and 80 mg twice daily in 2/21 patients. Total daily doses ranging from 80 mg to 240 mg for 12 months maintained gastric acid output below the target levels of 10 mEq/h in patients without prior gastric acid-reducing surgery and below 5 mEq/hr in patients with prior gastric acid-reducing surgery. At the Month 12 final visit, 18/20 (90%) patients had Basal Acid Output (BAO) under satisfactory control (median BAO = 0.17 mmol/hr). Of the 18 patients evaluated with a starting dose of 40 mg twice daily, 13 (72%) had their BAO controlled with the original dosing regimen at the final visit. See **Table 13**.

**Table 13: Adequate Acid Suppression at Final Visit by Dose Regimen**

| Esomeprazole magnesium dose at the Month 12 visit | BAO under adequate control at the Month 12 visit (N = 20)* |
|---|---|
| 40 mg twice daily | 13/15 |
| 80 mg twice daily | 4/4 |
| 80 mg three times daily | 1/1 |

* One patient was not evaluated.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Esomeprazole Magnesium Delayed-Release Capsules USP, 20 mg, are available as off-white to pale yellow granule-filled, light turquoise blue, opaque, hard-gelatin capsules, spin-printed "2" and "6450" on the cap and "20 mg" on the body in gold ink containing 20 mg esomeprazole packaged in bottles of 30, 90, and 1000 capsules.

| | |
|---|---|
| NDC 0093-**6450**-56 | bottle of 30 |
| NDC 0093-**6450**-98 | bottle of 90 |
| NDC 0093-**6450**-10 | bottle of 1000 |

Esomeprazole Magnesium Delayed-Release Capsules USP, 40 mg, are available as off-white to pale yellow granule-filled, light turquoise blue, opaque, hard-gelatin capsules, spin-printed "2" and "6451" on the cap and "40 mg" on the body in gold ink containing 40 mg esomeprazole packaged in bottles of 30, 90, and 1000 capsules.

| | |
|---|---|
| NDC 0093-**6451**-56 | bottle of 30 |
| NDC 0093-**6451**-98 | bottle of 90 |
| NDC 0093-**6451**-10 | bottle of 1000 |

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

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

KEEP CONTAINER TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

## 17 PATIENT COUNSELING INFORMATION

"See FDA-Approved Medication Guide"

- Advise patients to let you know if they are taking, or begin taking, other medications, because esomeprazole magnesium can interfere with antiretroviral drugs and drugs that are affected by gastric pH changes [*see Drug Interactions (7.1)*].
- Let patients know that antacids may be used while taking esomeprazole magnesium.
- Advise patients to take esomeprazole magnesium at least one hour before a meal.
- For patients who are prescribed esomeprazole magnesium delayed-release capsules, advise them not to chew or crush the capsules.
- Advise patients that, if they open esomeprazole magnesium delayed-release capsules to mix the granules with food, the granules should only be mixed with applesauce. Use with other foods has not been evaluated and is not recommended.
- For patients who are advised to open the esomeprazole magnesium delayed-release capsules before taking them, instruct them in the proper technique for administration [*see Dosage and Administration (2.)*] and tell them to follow the dosing instructions in the PATIENT INFORMATION insert included in the package. Instruct patients to rinse the syringe with water after each use.

Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea [*see Warnings and Precautions (5.5)*].

Advise patients to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany as these may be signs of hypomagnesemia [*see Warnings and Precautions (5.8)*].

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Rev. B 1/2015

# MEDICATION GUIDE

## Esomeprazole (ES-oh-MEP-ra-zole) Magnesium (mag-NEE-zee-um) Delayed-Release Capsules USP

Read the Medication Guide that comes with esomeprazole magnesium delayed-release capsules before you start taking esomeprazole magnesium delayed-release capsules 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 is the most important information I should know about esomeprazole magnesium delayed-release capsules?**

**Esomeprazole magnesium delayed-release capsules can help your acid-related symptoms, but you could still have serious stomach problems. Talk with your doctor.**

**Esomeprazole magnesium delayed-release capsules can cause serious side effects, including:**

- **Diarrhea**. Esomeprazole magnesium delayed-release capsules may increase your risk of getting severe diarrhea. This diarrhea may be caused by an infection *(Clostridium difficile)* in your intestines.

  Call your doctor right away if you have watery stool, stomach pain, and fever that does not go away.
- **Bone fractures**. People who take multiple daily doses of Proton Pump Inhibitor medicines for a long period of time (a year or longer) may have an increased risk of fractures of the hip, wrist, or spine. You should take esomeprazole magnesium delayed-release capsules exactly as prescribed, at the lowest dose possible for your treatment and for the shortest time needed. Talk to your doctor about your risk of bone fracture if you take esomeprazole magnesium delayed-release capsules.

  Esomeprazole magnesium delayed-release capsules can have other serious side effects. See "**What are the possible side effects of esomeprazole magnesium delayed-release capsules?**"

**What are esomeprazole magnesium delayed-release capsules?**

Esomeprazole magnesium delayed-release capsules are a prescription medicine called a proton pump inhibitor (PPI). Esomeprazole magnesium delayed-release capsules reduce the amount of acid in your stomach.

Esomeprazole magnesium delayed-release capsules are used in adults:

- for 4 to 8 weeks to treat the symptoms of gastroesophageal reflux disease (GERD). Esomeprazole magnesium delayed-release capsules may also be prescribed to heal acid-related damage to the lining of the esophagus (erosive esophagitis), and to help continue this healing.

  GERD happens when acid in your stomach backs up into 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.
- for up to 6 months to reduce the risk of stomach ulcers in some people taking pain medicines called non-steroidal anti-inflammatory drugs (NSAIDs).
- to treat patients with a stomach infection (*Helicobacter pylori*), along with the antibiotics amoxicillin and clarithromycin.
- for the long-term treatment of conditions where your stomach makes too much acid, including Zollinger-Ellison syndrome. Zollinger-Ellison syndrome is a rare condition in which the stomach produces a more than normal amount of acid.

For children and adolescents 1 year to 17 years of age, esomeprazole magnesium delayed-release capsules may be prescribed for up to 8 weeks for short-term treatment of GERD.

**Who should not take esomeprazole magnesium delayed-release capsules?**

Do not take esomeprazole magnesium delayed-release capsules if you:

- are allergic to esomeprazole magnesium or any of the ingredients in esomeprazole magnesium delayed-release capsules. See the end of this Medication Guide for a complete list of ingredients in esomeprazole magnesium delayed-release capsules.
- are allergic to any other Proton Pump Inhibitor (PPI) medicine.

**What should I tell my doctor before taking esomeprazole magnesium delayed-release capsules?**

**Before you take esomeprazole magnesium delayed-release capsules, tell your doctor if you:**

- have been told that you have low magnesium levels in your blood
- have liver problems
- are pregnant or plan to become pregnant. It is not known if esomeprazole magnesium delayed-release capsules can harm your unborn baby.
- are breastfeeding or planning to breastfeed. Esomeprazole magnesium may pass into your breast milk. Talk to your doctor about the best way to feed your baby if you take esomeprazole magnesium delayed-release capsules.

**Tell your doctor about all of the medicines you take**, including prescription and non-prescription drugs, vitamins and herbal supplements. Esomeprazole magnesium delayed-release capsules may affect how other medicines work, and other medicines may affect how esomeprazole magnesium delayed-release capsules work.

Especially tell your doctor if you take:

- warfarin (Coumadin, Jantoven)
- ketoconazole (Nizoral)
- voriconazole (Vfend)
- atazanavir (Reyataz)
- nelfinavir (Viracept)
- saquinavir (Fortovase)
- products that contain iron
- digoxin (Lanoxin)
- St. John's Wort (*Hypericum perforatum*)
- rifampin (Rimactane, Rifater, Rifamate)
- cilostazol (Pletal)
- diazepam (Valium)
- tacrolimus (Prograf)
- erlotinib (Tarceva)
- methotrexate
- clopidogrel (Plavix)
- mycophenolate mofetil (Cellcept)

**How should I take esomeprazole magnesium delayed-release capsules?**

- Take esomeprazole magnesium delayed-release capsules exactly as prescribed by your doctor.
- Do not change your dose or stop esomeprazole magnesium delayed-release capsules without talking to your doctor.
- Take esomeprazole magnesium delayed-release capsules at least 1 hour before a meal.
- Swallow esomeprazole magnesium delayed-release capsules whole. **Never chew or crush esomeprazole magnesium delayed-release capsules.**
- If you have difficulty swallowing esomeprazole magnesium delayed-release capsules, you may open the capsule and empty the contents into a tablespoon of applesauce. Do not crush or chew the granules. Be sure to swallow the applesauce right away. Do not store it for later use.
- If you forget to take a dose of esomeprazole magnesium delayed-release capsules, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose on time. Do not take a double dose to make up for a missed dose.
- If you take too many esomeprazole magnesium delayed-release capsules, call your doctor or local poison control center right away, or go to the nearest hospital emergency room.
- See the "Instructions for Use" at the end of this Medication Guide for instructions how to mix and give esomeprazole magnesium delayed-release capsules through a nasogastric tube or gastric tube.

**What are the possible side effects of esomeprazole magnesium delayed-release capsules?**

**Esomeprazole magnesium delayed-release capsules can cause serious side effects, including:**

- See "**What is the most important information I should know about esomeprazole magnesium delayed-release capsules?**"
- **Chronic (lasting a long time) inflammation of the stomach lining (Atrophic Gastritis).** Using esomeprazole magnesium delayed-release capsules for a long period of time may increase the risk of inflammation to your stomach lining. You may or may not have symptoms. Tell your doctor if you have stomach pain, nausea, vomiting, or weight loss.
- **Vitamin B-12 deficiency.** Esomeprazole magnesium reduces the amount of acid in your stomach. Stomach acid is needed to absorb vitamin B-12 properly. Talk with your doctor about the possibility of vitamin B-12 deficiency if you have been on esomeprazole magnesium for a long time (more than 3 years).
- **Low magnesium levels in your body.** Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment.

  You may or may not have symptoms of low magnesium.

  **Tell your doctor right away if you have any of these symptoms:**
  - seizures
  - dizziness
  - abnormal or fast heart beat
  - jitteriness
  - jerking movements or shaking (tremors)
  - muscle weakness
  - spasms of the hands and feet
  - cramps or muscle aches
  - spasm of the voice box

Your doctor may check the level of magnesium in your body before you start taking esomeprazole magnesium delayed-release capsules or during treatment if you will be taking esomeprazole magnesium delayed-release capsules for a long period of time.

The most common side effects with esomeprazole magnesium delayed-release capsules may include:

- headache
- diarrhea
- nausea
- gas
- abdominal pain
- constipation
- dry mouth
- drowsiness

Other side effects:

**Serious allergic reactions.** Tell your doctor if you get any of the following symptoms with esomeprazole magnesium delayed-release capsules:

- rash
- face swelling
- throat tightness
- difficulty breathing

Your doctor may stop esomeprazole magnesium delayed-release capsules if these symptoms happen.

Tell your doctor if you have any side effects that bother you or that do not go away. These are not all the possible side effects with esomeprazole magnesium delayed-release capsules.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store esomeprazole magnesium delayed-release capsules?**

- Store esomeprazole magnesium delayed-release capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the container of esomeprazole magnesium delayed-release capsules closed tightly.

**Keep esomeprazole magnesium delayed-release capsules and all medicines out of the reach of children.**

**General information about esomeprazole magnesium delayed-release capsules**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use esomeprazole magnesium delayed-release capsules for a condition for which they were not prescribed. Do not give esomeprazole magnesium delayed-release capsules to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about esomeprazole magnesium delayed-release capsules. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about esomeprazole magnesium delayed-release capsules that is written for health professionals.

For more information about esomeprazole magnesium delayed-release capsules, call 1-888-838-2872.

**What are the ingredients in esomeprazole magnesium delayed-release capsules?**

**Active Ingredient**: esomeprazole (present as 21.69 mg or 43.38 mg esomeprazole magnesium dihydrate)

**Inactive ingredients in esomeprazole magnesium delayed-release capsules (including the capsule shells)**: FD&C blue #1, gelatin, hypromellose, methacrylic acid copolymer dispersion, polysorbate 80, propylene glycol, shellac, sugar spheres, talc, titanium dioxide, triethyl citrate, and yellow iron oxide.

**Instructions for Use**

For instructions on taking esomeprazole magnesium delayed-release capsules, see the section of this leaflet called "**How should I take esomeprazole magnesium delayed-release capsules?**"

Esomeprazole magnesium delayed-release capsules may be given through a nasogastric tube (NG tube) or gastric tube, as prescribed by your doctor. Follow the instructions below:

- Open the capsule and empty the granules into a 60 mL catheter tipped syringe. Mix with 50 mL of water.

  Use only a catheter tipped syringe to give esomeprazole magnesium through a NG tube.
- Replace the plunger and shake the syringe well for 15 seconds. Hold the syringe with the tip up and check for granules in the tip.
- Give the medicine right away.
- Do not give the granules if they have dissolved or have broken into pieces.
- Attach the syringe to the NG tube. Give the medicine in the syringe through the NG tube into the stomach.
- After giving the granules, flush the NG tube with more water.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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**MEDICATION GUIDE**
**Esomeprazole (ES-oh-MEP-ra-zole) Magnesium (mag-NEE-zee-um) Delayed-Release Capsules USP**

Read the Medication Guide that comes with esomeprazole magnesium delayed-release capsules before you start taking esomeprazole magnesium delayed-release capsules 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 is the most important information I should know about esomeprazole magnesium delayed-release capsules?**

**Esomeprazole magnesium delayed-release capsules may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your doctor.**

**Esomeprazole magnesium delayed-release capsules can cause serious side effects, including:**

- **Diarrhea**. Esomeprazole magnesium delayed-release capsules may increase your risk of getting severe diarrhea. This diarrhea may be caused by an infection *(Clostridium difficile)* in your intestines.

  Call your doctor right away if you have watery stool, stomach pain, and fever that does not go away.
- **Bone fractures**. People who take multiple daily doses of Proton Pump Inhibitor medicines for a long period of time (a year or longer) may have an increased risk of fractures of the hip, wrist, or spine. You should take esomeprazole magnesium delayed-release capsules exactly as prescribed, at the lowest dose possible for your treatment and for the shortest time needed. Talk to your doctor about your risk of bone fracture if you take esomeprazole magnesium delayed-release capsules.

  Esomeprazole magnesium delayed-release capsules can have other serious side effects. See **"What are the possible side effects of esomeprazole magnesium delayed-release capsules?"**

**What are esomeprazole magnesium delayed-release capsules?**

Esomeprazole magnesium delayed-release capsules are a prescription medicine called a proton pump inhibitor (PPI). Esomeprazole magnesium delayed-release capsules reduce the amount of acid in your stomach.

Esomeprazole magnesium delayed-release capsules are used in adults:

- for 4 to 8 weeks to treat the symptoms of gastroesophageal reflux disease (GERD). Esomeprazole magnesium delayed-release capsules may also be prescribed to heal acid-related damage to the lining of the esophagus (erosive esophagitis), and to help continue this healing.

  GERD happens when acid in your stomach backs up into 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.
- for up to 6 months to reduce the risk of stomach ulcers in some people taking pain medicines called non-steroidal anti-inflammatory drugs (NSAIDs).
- to treat patients with a stomach infection (*Helicobacter pylori*), along with the antibiotics amoxicillin and clarithromycin.
- for the long-term treatment of conditions where your stomach makes too much acid, including Zollinger-Ellison syndrome. Zollinger-Ellison syndrome is a rare condition in which the stomach produces a more than normal amount of acid.

For children and adolescents 1 year to 17 years of age, esomeprazole magnesium delayed-release capsules may be prescribed for up to 8 weeks for short-term treatment of GERD.

**Who should not take esomeprazole magnesium delayed-release capsules?**

Do not take esomeprazole magnesium delayed-release capsules if you:

- are allergic to esomeprazole magnesium or any of the ingredients in esomeprazole magnesium delayed-release capsules. See the end of this Medication Guide for a complete list of ingredients in esomeprazole magnesium delayed-release capsules.
- are allergic to any other Proton Pump Inhibitor (PPI) medicine.

**What should I tell my doctor before taking esomeprazole magnesium delayed-release capsules?**

**Before you take esomeprazole magnesium delayed-release capsules, tell your doctor if you:**

- have been told that you have low magnesium levels in your blood
- have liver problems
- are pregnant or plan to become pregnant. It is not known if esomeprazole magnesium delayed-release capsules can harm your unborn baby.
- are breastfeeding or planning to breastfeed. Esomeprazole magnesium may pass into your breast milk. Talk to your doctor about the best way to feed your baby if you take esomeprazole magnesium delayed-release capsules.

**Tell your doctor about all of the medicines you take,** including prescription and non-prescription drugs, vitamins and herbal supplements. Esomeprazole magnesium delayed-release capsules may affect how other medicines work, and other medicines may affect how esomeprazole magnesium delayed-release capsules work.

Especially tell your doctor if you take:

- warfarin (Coumadin, Jantoven)
- ketoconazole (Nizoral)
- voriconazole (Vfend)
- atazanavir (Reyataz)
- nelfinavir (Viracept)
- saquinavir (Fortovase)
- products that contain iron
- digoxin (Lanoxin)
- St. John's Wort (*Hypericum perforatum*)
- rifampin (Rimactane, Rifater, Rifamate)
- cilostazol (Pletal)
- diazepam (Valium)
- tacrolimus (Prograf)
- erlotinib (Tarceva)
- methotrexate
- clopidogrel (Plavix)
- mycophenolate mofetil (Cellcept)

**How should I take esomeprazole magnesium delayed-release capsules?**

- Take esomeprazole magnesium delayed-release capsules exactly as prescribed by your doctor.
- Do not change your dose or stop esomeprazole magnesium delayed-release capsules without talking to your doctor.
- Take esomeprazole magnesium delayed-release capsules at least 1 hour before a meal.
- Swallow esomeprazole magnesium delayed-release capsules whole. **Never chew or crush esomeprazole magnesium delayed-release capsules.**
- If you have difficulty swallowing esomeprazole magnesium delayed-release capsules, you may open the capsule and empty the contents into a tablespoon of applesauce. Do not crush or chew the granules. Be sure to swallow the applesauce right away. Do not store it for later use.
- If you forget to take a dose of esomeprazole magnesium delayed-release capsules, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose on time. Do not take a double dose to make up for a missed dose.
- If you take too many esomeprazole magnesium delayed-release capsules, call your doctor or local poison control center right away, or go to the nearest hospital emergency room.
- See the "Instructions for Use" at the end of this Medication Guide for instructions how to mix and give esomeprazole magnesium delayed-release capsules through a nasogastric tube or gastric tube.

**What are the possible side effects of esomeprazole magnesium delayed-release capsules?**

**Esomeprazole magnesium delayed-release capsules can cause serious side effects, including:**

- **See "What is the most important information I should know about esomeprazole magnesium delayed-release capsules?"**
- **Chronic (lasting a long time) inflammation of the stomach lining (Atrophic Gastritis).** Using esomeprazole magnesium delayed-release capsules for a long period of time may increase the risk of inflammation to your stomach lining. You may or may not have symptoms. Tell your doctor if you have stomach pain, nausea, vomiting, or weight loss.
- **Vitamin B-12 deficiency.** Esomeprazole magnesium reduces the amount of acid in your stomach. Stomach acid is needed to absorb vitamin B-12 properly. Talk with your doctor about the possibility of vitamin B-12 deficiency if you have been on esomeprazole magnesium for a long time (more than 3 years).
- **Low magnesium levels in your body.** Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment.

  You may or may not have symptoms of low magnesium.

  **Tell your doctor right away if you have any of these symptoms:**
  - seizures
  - dizziness
  - abnormal or fast heart beat
  - jitteriness
  - jerking movements or shaking (tremors)
  - muscle weakness
  - spasms of the hands and feet
  - cramps or muscle aches
  - spasm of the voice box

Your doctor may check the level of magnesium in your body before you start taking esomeprazole magnesium delayed-release capsules or during treatment if you will be taking esomeprazole magnesium delayed-release capsules for a long period of time.

The most common side effects with esomeprazole magnesium delayed-release capsules may include:

- headache
- diarrhea
- nausea
- gas
- abdominal pain
- constipation
- dry mouth
- drowsiness

Other side effects:

**Serious allergic reactions.** Tell your doctor if you get any of the following symptoms with esomeprazole magnesium delayed-release capsules:

- rash
- face swelling
- throat tightness
- difficulty breathing

Your doctor may stop esomeprazole magnesium delayed-release capsules if these symptoms happen.

Tell your doctor if you have any side effects that bother you or that do not go away. These are not all the possible side effects with esomeprazole magnesium delayed-release capsules.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store esomeprazole magnesium delayed-release capsules?**

- Store esomeprazole magnesium delayed-release capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the container of esomeprazole magnesium delayed-release capsules closed tightly.

**Keep esomeprazole magnesium delayed-release capsules and all medicines out of the reach of children.**

**General information about esomeprazole magnesium delayed-release capsules**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use esomeprazole magnesium delayed-release capsules for a condition for which they were not prescribed. Do not give esomeprazole magnesium delayed-release capsules to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about esomeprazole magnesium delayed-release capsules. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about esomeprazole magnesium delayed-release capsules that is written for health professionals.

For more information about esomeprazole magnesium delayed-release capsules, call 1-888-838-2872.

**What are the ingredients in esomeprazole magnesium delayed-release capsules?**

**Active Ingredient**: esomeprazole (present as 21.69 mg or 43.38 mg esomeprazole magnesium dihydrate)

**Inactive ingredients in esomeprazole magnesium delayed-release capsules (including the capsule shells):** FD&C blue #1, gelatin, hypromellose, methacrylic acid copolymer dispersion, polysorbate 80, propylene glycol, shellac, sugar spheres, talc, titanium dioxide, triethyl citrate, and yellow iron oxide.

**Instructions for Use**

For instructions on taking esomeprazole magnesium delayed-release capsules, see the section of this leaflet called "**How should I take esomeprazole magnesium delayed-release capsules?**"

Esomeprazole magnesium delayed-release capsules may be given through a nasogastric tube (NG tube) or gastric tube, as prescribed by your doctor. Follow the instructions below:

- Open the capsule and empty the granules into a 60 mL catheter tipped syringe. Mix with 50 mL of water.

  Use only a catheter tipped syringe to give esomeprazole magnesium through a NG tube.
- Replace the plunger and shake the syringe well for 15 seconds. Hold the syringe with the tip up and check for granules in the tip.
- Give the medicine right away.
- Do not give the granules if they have dissolved or have broken into pieces.
- Attach the syringe to the NG tube. Give the medicine in the syringe through the NG tube into the stomach.
- After giving the granules, flush the NG tube with more water.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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North Wales, PA 19454

Rev. B 1/2015

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 78003

# LABELING REVIEWS

***** This document contains proprietary information that cannot be released to the public*****

# LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| **Date of This Review** | 1/7/2015 |
| **ANDA Number** | 078003 |
| **Review Cycle Number** | 7th Cycle |
| **Applicant Name** | IVAX Pharmaceuticals, Inc. |
| **Established Name** | Esomeprazole Magnesium Delayed-release Capsules, USP |
| **Strength(s)** | 20 mg and 40 mg |
| **Proposed Proprietary Name** | None |
| **DARRTS Received Dates** | 8/22/2014 & 1/5/2015 |
| **Labeling Reviewer** | Chan Park |
| **Labeling Team Leader** | Lisa Kwok |

## Review Conclusion

☒ No Comments – The Labels and Labeling are ready for Full Approval

☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for the Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

## 1.1 PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment. Include the previous review (s) finalized date (s).

**Finalized 6/19/2014**

**1. CONTAINER**

a. Reduce the prominence of the company logo. Please ensure that the prominence of the company logo be less prominent than that of the drug product name and strength.
b. Please use title case for the drug product name for better recognition of the drug name.
c. Include the expiration date rather than the issue date.

**2. INSERT**

a. Replace the term "Nexium" (without the dosage form associated) with "esomeprazole magnesium" rather than "esomeprazole" throughout the text.
b. Upon further review, we note that the information for the age group of less than 1 year is specifically associated with the oral suspension only. For this reason, we ask that you the remove any information associated with the age group of less than 1 year old from you labeling throughout the text.

**3. MEDICATION GUIDE**

See comment under INSERT.

**Reviewer Comments:** ***The comment 1(b) needs to be further addressed in the Post-Approval Revision.***

## 1.2 ADDITIONAL BACKGROUND INFORMATION THAT IS PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence (s) and/or information date (s).

**Reviewer Comments: The sponsor revised the labeling to be in accordance with the labeling for Nexium® delayed-release capsules (NDA 021153/S-050), approved 12/19/2014.**

## 2. OVERALL ASSESSMENT OF MATERIALS REVIEWED

| Table 1: Review Summary of Container Label and Carton Labeling | | | |
|---|---|---|---|
| | Packaging Sizes | Submission Date | Recommendation |
| Container ☐ Draft ☒ FPL | 30s, 90s, 1000s | 8/22/2014 | ☒ Satisfactory ☐ Revise |
| Blister ☐ Draft ☐ FPL | | | ☐ Satisfactory ☐ Revise |
| Carton ☐ Draft ☐ FPL | | | ☐ Satisfactory ☐ Revise |
| Unit Dose Carton ☐ Draft ☐ FPL | | | ☐ Satisfactory ☐ Revise |
| **Table 2 Review Summary of Prescribing Information and Patient Labeling** | | | |
| | Revision Date and/or code | Submission Date | Recommendation |
| Prescribing Info ☐ Draft ☒ FPL | 12/2014 | 1/5/2015 | ☒ Satisfactory ☐ Revise |
| Medication Guide ☐ Draft ☒ FPL | 12/2014 | 1/5/2015 | ☒ Satisfactory ☐ Revise |

| | | | |
|---|---|---|---|
| Patient Information ☐ Draft ☐ FPL | | | ☐ Satisfactory ☐ Revise |
| PPI ☐ Draft ☐ FPL | | | ☐ Satisfactory ☐ Revise |
| SPL ☐ - DLDE | 12/2014 | 1/5/2015 | ☒ Satisfactory ☐ Revise |

## 3. MODEL CONTAINER LABELS FOR ANDA

In Table 2 below, check all sources for Model container labels and carton labeling (secondary packaging) that applies.

| Table 2: Review Model Labeling for Container Label and Carton Labeling (Check all sources that apply) | |
|---|---|
| **Source** | **Date of source document (i.e. supplement approval date, annual report date)** |
| ☐ **drugs@fda NDA 0**NA to enter text. | NA to enter text. |
| ☐ **DARRTS** NA to enter text. | NA to enter text. |
| ☒ **DailyMed** NA to enter text. | **Rev. 3/2014** |
| ☒ **Annual Report** NA to enter text. | **A-12, submitted 4/11/2013** |
| ☐ **Other** NA to enter text. | NA to enter text. |

**Model labels and carton labeling. [Insert or paste images below]**

## 4. PRESCRIBING INFORMATION MODEL LABELING

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Table 3.

| Table 3: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply) | | |
|---|---|---|
| ☒ MOST RECENTLY APPROVED REFERENCE LISTED DRUG | | |
| NDA 021153 | Proprietary Name - Nexium | Approval date: 12/19/2014 |
| S- 050 | Description of Supplement: These supplemental new drug applications provides for revisions to the labeling for Nexium, consistent with our October 30, 2014 Safety Labeling Change Notification Letter. Additionally, there are minor editorial agreed upon labeling changes. | |
| ☐ BPCA or PREA TEMPLATE - No | | |
| ☐ OTHER (Describe): No | | |

**NOTE - NDA 21153/S-050 is for an approval of the Safety Class change request dated 10/30/2014 as follows:**

"This information pertains to the risk of Vitamin B12 deficiency with long-term daily treatment of

proton pump inhibitors (PPIs) and the risk of concomitant dosing of mycophenolate mofetil with PPIs resulting in reduced systemic exposure of mycophenolate mofetil as reported in current"

literature.

***Reviewer Assessment:***

Are the labeling contained in the submission the same as the review model labeling? **YES**
Are the differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **YES**

**Reviewer Comments:** The information for the age group of less than 1 year is specifically associated with the oral suspension only. For this reason, we asked the sponsor to remove any information associated with the age group of less than 1 year old from the labeling throughout the text and the sponsor complied with this request.

## 5. PATENTS AND EXCLUSIVITIES

Table 4 describes how the applicant certified to the Orange Book patent(s) for the Model Labeling and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

**Table 4: Impact of Model Labeling Patents on ANDA Labeling**

| Patent Number | Patent Expiration | Patent Use Code | Patent Use Code Definition | How Applicant Filed | Labeling Impact |
|---|---|---|---|---|---|
| NA to enter text. | NA to enter text. | NA to enter text. | NA to enter text. | NA to enter text. | NA to enter text. |

Patent Data

| Appl No | Prod No | Patent No | Patent Expiration | Patent Use Code | Patent Certification | Labeling Impact |
|---|---|---|---|---|---|---|
| N021153 | 001 | 5690960*PED | May 25, 2015 | U - 373 | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 373 | PIV | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 729 | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 770 | | |
| N021153 | 001 | 5714504*PED | Aug 3, 2015 | U - 373 | | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 373 | PIV | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 729 | | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 770 | | |
| N021153 | 001 | 5877192*PED | Nov 27, 2014 | U - 373 | | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 373 | PIV | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 729 | | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 770 | | |

| | | | | | |
|---|---|---|---|---|---|
| N021153 | 001 | 5900424*PED | Nov 4, 2016 | U - 373 | |
| N021153 | 001 | 6147103 | Oct 9, 2018 | | PIV |
| N021153 | 001 | 6147103*PED | Apr 9, 2019 | | |
| N021153 | 001 | 6166213 | Oct 9, 2018 | | PIV |
| N021153 | 001 | 6166213*PED | Apr 9, 2019 | | |
| N021153 | 001 | 6191148 | Oct 9, 2018 | | PIV |
| N021153 | 001 | 6191148*PED | Apr 9, 2019 | | |
| N021153 | 001 | 6369085 | May 25, 2018 | U - 729 | PIV |
| N021153 | 001 | 6369085 | May 25, 2018 | U - 770 | |
| N021153 | 001 | 6369085*PED | Nov 25, 2018 | | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 469 | PIV |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 729 | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 770 | |
| N021153 | 001 | 6428810*PED | May 3, 2020 | U - 469 | |
| N021153 | 001 | 6875872 | May 27, 2014 | | PIV |
| N021153 | 001 | 6875872*PED | Nov 27, 2014 | | |
| N021153 | 001 | 7411070 | May 25, 2018 | | PIV |
| N021153 | 001 | 7411070*PED | Nov 25, 2018 | | |
| N021153 | 001 | 8466175 | May 25, 2018 | U-1417 | PIV* |
| N021153 | 001 | 8466175*PED | Nov 25, 2018 | | |

**Exclusivities:**

There is no unexpired exclusivity for this product.

| Code | Definition |
|---|---|
| U - 373 | GENERAL USE CLAIM SUBMITTED FOR 12 NEXIUM PATIENTS STATING "PERTINENT TO THE CAPSULE FORMULATION FOR NEXIUM AND ITS INDICATIONS FOR THE TREATMENT OF GERD AND ERADICATION OF H.PYLORI TO REDUCE THE RISK OF |

DUODENAL ULCER RECURRENCE

U - 729 TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD), RISK-REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER, H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE

U - 770 LONG-TERM TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS

U - 469 TREATMENT OF GASTROESOPHAGEAL REFLEX DISEASE (GERD) AND ERADICATION OF H.PYLORI TO REDUCE RISK OF DUODENAL ULCER RECURRENCE

U – 1417 USE FOR TREATMENT OF HELICOBACTER INFECTIONS

*The sponsor certified to PATENT "8,466,175" on 8/16/2013.

***Reviewer Assessment:***

Is the applicant's "patent carve out" acceptable? **NA**

**Reviewer Comments: None**

Table 5 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the Exclusivity Code column.

| Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling | | | |
|---|---|---|---|
| Exclusivity Code | Exclusivity Code Definition | Exclusivity Expiration | Labeling Impact |
| NA | NA to enter text. | NA to enter text. | NA to enter text. |

***Reviewer Assessment:***

Is the applicant's "exclusivity carve out" acceptable? **NA**

**Reviewer Comments: None**

## 6. United States Pharmacopeia (USP) & Pharmacopeia Forum (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph and determined how the monograph impacts the ANDA labeling with respect to packaging and storage. The results of this search are provided in Table 6.

| Table 6: USP and PF Search Results | | | |
|---|---|---|---|
| | Date Searched | Monograph? YES or NO | Labeling statements found<br>NA if no monograph |
| USP | 1/7/2015 | YES | Packaging and Storage: Preserve in tight containers. Store at room temperature. |
| PF | 1/7/2015 | YES | Add the following : Esomeprazole magnesium delayed-release capsules |

## 7. DESCRIPTION and HOW SUPPLIED sections and Manufactured by Statement

Did the Description, and How Supplied Sections and Manufactured by statement change from the previous review? **NO**

If YES complete the relevant Tables below, if NO, go to section 8

Tables 8, 9, and 10 describe if any changes have occurred in the DESCRIPTION (e.g., inactives), HOW SUPPLIED (e.g., description of dosage form, package sizes and drug product manufacturing statement), and manufacturing statements sections of the Prescribing Information when compared to the previous labeling review.

| Table 8: Comparison of DESCRIPTION Section | | |
|---|---|---|
| **Previous Labeling Review** | **Currently Proposed** | **Assessment** |
| | | |

| Table 9: Comparison of HOW SUPPLIED Section | | |
|---|---|---|
| **Previously Labeling Review** | **Currently Proposed** | **Assessment** |
| | | |

| Table 10: Manufactured by statement | | |
|---|---|---|
| **Previously Labeling Review** | **Currently Proposed** | **Assessment** |
| | | |

## 8. POST APPROVAL REVISIONS

a. CONTAINER
   Revise “ESOMEPRAZOLE MAGNESIUM” to read “Esomeprazole Magnesium” using title case.
b. MEDICATION GUIDE – What are esomeprazole magnesium delayed-release capsules?
   Include the following statement as the last paragraph in this section:

(b) (4)

***** This document contains proprietary information that cannot be released to the public*****

# (APPROVAL SUMMARY)
# ORIGINAL LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| **Date of This Review** | 11/18/2014 |
| **ANDA Application Number** | 078003 |
| **Review Cycle Number** | 7th Cycle |
| **Applicant Name** | IVAX Pharmaceuticals, Inc. |
| **Established Name** | Esomeprazole Magnesium Delayed-release Capsules, USP |
| **Strength(s)** | 20 mg and 40 mg |
| **Proposed Proprietary Name** | None |
| **DARRTS Received Date** | 8/22/2014 |
| **Labeling Reviewer** | Chan Park |
| **Labeling Team Leader** | Lisa Kwok |

## Review Conclusion

☒ No Comments – The Labels and Labeling are ready for Full Approval.

☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for the Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

**LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT**

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated 8/22/2014.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

## 1. MATERIAL ANALYSIS

The results for each material reviewed in this section provide the basis for the labeling comments to the Applicant and other review disciplines.

### 1.1 GENERAL

#### 1.1.1 Established Name Assessment

We compared the established names of this ANDA, the Model Labeling and the USP to determine if the established name presented on the labeling is acceptable.

| Table 1: Comparison of Established Names | |
|---|---|
| **Model Labeling:** | Esomeprazole magnesium delayed-release capsules |
| **ANDA:** | Esomeprazole magnesium delayed-release capsules |
| **USP:** | Esomeprazole magnesium delayed-release capsules |

***Reviewer Assessment:***

Is the established name for ANDA acceptable? **YES**
Is the established (and proprietary name) displayed in a manner consistent 21 CFR 201.10? **YES**
Is title case used in established name? **NO**
Is established name on list of name pairs that use Tall Man lettering found on FDA webpage? **NA**

**Comment: Recommend the use of the title case on the container for better recognition of the drug name. (Post-approval)**

#### 1.1.2 United States Pharmacopeia (USP) & Pharmacopeia Forum (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph and determined how the monograph impacts the ANDA labeling with respect to packaging and storage. The results of this search are provided in Table 2.

| Table 2: USP and PF Search Results | | | |
|---|---|---|---|
| | Date Searched | Monograph | Copy of Information from USP or PF |
| USP | 11/18/2014 | YES | Packaging and Storage: Preserve in tight containers. Store at room temperature. |
| PF | NA | NA | NA |

N/A – The drug product is not the subject of a USP monograph and/or proposed monograph.

***Reviewer Assessment:***

Does the ANDA labeling require revision or is clarification needed from other review disciplines based on the comparison of USP or PF label/labeling requirements? **NO**
Do required labeling statements appear on/in the ANDA labeling? **YES**
Are the USP packaging and storage recommendations reflected in the labels and labeling? **YES**

**Comment: Acceptable**

### 1.2 CONTAINER LABEL

We evaluated the container labels for the inclusion of all required statements and safety considerations. Our review is based on the following model labels that were used for comparison to the submitted ANDA labeling.

| Table 3: Review Model Labeling for Container Label and Carton Labeling (Check all sources that apply) | | |
|---|---|---|
| | | Supplement Approval Date or Annual Report Date |
| drugs@fda | NO | N/A |
| DARRTS | NO | N/A |
| DailyMed | YES | Revised 3/2014 |
| Annual Report | NO | N/A |

### 1.2.1 Model labels and carton labeling. [Insert images below]

### 1.2.2 Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

We used the draft Guidance for Industry titled Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors for the following assessment.

***Reviewer Assessment:***

Does the following information appear as the most prominent information on the Principal Display Panel?
- Proprietary name? **NA**
- Established name? **YES**
- Product strength? **YES**
- Route(s) of administration (other than oral)? **NA**
- Warnings (if any) or cautionary statements (if any)? **NA**

Does the following information appear of lesser prominence on the Principal Display Panel?
- Rx-only statement? **YES**
- Net quantity statement? **YES**
- Manufacturer logo? **NO**

Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**

**Comment: Reduce the prominence of the company logo. (Post-AP)**

### 1.2.3 Other Container Label Considerations

***Reviewer Assessment:***

Does this container meet the "too small" exemption found in 21 CFR 201.10(i)? **NA**
Are all abbreviations acceptable? (i.e., mg, mcg, HCl)? **NA**
Are multiple strengths differentiated by use of different color or other acceptable means? **YES**
Does the net quantity statement appear separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded)? **YES**
Are the rules governing leading and terminal zeroes, decimals, and commas followed? **NA**
If other than oral use, is the route of administration correctly described? **NA**
Are all required warning statements that appear on Model Labels properly displayed? **NA**
Is expiration date properly displayed? **NO**
Is bar code properly display per 21 CFR 201.25(c)(2)? **YES**
Is NDC properly displayed? **YES**
Is controlled substance symbol properly displayed? **NA**
Is the "Usual Dosage" on side panel and is it acceptable? **YES**
Is there a product strength equivalency statement on side panel? **YES**

**Comment: The sponsor included the revision date in lieu of the expiration date. Ensure to include the expiration date.**

### 1.2.4 Container Label for Small Volume Parenteral Solutions:

Is container for small volume parenteral solution? **NA**
If YES go to Reviewer Assessment below, if NO go to section 1.2.5.

***Reviewer Assessment:***

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **NA**
If volume < 1 mL, is the strength per fraction of a milliliter the only expression of strength?**NA**
Is there text on the cap/ferrule overseal of this injectable product? **NA**
- If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**

Is the cap color for this injectable product ***not*** black? **NA**
Are inactive ingredients listed on label as required by regulations? **NA**
Is the Aluminum content statement present for products used in TPN? **NA**

**Comment: NA**

### 1.2.5 Container Label for Sterile Solid Injectable:

Is container for sterile solid injectable? **NA**
If YES go to Reviewer Assessment below, if NO go to section 2.2.6.

***Reviewer Assessment:***

Is the strength in terms of the total amount of drug per vial? **NA**
Are instructions for reconstituting the product and the resultant concentration if space permits? **NA**
Are inactive ingredients listed on label as required by regulations? **NA**

**Comment: NA**

### 1.2.6 Container Label for Pharmacy Bulk Package:

Is container a Pharmacy Bulk Package? **NA**
If YES go to Reviewer Assessment below, if NO go to section 2.2.7.

***Reviewer Assessment:***

Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **NA**
Does the container label include graduation marks? **NA**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**

**Comment: NA**

### 1.2.7 Unit Dose Blister Labels

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.8

***Reviewer Assessment:***

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **NA**
Do proprietary name, established name, strength, lot number, expiration date, bar code, and manufacturer appear on each blister cell? **NA**
Does the established name describe only one unit (e.g. "tablet" rather than "tablets")? **NA**

(b) (4)

### 1.2.8 OVER THE COUNTER (OTC) Label

Is this label for an OTC product? NO
If YES go to Reviewer Assessment below, if NO go to section 2.2.9

***Reviewer Assessment:***

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **NA**
Does packaging meet the requirements for Special Packaging under the Poison Prevention Act and defined per 16 CFR 1700? **NA**
Does packaging meet the tamper-evident requirements 21 CFR 211.132? **NA**
Does "Questions?" have a toll-free number no less than size 6 pt. font per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" [21 CFR 201.66 (c)(5)(vii)]? **NA**
Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**

**Comment: NA**

### 1.2.9 Presentation of Manufacturer/Distributor/Packer on Labeling

We compared the name and address of the manufacturer of this product to the name and address listed on the labels and labeling to determine if the labeling statements are consistent with the regulations (21 CFR 201.1). Table 4 provides a description of this comparison. [NOTE: This presentation/assessment may apply to other labeling submitted].

| Table 4: Comparison of Manufacturer/Distributor/Packer Labeling Statements | |
|---|---|
| **Name and Address of Facility ANDA Manufactured** | Copal Ltd. Kurkumbh, India |
| **Name and Address on ANDA Labels** | Manufactured In India by: Cipla Ltd.<br>Kurkumbh, India<br>Manufactured For:<br>TEVA PHARMACEUTICALS USA, Inc.<br>North Wales, PA 18454 |
| **Name and Address on ANDA Labeling** | Manufactured In India By:<br>**CIPLA LTD.**<br>Kurkumbh, India<br>Manufactured For:<br>TEVA PHARMACEUTICALS USA, Inc.<br>North Wales, PA 18454 |

***Reviewer Assessment:***

Does the labeling have the required qualifiers per 21 CFR 201.1? **YES**
For Foreign manufacturers, does the labeling have the country of origin? **YES**
For Foreign manufacturers, does the labeling have a US contact/distributor? **YES**

**Comment: Acceptable**

### 1.2.10 Description of the Container/Closure

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

***Reviewer Assessment:***

Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **YES**
If the closure is not child-resistant, does the container or carton require a labeling statement warning the product is not child-resistant? **YES**
Are the tamper evident requirements met for OTC and Controlled Substances? **NA**
Does this ophthalmic products cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**
Does this light sensitive product contain necessary labeling statements? **NA**
Does this hygroscopic product contain necessary labeling statements? **NA**

**Comment: Acceptable**

### 1.2.11 Storage and Dispensing Recommendations

We compared the storage and dispensing statements that appear on the ANDA labels to the model labeling and USP to confirm the statements do not conflict and the format is consistent with USP and OGD standards (see Table 5). [NOTE: This assessment may apply to other labeling submitted]

| Table 5: Model Labeling and ANDA Storage/Dispensing Recommendations |
|---|
| **Model Labeling** |
| Insert – Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep NEXIUM Delayed-Release Capsules container tightly closed.<br>. Dispense in a tight container if the product package is subdivided |
| Container – Keep container tightly closed. Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].<br>Carton – Keep container tightly closed. Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. This unit-dose package is not child resistant. |
| **ANDA** |
| Insert - Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Keep container tightly closed. |
| Container - Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Keep container tightly closed. Pharmacist: Dispense in a tight container as defined in the<br>USP, with a child-resistant closure (as required). |
| USP - Packaging and Storage: Preserve in tight containers. Store at room temperature. |
| |

***Reviewer Assessment:***

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **YES**
Are the storage temperature recommendations acceptable? **YES**
Does the temperature statement conform to the OGD format for controlled room temperature? **YES**

**Comment: Acceptable**

### 1.2.12 Related Applications Containing the Same Active Ingredient

We evaluated the following applications that contain the same active ingredient from the same applicant to determine if the labels and labeling are adequately differentiated from one another.

***Reviewer Assessment:***

Are the labels and labeling of these products differentiated to avoid selection errors? **NA**

**Comment: N/A**

#### 1.2.13 Comparison of ANDA Inactive Ingredients to Model

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling. Specific inactive ingredients that require special warnings, precautions, or label/labeling statements are in Table 6.

**Table 6: Inactive Ingredients contained in Model Product and ANDA that require special labeling statements**

| Model Labeling | ANDA |
|---|---|
| None | None |

***Reviewer Assessment:***

Do any of the inactive ingredients need a labeling statement required by regulations? **NO**
If the labeling includes "Does not contain …" statements – Has this statement been verified by chemistry? **NA**

**Comment: None**

### 1.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING

#### 1.3.1 General

***Reviewer Assessment:***

Do all required label statements and safety considerations assessed above for CONTAINER labels appear on the carton? NA
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **NA**
For unit dose blister that are not child-resistant is there a statement indicating the package is not child-resistant. For example, "This package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used"? **NA**
If country of origin is not on Container, does appear on outer packaging labeling? **NA**

(b) (4)

### 1.4 PRESCRIBING INFORMATION

#### 1.4.1 Model Labeling

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Table 7.

| Table 7: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply) | | |
|---|---|---|
| ☐ MOST RECENTLY APPROVED REFERENCE LISTED DRUG | | |
| NDA 021153 | Proprietary Name Nexium® | 03/27/2014 |
| S-046 | Description of Supplement - Provides for revisions to the labeling regarding chromgranin A, hypokalaemia in connection with hypomagnesaemia, hypocalcaemia in connection with hypomagnesaemia, and ECL cell hyperplasia. | |
| ☐ BPCA TEMPLATE – N/A | | |
| ☐ OTHER (Describe ) - **The information for the age group of less than 1 year is specifically associated with the oral suspension only. The sponsor removed any information associated with the age group of less than 1 year old from the labeling per the Agency's request.** | | |

***Reviewer Assessment:***

Are the labels and labeling contained in the submission the same as the review model labeling? **YES**
Are the differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **YES**

**Comment: The font size of the final printed insert and medication guide is 6 pts and 10 pts, respectively.**

### 1.4.2 Patents and Exclusivities (11/18/2014)

Are there any unexpired patents or marketing exclusivities for Model Labeling? **YES**

If YES go to the table and assessments below.
If NO go to section 2.4.3.
Table 8 describes how the applicant certified to the Orange Book patent(s) for the Model Labeling and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

Patent Data

| Appl No | Prod No | Patent No | Patent Expiration | Patent Use Code | Patent Certification | Labeling Impact |
|---|---|---|---|---|---|---|
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 373 | PIV | None |
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 729 | | |
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 770 | | |
| N021153 | 001 | 5690960*PED | May 25, 2015 | U - 373 | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 373 | PIV | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 729 | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 770 | | |

| | | | | | |
|---|---|---|---|---|---|
| N021153 | 001 | 5714504*PED | Aug 3, 2015 | U - 373 | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 373 | PIV |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 729 | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 770 | |
| N021153 | 001 | 5877192*PED | Nov 27, 2014 | U - 373 | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 373 | PIV |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 729 | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 770 | |
| N021153 | 001 | 5900424*PED | Nov 4, 2016 | U - 373 | |
| N021153 | 001 | 6147103 | Oct 9, 2018 | | PIV |
| N021153 | 001 | 6147103*PED | Apr 9, 2019 | | |
| N021153 | 001 | 6166213 | Oct 9, 2018 | | PIV |
| N021153 | 001 | 6166213*PED | Apr 9, 2019 | | |
| N021153 | 001 | 6191148 | Oct 9, 2018 | | PIV |
| N021153 | 001 | 6191148*PED | Apr 9, 2019 | | |
| N021153 | 001 | 6369085 | May 25, 2018 | U - 729 | PIV |
| N021153 | 001 | 6369085 | May 25, 2018 | U - 770 | |
| N021153 | 001 | 6369085*PED | Nov 25, 2018 | | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 469 | PIV |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 729 | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 770 | |
| N021153 | 001 | 6428810*PED | May 3, 2020 | U - 469 | |
| N021153 | 001 | 6875872 | May 27, 2014 | | PIV |
| N021153 | 001 | 6875872*PED | Nov 27, 2014 | | |

| | | | | |
|---|---|---|---|---|
| N021153 | 001 | 7411070 | May 25, 2018 | PIV |
| N021153 | 001 | 7411070*PED | Nov 25, 2018 | |
| N021153 | 001 | 8466175 | May 25, 2018U-1417 | PIV* |
| N021153 | 001 | 8466175*PED | Nov 25, 2018 | |

**Exclusivities:**

There is no unexpired exclusivity for this product.

Code Definition

U - 373 GENERAL USE CLAIM SUBMITTED FOR 12 NEXIUM PATIENTS STATING "PERTINENT TO THE CAPSULE FORMULATION FOR NEXIUM AND ITS INDICATIONS FOR THE TREATMENT OF GERD AND ERADICATION OF H.PYLORI TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE

U - 729 TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD), RISK-REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER, H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE

U - 770 LONG-TERM TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS

U - 469 TREATMENT OF GASTROESOPHAGEAL REFLEX DISEASE (GERD) AND ERADICATION OF H.PYLORI TO REDUCE RISK OF DUODENAL ULCER RECURRENCE

U – 1417 USE FOR TREATMENT OF HELICOBACTER INFECTIONS

*The sponsor certified to PATENT "8,466,175" on 8/16/2013.

***Reviewer Assessment:***

**Is the applicant's "patent carve out" acceptable?** NA

**Comment: N/A**

Table 9 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the Exclusivity Code column.

| Table 9: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling | | | |
|---|---|---|---|
| **Exclusivity Code** | **Exclusivity Code Definition** | **Exclusivity Expiration** | **Labeling Impact** |
| **NA** | | | |

***Reviewer Assessment:***

| Is the applicant's "exclusivity carve out" acceptable? **NA** |
|---|

**Comment: NA**

### 1.4.3 Comparison of ANDA Inactive Ingredients to Model Labeling (Topical And Oral Products Only)

Is submitted labeling for a topical or **oral product**? **YES**

If YES, complete table 10 and assessment below.
If NO, go to section 2.4.4.
We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling. Specific inactive ingredients that require special warnings, precautions, or label/labeling statements are in Table 10.

**Table 10: Inactive Ingredients contained in Model Product and ANDA that require special statements**

| Model Labeling Inactive Ingredients | ANDA Inactive Ingredients |
|---|---|
| None | None |

***Reviewer Assessment:***

| Is the DESCRIPTION section of the labeling consistent with the component and composition statement contained in the Application? **YES**<br>Are the required labeling statements present in the ANDA labeling? **NA** |
|---|

**Comment: Acceptable**

### 1.4.4 Comparison of ANDA Inactive Ingredients to Model Labeling (Ophthalmic, Injectable, And Otic Products Only)

Is submitted labeling for an ophthalmic, injectable, or an otic product? **NO**

If YES, complete table 11 and assessment below.
If NO go to section 1.4.5.

We compared the list of inactive ingredients and the amount of the inactive ingredient contained in this product as to those contained in the Model Labeling to determine if all components and composition are the same and if they are listed accurately on the labels a labeling. Additionally, we evaluated whether or not any components require special warnings, precautions, or labeling statements. Below is the table submitted in the Quality Overall Summary that describes the components and composition of this product.

**Table 11: Inactive Ingredients contained in Model Product and ANDA**

| Model Labeling Inactive Ingredients | ANDA Inactive Ingredients |
|---|---|
| | |

***Reviewer Assessment:***

Is the DESCRIPTION section of the labeling consistent with the component and composition statement contained in the application? **NA**
Are the required labeling statements present in the ANDA labeling? **NA**
If the labeling includes "Does not contain …" statements – Has this statement been verified by chemistry? **NA**
For LVP, SVP, and PBP, is there an aluminum statement under WARNINGS 201.323 for TPN products? **NA**
For LVP is there an aluminum statement in PRECAUTIONS 201.323(b)? **NA**

**Comment: NA**

### 1.4.5 How Supplied Section

We compared the descriptions of the model product to the ANDA finished product to determine if the scoring, film coating and imprinting are the same. Product differences are highlighted in Table 12 and will be referred to the appropriate review discipline for evaluation. Additionally, we evaluated if the text contained in the HOW SUPPLIED section is accurate based on the ANDA finished product description.

| Table 12: Comparison of Model Labeling to ANDA finished product | |
|---|---|
| **Model Labeling** | **20 mg**: opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and NEXIUM 20 mg in yellow on the body<br>**40 mg:** opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and NEXIUM 40 mg in yellow on the body. |
| **ANDA** | Esomeprazole Magnesium Delayed-Release Capsules USP, 20 mg, are available as off-white to pale yellow granule-filled, light turquoise blue, opaque, hard-gelatin capsules, spin-printed " " and "6450" on the cap and "20 mg" on the body in gold ink containing 20 mg esomeprazole packaged in bottles of 30, 90, and 1000 capsules.<br>NDC 0093-6450-56 bottle of 30<br>NDC 0093-6450-98 bottle of 90<br>NDC 0093-6450-10 bottle of 1000<br>Esomeprazole Magnesium Delayed-Release Capsules USP, 40 mg, are available as off-white to pale yellow granule-filled, light turquoise blue, opaque, hard-gelatin capsules, spin-printed " " and "6451" on the cap and "40 mg" on the body in gold ink containing 40 mg esomeprazole packaged in bottles of 30, 90, and 1000 capsules.<br>NDC 0093-6451-56 bottle of 30<br>NDC 0093-6451-98 bottle of 90<br>NDC 0093-6451-10 bottle of 1000 |

***Reviewer Assessment:***

Is the description of the finished product accurate in the HOW SUPPLIED section of the insert? **YES**
Are the packaging sizes acceptable as compared to the Model Labeling? **YES**
Does the packaging configuration require the addition or deletion of labeling statements based on the comparison to Model Labeling and/or stability data? **NO**

**Comment: Acceptable**

### 1.4.6 Previous Labeling Reviews for ANDA and/or Related Correspondence

Table 13 contains a listing of previously completed OGD labeling reviews and other correspondence relating to this application from DARRTS. We reviewed this information to determine if previous labeling comments were addressed by the applicant or if there is new information that may impact the labeling.

| Table 13: Completed Labeling Reviews or Other Correspondence for Application Under Review | | |
|---|---|---|
| Search Date | Finalized Date of DARRTS Document | Were Previous Comments Addressed? (Yes/No/Explain) |
| 11/18/2014 | 6/19/2014 | Yes (Removal of specific information associated with the age group of less than 1 year.) |

### 1.5 MEDICATION GUIDE

We evaluated the medication guide to ensure the text is the same as the model labeling. We also ensured the directive appears on the container (b) (4) labeling.

***Reviewer Assessment:***

Does the format meet the requirements of 21 CFR 201.80? **YES**
Are the dispensing and distributions requirements of 21 CFR 201.24 met? **YES**
Has the Applicant committed to provide a sufficient number of medication guides? **YES**
Is the phonetic spelling of the proprietary name present? **YES**
Is the dispensing directive present on the container (b) (4) labeling? **YES**
Is FDA 1-800-FDA-1088 phone number included? **YES**
Is font a minimum size 10 font? **YES**

**Comment: Acceptable**

### 1.6 OTHER PATIENT LABELING

None

### 1.7 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA. Additionally, we compared the size of the model and ANDA tablet/capsule size to determine if the size of the ANDA tablet/capsule poses a safety risk or require a labeling statement (see Table 14).

| Table 14: Comparison of Model and ANDA Tablet/Capsule Size | |
|---|---|
| Model Labeling | 20 mg (14 mm); 40 mg (14 mm) |
| ANDA Labeling | 20 mg (14 mm); 40 mg (16 mm) |

***Reviewer Assessment:***

Are the data elements consistent with the information submitted in the ANDA? **YES**
Is the tablet/capsule size similar to the RLD? **YES**

**Comment: Acceptable**

## 2. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 15 and 16 provide a summary of recommendations for each material analyzed in this review.

| Table 15: Review Summary of Container Label and Carton Labeling | | | |
|---|---|---|---|
| | Packaging Sizes | Submission Date | Recommendation |
| Container ☐ Draft ☒ FPL | 30s, 90s, 1000s | 8/22/2014 | ☒ Satisfactory ☐ Revise |
| **Table 16 Review Summary of Prescribing Information and Patient Labeling** | | | |
| | Revision Date and/or code | Submission Date | Recommendation |
| Prescribing Info ☐ Draft ☒ FPL | 7/2014 | 8/22/2014 | ☒ Satisfactory ☐ Revise |
| Medication Guide ☐ Draft ☒ FPL | 7/2014 | 8/22/2014 | ☒ Satisfactory ☐ Revise |
| SPL ☒ (DLDE) | 8/2014 | 8/22/2014 | ☒ Satisfactory ☐ Revise |

## 3. QUESTIONS AND COMMENTS FOR NA

During the course of this review, we sought clarification on the following issues to determine if a label or labeling revision is necessary.

***Reviewer Assessment:***

| Do the response(s) received require a label and/or labeling revision? **NA** |
|---|
| **Comment: N/A** |

## 4. SPECIAL CONSIDERATIONS

**NOTE:** The information for the age group of less than 1 year is specifically associated with the oral suspension only. The sponsor remove any information associated with the age group of less than 1 year old from the labeling per the Agency's request.

## 5. POST APPROVAL REVISIONS

**CONTAINER – 30s, 90s, 1000s**

a. Reduce the prominence of the company logo.
b. Recommend the use of title case for the drug product name.
c. Include the Exp. date rather than Rev. Date.
(**NOTE:** These comments were forwarded to the sponsor in the last deficiency letter, but the sponsor only partially complied with the comments.)

***** This document contains proprietary information that cannot be released to the public*****

# ORIGINAL LABELING REVIEW

**Division of Labeling Review**
**Office of Regulatory Operations**
**Office of Generic Drugs (OGD)**

**Center for Drug Evaluation and Research (CDER)**

| | |
|---|---|
| **Date of This Review** | 6/11/2014 |
| **ANDA Application Number** | 078003 |
| **Review Cycle Number** | 6th Cycle |
| **Applicant Name** | IVAX Pharmaceuticals, Inc. |
| **Established Name** | Esomeprazole Magnesium Delayed-release Capsules, USP |
| **Strength(s)** | 20 mg and 40 mg |
| **Proposed Proprietary Name** | None |
| **DARRTS Received Date** | 5/16/2014 |
| **Labeling Reviewer** | Chan Park |
| **Acting Labeling Team Leader** | Lisa Kwok |

**Review Conclusion**

☐ No Comments – The Labels and Labeling are ready for CLICK HERE.

☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for the Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

## LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

1. **CONTAINER**
   a. Reduce the prominence of the company logo. Please ensure that the prominence of the company logo be less prominent than that of the drug product name and strength.
   b. Please use title case for the drug product name for better recognition of the drug name.

c. Include the expiration date rather than the issue date.

2. **INSERT**
   a. Replace the term "Nexium" (without the dosage form associated) with "esomeprazole magnesium" rather than "esomeprazole" throughout the text.
   b. Upon further review, we note that the information for the age group of less than 1 year is specifically associated with the oral suspension only. For this reason, we ask that you the remove any information associated with the age group of less than 1 year old from you labeling throughout the text.

3. **MEDICATION GUIDE**
   See comment under INSERT.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

## MATERIAL ANALYSIS

The results for each material reviewed in this section provide the basis for the labeling comments to the Applicant and other review disciplines.

### 1.1 GENERAL

#### 1.1.1 Established Name Assessment

We compared the established names of this ANDA, the Model Labeling and the USP to determine if the established name presented on the labeling is acceptable.

| Table 1: Comparison of Established Names | |
|---|---|
| **Model Labeling:** | Esomeprazole magnesium delayed-release capsules |
| **ANDA:** | Esomeprazole magnesium delayed-release capsules |
| **USP:** | Esomeprazole magnesium delayed-release capsules |

***Reviewer Assessment:***

Is the established name for ANDA acceptable? **YES**
Is the established (and proprietary name) displayed in a manner consistent 21 CFR 201.10? **YES**

Is title case used in established name? **NO**
Is established name on list of name pairs that use Tall Man lettering found on FDA webpage? **NA**

**Comment: Recommend the use of the title case for the drug name on the container. (Post – AP)**

### 1.1.2 United States Pharmacopeia (USP) & Pharmacopeia Forum (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph and determined how the monograph impacts the ANDA labeling with respect to packaging and storage. The results of this search are provided in Table 2.

| Table 2: USP and PF Search Results | | | |
|---|---|---|---|
| | Date Searched | Monograph | Copy of Information from USP or PF |
| USP | 6/11/2014 | YES | Packaging and Storage: Preserve in tight containers. Store at room temperature. |
| PF | 6/11/2014 | YES | Add the following : Esomeprazole magnesium delayed-release capsules |

N/A – The drug product is not the subject of a USP monograph and/or proposed monograph.

***Reviewer Assessment:***

Does the ANDA labeling require revision or is clarification needed from other review disciplines based on the comparison of USP or PF label/labeling requirements? **NO**
Do required labeling statements appear on/in the ANDA labeling? **YES**
Are the USP packaging and storage recommendations reflected in the labels and labeling? **YES**

**Comment: Acceptable**

## 1.2 CONTAINER LABEL

We evaluated the container labels for the inclusion of all required statements and safety considerations. Our review is based on the following model labels that were used for comparison to the submitted ANDA labeling.

| Table 3: Review Model Labeling for Container Label and Carton Labeling (Check all sources that apply) | | |
|---|---|---|
| | | Supplement Approval Date or Annual Report Date |
| drugs@fda | NO | N/A |
| DARRTS | NO | N/A |
| DailyMed | YES | Revised 3/2014 |
| Annual Report | YES | Submitted 4/11/2013 |

### 1.2.1 Model labels and carton labeling. [Insert images below]

### 1.2.2 Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

We used the draft Guidance for Industry titled Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors for the following assessment.

***Reviewer Assessment:***

Does the following information appear as the most prominent information on the Principal Display Panel?

Proprietary name? **NA**
Established name? **YES**
Product strength? **YES**
Route(s) of administration (other than oral)? **NA**
Warnings (if any) or cautionary statements (if any)? **NA**

Does the following information appear of lesser prominence on the Principal Display Panel?

Rx-only statement? **YES**
Net quantity statement? **YES**
Manufacturer logo? **NO**

Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**

**Comment: Reduce the prominence of the company logo.**

### 1.2.3 Other Container Label Considerations

***Reviewer Assessment:***

Does this container meet the "too small" exemption found in 21 CFR 201.10(i)? **NA**
Are all abbreviations acceptable? (i.e., mg, mcg, HCl)? **NA**
Are multiple strengths differentiated by use of different color or other acceptable means? **YES**
Does the net quantity statement appear separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded)? **YES**
Are the rules governing leading and terminal zeroes, decimals, and commas followed? **NA**
If other than oral use, is the route of administration correctly described? **NA**
Are all required warning statements that appear on Model Labels properly displayed? **NA**
Is expiration date properly displayed? **NO**
Is bar code properly display per 21 CFR 201.25(c)(2)? **YES**
Is NDC properly displayed? **YES**
Is controlled substance symbol properly displayed? **NA**
Is the "Usual Dosage" on side panel and is it acceptable? **YES**
Is there a product strength equivalency statement on side panel? **YES**

**Comment: The sponsor included the issue date in lieu of the expiration date. Ensure to include the expiration date.**

### 1.2.4 Container Label for Small Volume Parenteral Solutions:

Is container for small volume parenteral solution? **NO**
If YES go to Reviewer Assessment below, if NO go to section 1.2.5.

***Reviewer Assessment:***

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **CLICK HERE**
If volume < 1 mL, is the strength per fraction of a milliliter the only expression of strength?**CLICK HERE**
Is there text on the cap/ferrule overseal of this injectable product? **CLICK HERE**
If YES, does text comply with the recommendations in USP General Chapter <1>? **CLICK HERE**
Is the cap color for this injectable product ***not*** black? **CLICK HERE**
Are inactive ingredients listed on label as required by regulations? **CLICK HERE**
Is the Aluminum content statement present for products used in TPN? **CLICK HERE**

**Comment: N/A**

### 1.2.5 Container Label for Sterile Solid Injectable:

Is container for sterile solid injectable? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.6.

***Reviewer Assessment:***

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**
Are instructions for reconstituting the product and the resultant concentration if space permits? **CLICK HERE**
Are inactive ingredients listed on label as required by regulations? **CLICK HERE**

**Comment: N/A**

### 1.2.6 Container Label for Pharmacy Bulk Package:

Is container a Pharmacy Bulk Package? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.7.

***Reviewer Assessment:***

Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **CLICK HERE**
Does the container label include graduation marks? **CLICK HERE**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **CLICK HERE**

**Comment: N/A**

### 1.2.7 Unit Dose Blister Labels

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.8

***Reviewer Assessment:***

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **CLICK HERE**
Do proprietary name, established name, strength, lot number, expiration date, bar code, and manufacturer appear on each blister cell? **CLICK HERE**
Does the established name describe only one unit (e.g. "tablet" rather than "tablets")? **CLICK HERE**

(b) (4)

### 1.2.8 OVER THE COUNTER (OTC) Label

Is this label for an OTC product? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.9

***Reviewer Assessment:***

| |
|---|
| Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **CLICK HERE**<br>Does packaging meet the requirements for Special Packaging under the Poison Prevention Act and defined per 16 CFR 1700? **CLICK HERE**<br>Does packaging meet the tamper-evident requirements 21 CFR 211.132? **CLICK HERE**<br>Does "Questions?" have a toll-free number no less than size 6 pt. font per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" [21 CFR 201.66 (c)(5)(vii)]? **CLICK HERE**<br>Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE** |

**Comment: N/A**

### 1.2.9 Presentation of Manufacturer/Distributor/Packer on Labeling

We compared the name and address of the manufacturer of this product to the name and address listed on the labels and labeling to determine if the labeling statements are consistent with the regulations (21 CFR 201.1). Table 4 provides a description of this comparison. [NOTE: This presentation/assessment may apply to other labeling submitted].

**Table 4: Comparison of Manufacturer/Distributor/Packer Labeling Statements**

| | |
|---|---|
| **Name and Address of Facility ANDA Manufactured** | Cipla Ltd. Kurkumbh, India |
| **Name and Address on ANDA Labels** | Manufactured In India by: Cipla Ltd.<br>Kurkumbh, India |
| **Name and Address on ANDA Labeling** | Manufactured In India By:<br>**CIPLA LTD.**<br>Kurkumbh, India |

***Reviewer Assessment:***

| |
|---|
| Does the labeling have the required qualifiers per 21 CFR 201.1? **YES**<br>For Foreign manufacturers, does the labeling have the country of origin? **YES**<br>For Foreign manufacturers, does the labeling have a US contact/distributor? **YES** |

**Comment: Acceptable**

### 1.2.10 Description of the Container/Closure

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

***Reviewer Assessment:***

| |
|---|
| Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **YES**<br>If the closure is not child-resistant, does the container (b) (4) require a labeling statement warning the product is not child-resistant? **YES**<br>Are the tamper evident requirements met for OTC and Controlled Substances? **NA**<br>Does this ophthalmic products cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**<br>Does this light sensitive product contain necessary labeling statements? **NA**<br>Does this hygroscopic product contain necessary labeling statements? **NA** |

**Comment: Acceptable**

### 1.2.11 Storage and Dispensing Recommendations

We compared the storage and dispensing statements that appear on the ANDA labels to the model labeling and USP to confirm the statements do not conflict and the format is consistent with USP and OGD standards (see Table 5). [NOTE: This assessment may apply to other labeling submitted]

**Table 5: Model Labeling and ANDA Storage/Dispensing Recommendations**

| **Model Labeling** |
|---|
| Insert – Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep NEXIUM Delayed-Release Capsules container tightly closed.<br>. Dispense in a tight container if the product package is subdivided |
| Container – Keep container tightly closed. Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].<br>Carton – Keep container tightly closed. Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. This unit-dose package is not child resistant. |
| **ANDA** |
| Insert - Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Keep container tightly closed. |
| Container - Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Keep container tightly closed. Pharmacist: Dispense in a tight container as defined in the USP, with a child-resistant closure (as required). |
| USP - Packaging and Storage: Preserve in tight containers. Store at room temperature. |
| |

***Reviewer Assessment:***

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **YES**
Are the storage temperature recommendations acceptable? **YES**
Does the temperature statement conform to the OGD format for controlled room temperature? **YES**

**Comment: Acceptable**

### 1.2.12 Related Applications Containing the Same Active Ingredient

We evaluated the following applications that contain the same active ingredient from the same applicant to determine if the labels and labeling are adequately differentiated from one another.

***Reviewer Assessment:***

Are the labels and labeling of these products differentiated to avoid selection errors? **NA**

**Comment: N/A**

### 1.2.13 Comparison of ANDA Inactive Ingredients to Model

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling. Specific inactive ingredients that require special warnings, precautions, or label/labeling statements are in Table 6.

**Table 6: Inactive Ingredients contained in Model Product and ANDA that require special labeling statements**

| Model Labeling | ANDA |
|---|---|
| None | None |

***Reviewer Assessment:***

Do any of the inactive ingredients need a labeling statement required by regulations? **NO**
If the labeling includes "Does not contain …" statements – Has this statement been verified by chemistry?
**NA**

**Comment: N/A**

## 1.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING

### 1.3.1 General

***Reviewer Assessment:***

Do all required label statements and safety considerations assessed above for CONTAINER labels appear on the carton? NA
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **NA**
For unit dose blister that are not child-resistant is there a statement indicating the package is not child-resistant. For example, "This package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used"? **NA**
If country of origin is not on Container, does appear on outer packaging labeling? **NA**

(b) (4)

## 1.4 PRESCRIBING INFORMATION

### 1.4.1 Model Labeling

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Table 7.

| Table 7: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply) | | |
|---|---|---|
| ☐ MOST RECENTLY APPROVED REFERENCE LISTED DRUG | | |
| NDA 021153 | Proprietary Name Nexium® | 03/27/2014 |
| S-046 | Description of Supplement - Provides for revisions to the labeling Regarding chromgranin A, hypokalaemia in connection with hypomagnesaemia, hypocalcaemia in connection with hypomagnesaemia and ECL cell hyperplasia. | |
| ☐ BPCA TEMPLATE – N/A | | |
| ☐ OTHER (Describe N/A | | |

***Reviewer Assessment:***

Are the labels and labeling contained in the submission the same as the review model labeling? **YES**
Are the differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **YES**

**Comment: The insert labeling should be revised with deletion of all information associated with the age group of less than 1 year old as it is specific to the oral suspension, but not capsules. (See "Special Consideration" below.)**

### 1.4.2 Patents and Exclusivities

Are there any unexpired patents or marketing exclusivities for Model Labeling? **YES**

If YES go to the table and assessments below.
If NO go to section 2.4.3.
Table 8 describes how the applicant certified to the Orange Book patent(s) for the Model Labeling and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

Patent Data

| Appl No | Prod No | Patent No | Patent Expiration | Patent Use | Patent Certification | Labeling Impact |
|---|---|---|---|---|---|---|

| | | | | Code | | |
|---|---|---|---|---|---|---|
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 373 | PIV | None |
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 729 | | |
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 770 | | |
| N021153 | 001 | 5690960*PED | May 25, 2015 | U - 373 | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 373 | PIV | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 729 | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 770 | | |
| N021153 | 001 | 5714504*PED | Aug 3, 2015 | U - 373 | | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 373 | PIV | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 729 | | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 770 | | |
| N021153 | 001 | 5877192*PED | Nov 27, 2014 | U - 373 | | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 373 | PIV | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 729 | | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 770 | | |
| N021153 | 001 | 5900424*PED | Nov 4, 2016 | U - 373 | | |
| N021153 | 001 | 6147103 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6147103*PED | Apr 9, 2019 | | | |
| N021153 | 001 | 6166213 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6166213*PED | Apr 9, 2019 | | | |
| N021153 | 001 | 6191148 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6191148*PED | Apr 9, 2019 | | | |
| N021153 | 001 | 6369085 | May 25, 2018 | U - 729 | PIV | |
| N021153 | 001 | 6369085 | May 25, 2018 | U - 770 | | |
| N021153 | 001 | 6369085*PED | Nov 25, 2018 | | | |

| | | | | | |
|---|---|---|---|---|---|
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 469 | PIV |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 729 | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 770 | |
| N021153 | 001 | 6428810*PED | May 3, 2020 | U - 469 | |
| N021153 | 001 | 6875872 | May 27, 2014 | | PIV |
| N021153 | 001 | 6875872*PED | Nov 27, 2014 | | |
| N021153 | 001 | 7411070 | May 25, 2018 | | PIV |
| N021153 | 001 | 7411070*PED | Nov 25, 2018 | | |
| N021153 | 001 | 8466175 | May 25, 2018 | U-1417 | PIV* |
| N021153 | 001 | 8466175*PED | Nov 25, 2018 | | |

**Exclusivities:**
There is no unexpired exclusivity for this product.

| Code | Definition |
|---|---|
| U - 373 | GENERAL USE CLAIM SUBMITTED FOR 12 NEXIUM PATIENTS STATING "PERTINENT TO THE CAPSULE FORMULATION FOR NEXIUM AND ITS INDICATIONS FOR THE TREATMENT OF GERD AND ERADICATION OF H.PYLORI TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U - 729 | TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD), RISK-REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER, H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U - 770 | LONG-TERM TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS |
| U - 469 | TREATMENT OF GASTROESOPHAGEAL REFLEX DISEASE (GERD) AND ERADICATION OF H.PYLORI TO REDUCE RISK OF DUODENAL ULCER RECURRENCE |

U – 1417 USE FOR TREATMENT OF HELICOBACTER INFECTIONS
*The sponsor certified to PATENT "8,466,175" on 8/16/2013.

***Reviewer Assessment:***
**Is the applicant's "patent carve out" acceptable?** NA

**Comment: See special Consideration below.**

Table 9 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the Exclusivity Code column.

| Table 9: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling | | | |
|---|---|---|---|
| Exclusivity Code | Exclusivity Code Definition | Exclusivity Expiration | Labeling Impact |
| NA | | | |

***Reviewer Assessment:***

Is the applicant's "exclusivity carve out" acceptable? **NA**

**Comment: None**

### 1.4.3 Comparison of ANDA Inactive Ingredients to Model Labeling (Topical And Oral Products Only)

Is submitted labeling for a topical or **oral product**? **YES**

If YES, complete table 10 and assessment below.
If NO, go to section 2.4.4.
We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling. Specific inactive ingredients that require special warnings, precautions, or label/labeling statements are in Table 10.

| Table 10: Inactive Ingredients contained in Model Product and ANDA that require special statements | |
|---|---|
| Model Labeling Inactive Ingredients | ANDA Inactive Ingredients |
| None | None |

***Reviewer Assessment:***

Is the DESCRIPTION section of the labeling consistent with the component and composition statement contained in the Application? **YES**
Are the required labeling statements present in the ANDA labeling? **YES**

**Comment: Acceptable**

### 1.4.4 Comparison of ANDA Inactive Ingredients to Model Labeling (Ophthalmic, Injectable, And Otic Products Only)

Is submitted labeling for an ophthalmic, injectable, or an otic product? **NO**

If YES, complete table 11 and assessment below.
If NO go to section 1.4.5.

We compared the list of inactive ingredients and the amount of the inactive ingredient contained in this product as to those contained in the Model Labeling to determine if all components and composition are the same and if they are listed accurately on the labels a labeling. Additionally, we evaluated whether or not any components require special warnings, precautions, or labeling statements. Below is the table submitted in the Quality Overall Summary that describes the components and composition of this product.

| Table 11: Inactive Ingredients contained in Model Product and ANDA | |
|---|---|
| Model Labeling Inactive Ingredients | ANDA Inactive Ingredients |
| | |

***Reviewer Assessment:***

Is the DESCRIPTION section of the labeling consistent with the component and composition statement contained in the application? **CLICK HERE**
Are the required labeling statements present in the ANDA labeling? **CLICK HERE**
If the labeling includes "Does not contain …" statements – Has this statement been verified by chemistry?
**CLICK HERE**
For LVP, SVP, and PBP, is there an aluminum statement under WARNINGS 201.323 for TPN products?
**CLICK HERE**
For LVP is there an aluminum statement in PRECAUTIONS 201.323(b)? **CLICK HERE**

**Comment: N/A**

### 1.4.5 How Supplied Section

We compared the descriptions of the model product to the ANDA finished product to determine if the scoring, film coating and imprinting are the same. Product differences are highlighted in Table 12 and will be referred to the appropriate review discipline for evaluation. Additionally, we evaluated if the text contained in the HOW SUPPLIED section is accurate based on the ANDA finished product description.

| Table 12: Comparison of Model Labeling to ANDA finished product | |
|---|---|
| **Model Labeling** | **20 mg**: opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and NEXIUM 20 mg in yellow on the body<br>**40 mg:** opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and NEXIUM 40 mg in yellow on the body. |
| **ANDA** | **20 mg**: Hard gelatin size '4' capsules having light turquoise blue opaque cap and lightturquoise blue opaque body with Ivax hour glass logo and "6450" spin printed on cap in gold ink and "20 mg" spin printed in gold ink on the body containing off white to pale yellow coloured pellets.<br>**40 mg**: Hard gelatin size '3' capsules having light turquoise blue opaque cap and light turquoise blue opaque body with Ivax hour glass logo and "6451" spin printed on cap in gold ink and "40 mg" spin printed in gold ink on the body containing off white to pale yellow coloured pellets. |

***Reviewer Assessment:***

Is the description of the finished product accurate in the HOW SUPPLIED section of the insert? **YES**
Are the packaging sizes acceptable as compared to the Model Labeling? **YES**
Does the packaging configuration require the addition or deletion of labeling statements based on the comparison to Model Labeling and/or stability data? **NO**

**Comment: Acceptable**

### 1.4.6 Previous Labeling Reviews for ANDA and/or Related Correspondence

Table 13 contains a listing of previously completed OGD labeling reviews and other correspondence relating to this application from DARRTS. We reviewed this information to determine if previous labeling comments were addressed by the applicant or if there is new information that may impact the labeling.

| Table 13: Completed Labeling Reviews or Other Correspondence for Application Under Review | | |
|---|---|---|
| **Search Date** | **Finalized Date of DARRTS Document** | **Were Previous Comments Addressed? (Yes/No/Explain)** |
| **6/12/2014** | **4/29/2014** | **Yes (Update of the insert & medication Guide)** |

### 1.5 MEDICATION GUIDE

We evaluated the medication guide to ensure the text is the same as the model labeling. We also ensured the directive appears on the container (b) (4) labeling.

***Reviewer Assessment:***

Does the format meet the requirements of 21 CFR 201.80? **YES**
Are the dispensing and distributions requirements of 21 CFR 201.24 met? **YES**
Has the Applicant committed to provide a sufficient number of medication guides? **YES**
Is the phonetic spelling of the proprietary name present? **N/A**
Is the dispensing directive present on the container (b) (4) labeling? **YES**
Is FDA 1-800-FDA-1088 phone number included? **YES**
Is font a minimum size 10 font? **YES**

**Comment: Acceptable**

### 1.6 Other Patient Labeling

None

### 1.7 Structured Product Labeling (SPL) Data Elements

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA. Additionally, we compared the size of the model and ANDA tablet/capsule size to determine if the size of the ANDA tablet/capsule poses a safety risk or require a labeling statement (see Table 14).

| Table 14: Comparison of Model and ANDA Tablet/Capsule Size | |
|---|---|
| **Model Labeling** | **20 mg (14 mm); 40 mg (14 mm)** |
| **ANDA Labeling** | **20 mg (14 mm); 40 mg (16 mm)** |

***Reviewer Assessment:***

Are the data elements consistent with the information submitted in the ANDA? **YES**
Is the tablet/capsule size similar to the RLD? **YES**

**Comment: Acceptable**

## 2. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 15 and 16 provide a summary of recommendations for each material analyzed in this review.

| Table 15: Review Summary of Container Label and Carton Labeling | | | |
|---|---|---|---|
| | Packaging Sizes | Submission Date | Recommendation |
| Container ☐ Draft ☒ FPL | 30s, 90s, 1000s | 3/31/2014 | ☐ Satisfactory ☒ Revise |
| **Table 16 Review Summary of Prescribing Information and Patient Labeling** | | | |
| | Revision Date and/or code | Submission Date | Recommendation |
| Prescribing Info ☐ Draft ☒ FPL | 4/2014 | 5/16/2014 | ☐ Satisfactory ☒ Revise |
| Medication Guide ☐ Draft ☒ FPL | 4/20/2014 | 5/16/2014 | ☐ Satisfactory ☒ Revise |
| SPL ☒ (DLDE) | 4/20/2014 | 5/16/2014 | ☒ Satisfactory ☐ Revise |

## 3. QUESTIONS AND COMMENTS FOR CLICK HERE

During the course of this review, we sought clarification on the following issues to determine if a label or labeling revision is necessary.

***Reviewer Assessment:***

| Do the response(s) received require a label and/or labeling revision? **NA** |
|---|

**Comment: N/A**

## 4. SPECIAL CONSIDERATIONS

NDA 021957 (2.5 mg, 5 mg, 20 mg, and 40 mg base/packet, Oral Suspension) and NDA 022101 (10 mg base/packet, Oral Suspension) were granted an exclusivity M-86 (LABELING CHANGES SUBMITTED IN RESPONSE TO PEDIATRIC WRITTEN REQUEST FOR INFANTS AGES BIRTH TO 11 MONTH INCLUSIVE REFLECTING LACK OF EFFICACY FOR GERD INDICATION FOR THIS PATIENT POPULATION), which expired on 12/18/2012 with pediatric extension. This exclusivity was NOT granted to the NDA 021153 (Capsules). **This implies that the information associated with the age group of less than 1 year is specifically associated with the oral suspension only. For this reason, we will have the sponsor silent on any information associated with the age group of less than 1 year old for the Capsules labeling.**

## 5. POST APPROVAL REVISIONS – N/A

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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.**

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/s/

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CHAN H PARK
06/19/2014

LISA H KWOK
06/19/2014

# Office of Generic Drugs

## REVIEW OF PROFESSIONAL LABELING (5th Cycle)

| | |
|---|---|
| ANDA Number: | 078003 |
| Date of Submission: | March 31, 2014 |
| Applicant: | IVAX Pharmaceuticals, Inc. |
| Established Name and Strength: | Esomeprazole Magnesium Delayed-release Capsules USP, 20 mg and 40 mg |
| Proposed Proprietary Name: | None |

**Labeling Comments below are considered:**

☒ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☐ No Comments (Labeling Approval Summary or Tentative Approval Summary)

**RPM Note - Labeling comments to be sent to the firm start below:**

- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

**Labeling Deficiencies determined on April 4, 2014, based on your submission dated March 31, 2014.**

1. PRESCRIBING INFORMATION/PHYSICIAN INSERT

   a. GENERAL

   Please update your labeling to be in accordance with the labeling for Nexium® Delayed-release Capsules (NDA 021153/S-046), approved March 27, 2014.

   b. HIGHLIGHTS OF PRESCRIBING INFORMATION

   Revise the drug title immediately above "Initial U.S. Approval" to read "**ESOMEPRAZOLE magnesium delayed-release capsules USP, for oral use**". We refer you to 21 CFR 201.57(a)(2) for guidance.

2. MEDICATION GUIDE

   See comment 1(a) above.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

**Note RPM** - Labeling comments end here

**REVISIONS NEEDED POST APPROVAL?**
**NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: Yes**
From: Park, Chan H
Sent: Friday, April 04, 2014 4:22 PM
Subject: ANDA 078003 (Esomeprazole Magnesium D-R Cap)

Hi Yangping,

It is to let you know that [redacted] (b) (4) [redacted] (b) (4) as indicated in the amendment dated 3/31/2014.
Thanks,

Chan

**Review Summary**

| Labeling Submitted | Date submitted | Final or Draft | Recommendation |
|---|---|---|---|
| CONTAINER – 30s, 90s and 1000s | March 31, 2014 | FINAL | AC for AP |
| INSERT | March 31, 2014 | FINAL | NAC |
| MEDICATION GUIDE | March 31, 2014 | FINAL | NAC |
| SPL - DLDE | Not submitted | | |

**FOR THE RECORD:**

1. **MODEL LABELING** – Nexium® delayed-release capsules (NDA 021153/S-046), approved March 27, 2014. This supplement was approved for revisions to the labeling regarding chromgranin A, hypokalaemia in connection with hypomagnesaemia, hypocalcaemia in connection with hypomagnesaemia, and ECL cell hyperplasia.

NDC 0186-5042-28

**Nexium®** **40 mg***
(esomeprazole magnesium)

**100 Delayed-Release Capsules**

**Rx only**

*Each delayed-release capsule contains
40 mg esomeprazole

USUAL ADULT DOSAGE: See package insert.

Keep container tightly closed.

Store at 25°C (77°F); excursions permitted to
15–30°C (59–86°F). [See USP Controlled Room
Temperature].

This unit-dose package is not child resistant.

NEXIUM and the color purple as applied to the capsule
are registered trademarks of the AstraZeneca group.
© AstraZeneca 2011

Manufactured for:
AstraZeneca LP, Wilmington, DE 19850
By: Merck Sharp & Dohme Corp.,
a subsidiary of Merck & Co., Inc.
Whitehouse Station, NJ 08889, USA

Product of France

7001207900
100 | No. 5042

AstraZeneca

MedWatch – No new information (4/4/2014)

2. This drug product is the subject of a USP monograph as of the 4/4/2014.
   Esomeprazole Magnesium Delayed-release Capsules
   Packaging and Storage: Preserve in tight containers. Store at room temperature.

3. The following is from the cover letter of the 9/22/2009 submission.

In response to the Agency's question regarding why IVAX **revised the description of its drug product from pellets to granules**. The November 23, 2005 original submission referenced innovator labeling approved June 6, 2005. In this labeling the innovator referred to their drug product as an enteric-coated pellet formulation. The innovator revised their labeling on April 27, 2007 to include an additional dosage form, i.e., delayed-release oral suspension. In this labeling the description of their product changed to enteric- coated granules which are common for

capsules and for suspensions. We believe the innovator used the terminology enteric-coated granules because the terms enteric-coated granules and enteric-coated pellets are interchangeable. We amended our labeling from pellets to granules to match the innovator's product and because the pellets are in the form of small granules.

4. The Nexium® labeling is combined for the capsules and oral-suspension.

5. INACTIVE INGREDIENTS: (Volume 1.1; page 25 and 548)
   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.

(b) (4)

| Ingredient | 20 mg (mg/Cap) | 40 mg (mg/Cap) | Wt/Wt (%) |
|---|---|---|---|

(b) (4)

(b) (4)

[redacted]

6. PATENTS/EXCLUSIVITIES (4/4/2014)

Patent Data

| Appl No | Prod No | Patent No | Patent Expiration | Patent Use Code | Patent Certification | Labeling Impact |
|---|---|---|---|---|---|---|
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 373 | PIV | None |
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 729 | | |
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 770 | | |
| N021153 | 001 | 5690960*PED | May 25, 2015 | U - 373 | | |
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| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 729 | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 770 | | |
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| N021153 | 001 | 5877192 | May 27, 2014 | U - 373 | PIV | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 729 | | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 770 | | |
| N021153 | 001 | 5877192*PED | Nov 27, 2014 | U - 373 | | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 373 | PIV | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 729 | | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 770 | | |
| N021153 | 001 | 5900424*PED | Nov 4, 2016 | U - 373 | | |
| N021153 | 001 | 6147103 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6147103*PED | Apr 9, 2019 | | | |
| N021153 | 001 | 6166213 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6166213*PED | Apr 9, 2019 | | | |
| N021153 | 001 | 6191148 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6191148*PED | Apr 9, 2019 | | | |

| | | | | | |
|---|---|---|---|---|---|
| N021153 | 001 | 6369085 | May 25, 2018 | U - 729 | PIV |
| N021153 | 001 | 6369085 | May 25, 2018 | U - 770 | |
| N021153 | 001 | 6369085*PED | Nov 25, 2018 | | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 469 | PIV |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 729 | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 770 | |
| N021153 | 001 | 6428810*PED | May 3, 2020 | U - 469 | |
| N021153 | 001 | 6875872 | May 27, 2014 | | PIV |
| N021153 | 001 | 6875872*PED | Nov 27, 2014 | | |
| N021153 | 001 | 7411070 | May 25, 2018 | | PIV |
| N021153 | 001 | 7411070*PED | Nov 25, 2018 | | |
| N021153 | 001 | 8466175 | May 25, 2018 | U- 1417 | PIV* |
| N021153 | 001 | 8466175*PED | Nov 25, 2018 | | |

**Exclusivities:**
There is no unexpired exclusivity for this product.

| Code | Definition |
|---|---|
| U - 373 | GENERAL USE CLAIM SUBMITTED FOR 12 NEXIUM PATIENTS STATING "PERTINENT TO THE CAPSULE FORMULATION FOR NEXIUM AND ITS INDICATIONS FOR THE TREATMENT OF GERD AND ERADICATION OF H.PYLORI TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U - 729 | TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD), RISK-REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER, H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U - 770 | LONG-TERM TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS |
| U - 469 | TREATMENT OF GASTROESOPHAGEAL REFLEX DISEASE (GERD) AND ERADICATION OF H.PYLORI TO REDUCE RISK OF DUODENAL ULCER RECURRENCE |

U – 1417 USE FOR TREATMENT OF HELICOBACTER INFECTIONS
***The sponsor certified to PATENT "8,466,175" on 8/16/2013.**

7. STORAGE AND DISPENSING STATEMENT:

- RLD: Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep NEXIUM Delayed-Release Capsules container tightly closed. Dispense in a tight container if the NEXIUM Delayed-Release Capsules product package is subdivided. Dispense in a tight container if the product package is subdivided.
- ANDA:

Insert and Bottles: Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Keep container tightly closed. Pharmacist: Dispense in a tight container as defined in the

USP, with a child-resistant closure (as required).

(b) (4)

8. PACKAGING CONFIGURATIONS ( 20 mg and 40 mg)

RLD – 30s, 90s, 1000s and unit dose packaging of 100

ANDA – Bottles of 30s, 90s and 1000s

NOTE: (b) (4) (b) (4) as indicated in the amendment dated 3/31/2014.

9. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.

FINISHED DOSAGE FORM: (Volume 1.5; pages 341 and 343)

- RLD:

20 mg: opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and NEXIUM 20 mg in yellow on the body

40 mg: opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and NEXIUM 40 mg in yellow on the body.

- ANDA:

20 mg: Hard gelatin size '4' capsules having light turquoise blue opaque cap and light turquoise blue opaque body with Ivax hour glass logo "⧗" and "6450" spin printed on cap in gold ink and "20 mg" spin printed in gold ink on the body containing off white to pale yellow coloured pellets.

40 mg: Hard gelatin size '3' capsules having light turquoise blue opaque cap and light turquoise blue opaque body with Ivax hour glass logo "⧗" and "6451" spin printed on cap in gold ink and "40 mg" spin printed in gold ink on the body containing off white to pale yellow coloured pellets.

10. CONTAINER/CLOSURE

CONTAINER/CLOSURE: (Volume 1.5; pages 3, 4, and 13) Container for 20 mg and 40 mg:

| Unit | Container | Closure |
|---|---|---|
| 30s | HDPE bottles | 33 mm CRC caps |
| 90s | HDPE bottles | 33 mm CRC caps |
| 1000s | HDPE bottles | 53 mm non-CRC caps |

11. MANUFACTURER: (Volume 1.2, page 253)
Cipla Ltd.
Kurkumbh, India

Manufactured for TEVA Pharmaceuticals USA (Previously IVAX Pharmaceuticals, Inc.)

12. BIOAVAILABILITY/BIOEQUIVALENCE:
Firm submitted fasting and fed bio studies for the 40 mg strength. In addition, the sponsor submitted studies on sprinkle of the content of the capsule on applesauce for the Agency's review.

13. Regarding the amount of active ingredients, refer to the question/response to/from the applicant.

**(Q)** DESCRIPTIONS
We note that you revised the text "... either 20 mg or 40 mg of esomeprazole (present as (b) (4) (b) (4) mg esomeprazole magnesium dehydrate" to read "... either 20 mg or 40 mg of esomeprazole (present as 21.69 mg or 43.38 mg esomeprazole magnesium dehydrate)". Please justify this revision and/or comment.

**Response:**
The Agency's March 8, 2012 Quality Deficiency - Minor requested a correction to our calculation of the molecular weight of esomeprazole. The correction to this calculation affected the listed amount of esomeprazole magnesium dihydrate per tablet. The corrected calculation and revised supporting documents were submitted in our September 20, 2013 Quality Minor Amendment/Response to Information Request.

14. MEDICATION GUIDE
Medication guides will be provided with each bottle at the rate of 1 per bottle of 30, 3 per bottle of 90, and 34 per bottle of 1000.

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Date of Review: April 4, 2014
Primary Reviewer: Chan Park
Acting Team Leader: Jeanne Skanchy

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Reference ID: 3497666

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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.**

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/s/

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CHAN H PARK
04/29/2014

JEANNE SKANCHY
04/29/2014

**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

---

ANDA Number: 078003

Date of Submission: August 8, 2012

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Esomeprazole Magnesium Delayed-Release Capsules USP, 20 mg and 40 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. It appears that you submitted all labeling pieces in draft. You are required to submit the labeling in final printed format for full approval.

   b. Please be advised that your drug product is now the subject of a USP monograph. We recommend that you include the designation “USP” in association with the drug product name on all labeling pieces. However, we encourage the inclusion of "USP" in association with your drug product name in the following sections only in the insert labeling: the TITLE, INDICATIONS AND USAGE, DESCRIPTION and HOW SUPPLIED/STORAGE AND HANDLING.

2. CONTAINER – 30s, 90s, and 1000s

   a. See GENRAL COMMENTS above.

   b. Although it is not required to include the bar code on the container label for the drug product which is directly dispensed to the patients, we encourage the inclusion of the bar code or/and comment.

   c. Please note that the patient information leaflet for the Nexium® Delayed-Release Capsules was replaced with medication guide on September 28, 2012. Please revise the pharmacist directive accordingly.

   d. 1000s

      We recommend that you include the statement “This package is not intended for household use.”

3. (b) (4)

4.

5. INSERT

a. GENRAL

i. See GENERAL COMMENTS above.

ii. Please note that updated Nexium® labeling was approved on October 9, 2012. Please revise your labeling accordingly. Please ensure that the highlight sections and the entire insert of the final printed labeling can easily be read and that the type size not be smaller than 6 points. We refer you to 21 CFR 201.56(d) regarding PLR format for further guidance.

b. DESCRIPTIONS

We note that you revised the text "…either 20 mg or 40 mg of esomeprazole (present as (b) (4) mg esomeprazole magnesium dehydrate" to read "…either 20 mg or 40 mg of esomeprazole (present as 21.69 mg or 43.38 mg esomeprazole magnesium dehydrate)". Please justify this revision and/or comment.

6. MEDICATION GUIDE

a. See GENRAL COMMENTS above.

Please note that the patient information leaflet for the Nexium® Capsules was replaced with medication guide September 28, 2012. Please submit your proposal for the medication guide.

b. Please describe your plan for supplying the medication guide with your product. (e.g., how many medication guides will you supply for each container size and how will these medication guides be supplied.)

c. Please be advised that the final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 points.

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you

subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

**NOTE TO CHEMIST:**

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**From:** Park, Chan H
**Sent:** Friday, March 30, 2012 1:35 PM
**To:** Pan, Yanping
**Cc:** Park, Chan H
**Subject:** ANDA 78003 (Esomeprazole Magnesium D-R Capsules)

Hi Yanping,

The RLD Nexium D-R Capsules contain API Esomeprazole Magnesium **trihydrate** 22.3 mg and 44.5 mg for 20 mg and 40 mg capsules, respectively while the generic contains (b) (4) (b) (4) mg of Esomeprazole Magnesium **dihydrate**, respectively. Would it be an issue? Thanks,

Chan

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**From:** Pan, Yanping
**Sent:** Wednesday, April 04, 2012 9:16 AM
**To:** Park, Chan H
**Cc:** Rajagopalan, Radhika
**Subject:** RE: ANDA 78003 (Esomeprazole Magnesium D-R Capsules)

Dear Chan,

I asked the firm same question. They explained that (b) (4) (b) (4)
That means Dihydrate form is in their Drug product.

As long as they demonstrate their DP is bioequivalent to RLD. The different polymorphic form in DP is acceptable.

Radhika, am I right?

Yanping

**From:** Rajagopalan, Radhika
**Sent:** Wednesday, April 04, 2012 1:34 PM
**To:** Pan, Yanping
**Cc:** Park, Chan H
**Subject:** RE: ANDA 78003 (Esomeprazole Magnesium D-R Capsules)

These andas for dihydrate were put on hold for several months per old policy. Now IO has agreed that dihydrates can be reviewed. So we are reviewing. Thanks
Radhika

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**FOR THE RECORD:**

1. MODEL LABELING – Nexium™ Delayed-Release Capsules (NDA 021153/S-042), approved October 9, 2012.

2. This drug product is the subject of a USP monograph as of the 10/16/2012.
   PF – No new information (10/16/2012)

3. The following is from the cover letter of the 9/22/2009 submission.

   In response to the Agency's question regarding **why IVAX revised the description of its drug product from *pellets* to *granules***. Our November 23, 2005 original submission referenced innovator labeling approved June 6, 2005. In this labeling the innovator referred to their drug product as an enteric-coated pellet formulation. The innovator revised their labeling April 27, 2007 to include an additional dosage form, i.e., delayed-release oral suspension. In this labeling the description of their product changed to enteric-coated granules which are common for capsules and for suspensions. We believe the innovator used the terminology enteric-coated granules because the terms enteric-coated granules and enteric-coated pellets are interchangeable. We amended our labeling from pellets to granules to match the innovator's product and because the **pellets are in the form of small granules.**

4. The Nexium® labeling is combined for the capsules and oral-suspension.

5. MedWAtch – Checked 10/16/2012.:

   **Proton Pump Inhibitors Information**

   Proton pump inhibitors (PPIs) are used to treat certain gastrointestinal disorders and work by reducing the amount of acid in the stomach. They are available both as prescription and as over-the-counter (OTC) medications.

   -
   **Current Safety Information**

   - FDA Drug Safety Communication: Clostridum difficile - associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs)[1]
     2/8/2012

   - FDA Drug Safety Podcast for Healthcare Professionals: *Clostridium difficile*-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs)[2]
     2/8/2012

6. INACTIVE INGREDIENTS: (Volume 1.1; page 25 and 548)

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.

(b) (4)

| Ingredient | 20 mg (mg/Cap | 40 mg (mg/Cap | Wt/Wt (%) |
|---|---|---|---|

(b) (4)

(b) (4)

7. PATENTS/EXCLUSIVITIES (10/16/2012)

**Patent Data**

| Appl No | Prod No | Patent No | Patent Expiration | Patent Use Code | Patent Certification | Labeling Impact |
|---|---|---|---|---|---|---|
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 373 | PIV | None |
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 729 | | |
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 770 | | |
| N021153 | 001 | 5690960*PED | May 25, 2015 | U - 373 | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 373 | PIV | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 729 | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 770 | | |
| N021153 | 001 | 5714504*PED | Aug 3, 2015 | U - 373 | | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 373 | PIV | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 729 | | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 770 | | |
| N021153 | 001 | 5877192*PED | Nov 27, 2014 | U - 373 | | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 373 | PIV | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 729 | | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 770 | | |
| N021153 | 001 | 5900424*PED | Nov 4, 2016 | U - 373 | | |
| N021153 | 001 | 6147103 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6147103*PED | Apr 9, 2019 | | | |
| N021153 | 001 | 6166213 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6166213*PED | Apr 9, 2019 | | | |
| N021153 | 001 | 6191148 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6191148*PED | Apr 9, 2019 | | | |
| N021153 | 001 | 6369085 | May 25, 2018 | U - 729 | PIV | |
| N021153 | 001 | 6369085 | May 25, 2018 | U - 770 | | |

| | | | | | |
|---|---|---|---|---|---|
| N021153 | 001 | 6369085*PED | Nov 25, 2018 | | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 469 | PIV |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 729 | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 770 | |
| N021153 | 001 | 6428810*PED | May 3, 2020 | U - 469 | |
| N021153 | 001 | 6875872 | May 27, 2014 | | PIV |
| N021153 | 001 | 6875872*PED | Nov 27, 2014 | | |
| N021153 | 001 | 7411070 | May 25, 2018 | | PIV |
| N021153 | 001 | 7411070*PED | Nov 25, 2018 | | |

**Exclusivity Data**

**There is no unexpired exclusivity for this product.**

| Code | Definition |
|---|---|
| U - 373 | GENERAL USE CLAIM SUBMITTED FOR 12 NEXIUM PATIENTS STATING "PERTINENT TO THE CAPSULE FORMULATION FOR NEXIUM AND ITS INDICATIONS FOR THE TREATMENT OF GERD AND ERADICATION OF H.PYLORI TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U - 729 | TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD), RISK-REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER, H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U - 770 | LONG-TERM TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS |
| U - 469 | TREATMENT OF GASTROESOPHAGEAL REFLEX DISEASE (GERD) AND ERADICATION OF H.PYLORI TO REDUCE RISK OF DUODENAL ULCER RECURRENCE |

8. STORAGE AND DISPENSING STATEMENT:

- RLD: Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep NEXIUM Delayed-Release Capsules container tightly closed. Dispense in a tight container if the NEXIUM Delayed-Release Capsules product package is
subdivided. Dispense in a tight container if the product package is subdivided.
- ANDA:

Insert and Bottles: Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Keep container tightly closed. Pharmacist: Dispense in a tight container as defined in the
USP, with a child-resistant closure (as required).

(b) (4)

- USP - ***Add the following:*** (as of 10/16/2012)

  ■Esomeprazole Magnesium Delayed-Release Capsules

10. PACKAGING CONFIGURATIONS ( 20 mg and 40 mg)

    RLD – 30s, 90s, 1000s and unit dose packaging of 100

    ANDA – Bottles of 30s, 90s and 1000s; (b) (4)

11. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.

FINISHED DOSAGE FORM: (Volume 1.5; pages 341 and 343)

- RLD:

20 mg: opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and NEXIUM 20 mg in yellow on the body

40 mg: opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and NEXIUM 40 mg in yellow on the body.

- ANDA:

20 mg: Hard gelatin size '4' capsules having light turquoise blue opaque cap and light turquoise blue opaque body with Ivax hour glass logo "⧗" and "6450" spin printed on cap in gold ink and "20 mg" spin printed in gold ink on the body containing off white to pale yellow coloured pellets.

40 mg: Hard gelatin size '3' capsules having light turquoise blue opaque cap and light turquoise blue opaque body with Ivax hour glass logo "⧗" and "6451" spin printed on cap in gold ink and "40 mg" spin printed in gold ink on the body containing off white to pale yellow coloured pellets.

12. CONTAINER/CLOSURE

CONTAINER/CLOSURE: (Volume 1.5; pages 3, 4, and 13)
Container for 20 mg and 40 mg:

| Unit | Container | Closure |
|---|---|---|
| 30s | HDPE bottles | 33 mm CRC caps |
| 90s | HDPE bottles | 33 mm CRC caps |
| 1000s | HDPE bottles | 53 mm non-CRC caps |

(b) (4)

[redacted]

13. MANUFACTURER: (Volume 1.2, page 253)
Cipla Ltd.
Kurkumbh, India

Manufactured for TEVA Pharmaceuticals USA (Previously IVAX Pharmaceuticals, Inc.)

14. BIOAVAILABILITY/BIOEQUIVALENCE:

Firm submitted fasting and fed bio studies for the 40 mg strength. In addition, the sponsor submitted studies on sprinkle of the content of the capsule on applesauce for the Agency's review.

15. REMS – None (10/16/2012)

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**Date of Review: 10/16/2012**

**Primary Reviewer: Chan Park**

**Team Leader: Koung Lee**

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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.**

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/s/

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CHAN H PARK
10/18/2012

KOUNG U LEE
10/18/2012

**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

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ANDA Number: ANDA 078003 Date of Submission: September 22, 2009

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. It appears that a patent "741170" was granted to the reference listed drug, Nexium Delayed-Release Capsules, per the electronic Orange Book. Please submit your patent certification regarding this patent.

   b. We acknowledge that all labeling pieces will be of actual size, color and clarity when final printed labeling is submitted.

   c. We strongly encourage you to include the point-to-point response to the Agency's comments as it would help expedite the review process.

2. CONTAINER – 30s, 90s, and 1000s

   a. Please revise to read as follows and/or comment:

      20 mg – *Each delayed–release capsules contains 20 mg esomeprazole (present as (b) (4) mg of esomeprazole magnesium dihydrate)

      40 mg - *Each delayed –release capsules contains 40 mg esomeprazole (present as (b) (4) mg of esomeprazole magnesium dihydrate)

   b. We recommend that you include a pharmacist directive regarding the patient information leaflet.

3. (b) (4)

4.

5. INSERT

   a. GENERAL

      Please note that updated Nexium® labeling was approved on January 20, 2012. Please revise your labeling accordingly. Please ensure that the highlight sections and the entire insert of the final printed labeling can easily be read and that the point type not be smaller than 6. We refer you to 21 CFR 201.56(d) regarding PLR format for further guidance..

   b. DESCRIPTION

As requested in the last deficiency letter, please list the components of the imprinting (b) (4), the dye(s) at a minimum, if there are any.

c. DOSAGE AND ADMINISTRATION

Please confirm that you submitted study on sprinkle of the content of the capsule on applesauce for the Agency's review.

6. PATIENT INFORMATION LEAFLET

a. See comment 5(a) above.

b. Please describe your plan for supplying the patient information leaflet with your product. (e.g., how many leaflets will you supply for each container size and how will these leaflets be supplied.)

c. We recommend that the font size of the final printed patient information leaflet be 6 pts, at a minimum, for sufficient readability.

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

If you have any questions, please call Chan Park at 240-276-8951 or send e-mail to chan.park@fda.hhs.gov

*{See appended electronic signature page}*

_____

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**NOTE TO CHEMIST:**

| | |
|---|---|
| **From:** | Park, Chan H |
| **Sent:** | Friday, March 30, 2012 1:35 PM |
| **To:** | Pan, Yanping |
| **Cc:** | Park, Chan H |
| **Subject:** | ANDA 78003 (Esomeprazole Magnesium D-R Capsules) |

Hi Yanping,

The RLD Nexium D-R Capsules contain API Esomeprazole Magnesium **trihydrate** 22.3 mg and 44.5 mg for 20 mg and 40 mg capsules, respectively while the generic contains (b) (4) mg of Esomeprazole Magnesium **dihydrate**, respectively. Would it be an issue? Thanks,

Chan

---

**FOR THE RECORD:**

1. MODEL LABELING – Nexium™ Delayed-Release Capsules (NDA 021153/S-040), approved 1/20/2012.

2. This drug product is **not** the subject of a USP monograph as of the 3/30/2012. The API (Esomeprazole Magnesium) is the subject of a USP monograph.

3. PF – Checked on 3/30/2012

   Esomeprazole Magnesium Delayed-Release Capsules. Because there is no existing USP monograph for this dosage form, a new monograph, based on validated methods of analyses, is proposed.

   Comment deadline: July 31, 2011
   Add the following:

   ■Esomeprazole Magnesium Delayed-Release Capsules

4. The following is from the cover letter of the 9/22/2012 submission.

   In response to the Agency's question regarding **why IVAX revised the description of its drug product from *pellets* to *granules***. Our November 23, 2005 original submission referenced innovator labeling approved June 6, 2005. In this labeling the innovator referred to their drug product as an enteric-coated pellet formulation. The innovator revised their labeling April 27, 2007 to include an additional dosage form, i.e., delayed-release oral suspension. In this labeling the description of their product changed to enteric- coated granules which are common for capsules and for suspensions. We believe the innovator used the terminology enteric-coated granules because the terms enteric-coated granules and enteric-coated pellets are interchangeable. We amended our labeling from pellets to granules to match the innovator's product and because the **pellets are in the form of small granules.**

5. The Nexium labeling is combined for the capsules and oral-suspension.

6. MedWAtch – Checked 3/30/2012:

   No information posted

7. INACTIVE INGREDIENTS: (Volume 1.1; page 25 and 548)
The listing of inactive ingredients in the DESCRIPTION section of the package insert is *inconsistent* with the listing of inactive ingredients found in the statement of components and composition. The firm did not include the components of the imprinting ink in the DESCRIPTION section of the insert. **The firm was asked to include the components of the imprinting ink in the DESCRIPTION section of the insert.**

(b) (4)

| Ingredient | 20 mg (mg/Cap) | 40 mg (mg/Cap) | Wt/Wt (%) |
|---|---|---|---|

(b) (4)

(b) (4)

8. PATENTS/EXCLUSIVITIES

**Patent Data**

| Appl No | Prod No | Patent No | Patent Expiration | Patent Use Code | Patent Certification | Labeling Impact |
|---|---|---|---|---|---|---|
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 373 | PIV | None |
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 729 | | |
| N021153 | 001 | 5690960 | Nov 25, 2014 | U - 770 | | |
| N021153 | 001 | 5690960*PED | May 25, 2015 | U - 373 | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 373 | PIV | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 729 | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | U - 770 | | |
| N021153 | 001 | 5714504*PED | Aug 3, 2015 | U - 373 | | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 373 | PIV | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 729 | | |
| N021153 | 001 | 5877192 | May 27, 2014 | U - 770 | | |
| N021153 | 001 | 5877192*PED | Nov 27, 2014 | U - 373 | | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 373 | PIV | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 729 | | |
| N021153 | 001 | 5900424 | May 4, 2016 | U - 770 | | |
| N021153 | 001 | 5900424*PED | Nov 4, 2016 | U - 373 | | |
| N021153 | 001 | 6147103 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6147103*PED | Apr 9, 2019 | | | |
| N021153 | 001 | 6166213 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6166213*PED | Apr 9, 2019 | | | |
| N021153 | 001 | 6191148 | Oct 9, 2018 | | PIV | |
| N021153 | 001 | 6191148*PED | Apr 9, 2019 | | | |
| N021153 | 001 | 6369085 | May 25, 2018 | U - 729 | PIV | |
| N021153 | 001 | 6369085 | May 25, 2018 | U - 770 | | |
| N021153 | 001 | 6369085*PED | Nov 25, 2018 | | | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 469 | PIV | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 729 | | |
| N021153 | 001 | 6428810 | Nov 3, 2019 | U - 770 | | |
| N021153 | 001 | 6428810*PED | May 3, 2020 | U - 469 | | |
| N021153 | 001 | 6875872 | May 27, 2014 | | PIV | |
| N021153 | 001 | 6875872*PED | Nov 27, 2014 | | | |
| N021153 | 001 | 7411070 | May 25, 2018 | | Not Filed | |
| N021153 | 001 | 7411070*PED | Nov 25, 2018 | | | |

**Exclusivity Data**

**There is no unexpired exclusivity for this product.**

| Code | Definition |
|---|---|
| U - 373 | GENERAL USE CLAIM SUBMITTED FOR 12 NEXIUM PATIENTS STATING "PERTINENT TO THE CAPSULE FORMULATION FOR NEXIUM AND ITS INDICATIONS FOR THE TREATMENT OF GERD AND ERADICATION OF H.PYLORI TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U - 729 | TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD), RISK-REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER, H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U - 770 | LONG-TERM TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS |
| U - 469 | TREATMENT OF GASTROESOPHAGEAL REFLEX DISEASE (GERD) AND ERADICATION OF H.PYLORI TO REDUCE RISK OF DUODENAL ULCER RECURRENCE |

**See GENERAL COMMENT regarding patent "070".**

9. STORAGE AND DISPENSING STATEMENT:

- RLD: Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep NEXIUM Delayed-Release Capsules container tightly closed. Dispense in a tight container if the NEXIUM Delayed-Release Capsules product package is subdivided. Dispense in a tight container if the product package is subdivided.
- ANDA:

Insert and Bottles: Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Keep container tightly closed. Pharmacist: Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

(b) (4)

10. PACKAGING CONFIGURATIONS ( 20 mg and 40 mg)

RLD – 30s, 90s, 1000s and unit dose packaging of 100

ANDA – Bottles of 30s, 90s and 1000s (b) (4)

11. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.

FINISHED DOSAGE FORM: (Volume 1.5; pages 341 and 343)

- RLD:

20 mg: opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and NEXIUM 20 mg in yellow on the body

40 mg: opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and NEXIUM 40 mg in yellow on the body.

- ANDA:

20 mg: Hard gelatin size '4' capsules having light turquoise blue opaque cap and light turquoise blue opaque body with Ivax hour glass logo " " and "6450" spin printed on cap in gold ink and "20 mg" spin printed in gold ink on the body containing off white to pale yellow coloured pellets.

40 mg: Hard gelatin size '3' capsules having light turquoise blue opaque cap and light turquoise blue opaque body with Ivax hour glass logo " " and "6451" spin printed on cap in gold ink and "40 mg" spin printed in gold ink on the body containing off white to pale yellow coloured pellets.

12. CONTAINER/CLOSURE

CONTAINER/CLOSURE: (Volume 1.5; pages 3, 4, and 13)
Container for 20 mg and 40 mg:

| Unit | Container | Closure |
|---|---|---|
| 30s | HDPE bottles | 33 mm CRC caps |
| 90s | HDPE bottles | 33 mm CRC caps |
| 1000s | HDPE bottles | 53 mm non-CRC caps |

(b) (4)

[redacted]

13. MANUFACTURER: (Volume 1.2, page 253)
Cipla Ltd.
Kurkumbh, India

Manufactured for TEVA Pharmaceuticals USA (Previously IVAX Pharmaceuticals, Inc.)

14. BIOAVAILABILITY/BIOEQUIVALENCE:
Firm submitted fasting and fed bio studies for the 40 mg strength.

See comment 5(c) above.

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**Date of Review: 4/2/2012** **Date of Submission: 9/22/2009**

**Primary Reviewer: Chan Park** **Date:**

**Team Leader: Koung Lee** **Date:**

C:\Documents and Settings\parkc\My Documents\78003.NA3.L.doc

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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.**

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/s/

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CHAN H PARK
04/02/2012

**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

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| | |
|---|---|
| ANDA Number: | 78-003 |
| Date of Submission: | May 29, 2008 and September 12, 2008 (Amendments) |
| Applicant's Name: | IVAX Pharmaceuticals, Inc.<br>(An indirect, wholly owned subsidiary of TEVA Pharmaceuticals USA) |
| Established Name: | Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg |
| Proprietary Name: | None proposed |

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Labeling Deficiencies:

1. CONTAINER [bottles of 30, 90 and 1000]

   a. Please submit final printed labels that are of actual size, color and clarity.

   b. Please revise the expression of quantity to read XX CAPSULES, rather than TABLETS.

   c. Please delete the pictorial of the capsule.

2. (b) (4)

3.

4. INSERT

   a. GENERAL COMMENTS

      i. Please revise your labeling to include a Patient Package Insert in accordance with the approved labeling for the referenced listed drug, Nexium® Delayed-Release Capsules, NDA 21-153/S-029, approved January 11, 2008 (see attachment).

      ii. Please explain why you have revised the description of the drug product in the insert from “pellets” to “granules”.

   b. DESCRIPTION: Please include the components of the imprinting ink in the list of inactive ingredients.

   c. CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption, first paragraph:

i. Revise the first sentence as follows: “Esomeprazole magnesium delayed-release capsules and Esomeprazole magnesium for delayed-release oral suspension contain a bioequivalent enteric-coated granule formulation of esomeprazole magnesium.”

ii. Add the following as the second sentence: “Bioequivalency is based on a single dose (40 mg) study in 94 healthy male and female volunteers under fasting condition.”

d. DOSAGE AND ADMINISTRATION

i. Replace the first paragraph with the following: “The recommended dosages are outlined in the table below. Esomeprazole delayed-release capsules should be taken at least one hour before meals.

ii. Table – Revise the title as follows: “Recommended Dosage Schedule of Esomeprazole”.

iii. Administration Options, third paragraph, first sentence – “Alternatively, for patients…”

iv. Administration Options, fourth paragraph, first sentence – “…60 mL catheter tipped syringe…”

v. Administration Options, fifth paragraph – Delete the fifth paragraph which states, “The suspension must be used immediately after preparation.”

Please revise your labels and labeling as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by- side comparison of your proposed labeling with your last submission with all differences annotated and explained.

*{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

Enclosure: Patient Package Insert

NOTES AND QUESTIONS TO THE CHEMIST:

None

FOR THE RECORD:
(Part of this review came from Chemistry Review #1 and 2)

1. MODEL LABELING: Nexium® Delayed-Release Capsules by AstraZeneca; NDA 21-153/S-027 approved April 27, 2007 and S-029 (Patient Package Insert) approved January 11, 2008

2. Esomeprazole Delayed-Release Capsule is not the subject of a USP Drug Product Monograph.

3. PATENTS/EXCLUSIVITIES: (Volume 1.1, page 17-19; revised volume 5.1)

**Patent Data**

| Appl No | Prod No | Patent No | Patent Expiration | Certification | Labeling Impact | Patent Use Code |
|---|---|---|---|---|---|---|
| 021153 | 002 | 4738974 | SEP 01,2007 | expired | none | U-635 |
| 021153 | 002 | 4738974 | SEP 01,2007 | expired | none | U-373 |
| 021153 | 002 | 4738974 | SEP 01,2007 | expired | none | U-770 |
| 021153 | 002 | 4738974*PED | MAR 01,2008 | expired | none | U-373 |
| 021153 | 002 | 4786505 | APR 20,2007 | expired | none | U-373 |
| 021153 | 002 | 4786505 | APR 20,2007 | expired | none | U-729 |
| 021153 | 002 | 4786505 | APR 20,2007 | expired | none | U-770 |
| 021153 | 002 | 4786505*PED | OCT 20,2007 | expired | none | U-373 |
| 021153 | 002 | 4853230 | APR 20,2007 | expired | none | U-373 |
| 021153 | 002 | 4853230 | APR 20,2007 | expired | none | U-729 |
| 021153 | 002 | 4853230 | APR 20,2007 | expired | none | U-770 |
| 021153 | 002 | 4853230*PED | OCT 20,2007 | expired | none | U-373 |
| 021153 | 002 | 5690960 | NOV 25,2014 | IV | none | U-729 |
| 021153 | 002 | 5690960 | NOV 25,2014 | IV | none | U-373 |
| 021153 | 002 | 5690960 | NOV 25,2014 | IV | none | U-770 |
| 021153 | 002 | 5690960*PED | MAY 25,2015 | IV | none | U-373 |
| 021153 | 002 | 5714504 | FEB 03,2015 | IV | none | U-373 |
| 021153 | 002 | 5714504 | FEB 03,2015 | IV | none | U-729 |
| 021153 | 002 | 5714504 | FEB 03,2015 | IV | none | U-770 |
| 021153 | 002 | 5714504*PED | AUG 03,2015 | IV | none | U-373 |
| 021153 | 002 | 5877192 | MAY 27,2014 | IV | none | U-373 |
| 021153 | 002 | 5877192 | MAY 27,2014 | IV | none | U-729 |
| 021153 | 002 | 5877192 | MAY 27,2014 | IV | none | U-770 |
| 021153 | 002 | 5877192*PED | NOV 27,2014 | IV | none | U-373 |
| 021153 | 002 | 5900424 | MAY 04,2016 | IV | none | U-373 |
| 021153 | 002 | 5900424 | MAY 04,2016 | IV | none | U-770 |
| 021153 | 002 | 5900424 | MAY 04,2016 | IV | none | U-729 |
| 021153 | 002 | 5900424*PED | NOV 04,2016 | IV | none | U-373 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 021153 | 002 | 6147103 | OCT 09,2018 | IV | none | |
| 021153 | 002 | 6147103*PED | APR 09,2019 | IV | none | |
| 021153 | 002 | 6166213 | OCT 09,2018 | IV | none | |
| 021153 | 002 | 6166213*PED | APR 09,2019 | IV | none | |
| 021153 | 002 | 6191148 | OCT 09,2018 | IV | none | |
| 021153 | 002 | 6191148*PED | APR 09,2019 | IV | none | |
| 021153 | 002 | 6369085 | MAY 25,2018 | IV | none | **U-770** |
| 021153 | 002 | 6369085 | MAY 25,2018 | IV | none | **U-729** |
| 021153 | 002 | 6369085*PED | NOV 25,2018 | IV | none | |
| 021153 | 002 | 6428810 | NOV 03,2019 | IV | none | **U-469** |
| 021153 | 002 | 6428810 | NOV 03,2019 | IV | none | **U-729** |
| 021153 | 002 | 6428810 | NOV 03,2019 | IV | none | **U-770** |
| 021153 | 002 | 6428810*PED | MAY 03,2020 | IV | none | **U-469** |
| 021153 | 002 | 6875872 | MAY 27,2014 | IV | none | |
| 021153 | 002 | 6875872*PED | NOV 27,2014 | IV | none | |

**Exclusivity Data**

| Appl No | Prod No | Exclusivity Code | Exclusivity Expiration | Labeling Impact |
|---|---|---|---|---|
| 021153 | 002 | I-484 | NOV 24,2007 | expired |
| **021153** | **002** | **I-504** | **OCT 11,2009** | **See note below*** |
| **021153** | **002** | **NPP** | **APR 28,2009** | **See note below*** |

| Code | Definition |
|---|---|
| U-635 | TREATMENT OF GERD, MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS AND RISK REDUCTION OF NSAID ASSOCIATED GASTRIC ULCERS |
| U-373 | GENERAL USE CLAIM SUBMITTED FOR 12 NEXIUM PATIENTS STATING "PERTINENT TO THE CAPSULE FORMULATION FOR NEXIUM AND ITS INDICATIONS FOR THE TREATMENT OF GERD AND ERADICATION OF H.PYLORI TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U-770 | LONG-TERM TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS |
| U-729 | TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD), RISK-REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER, H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U-469 | TREATMENT OF GASTROESOPHAGEAL REFLEX DISEASE (GERD) AND ERADICATION OF H.PYLORI TO REDUCE RISK OF DUODENAL ULCER RECURRENCE |
| I-484 | FOR THE RISK REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCERS |
| I-504 | TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS INCLUDING ZOLLINGER-ELLISON SYNDROME |
| NPP | NEW PATIENT POPULATION |

***In the May 29, 2008 Patent Amendment, the firm stated that they will not engage in commercial distribution prior to the expiry of the NPP and I-504 exclusivities.**

4. INACTIVE INGREDIENTS: (Volume 1.1; page 25 and 548)
The listing of inactive ingredients in the DESCRIPTION section of the package insert is *inconsistent* with the listing of inactive ingredients found in the statement of components and composition. The firm did not include the components of the imprinting ink in the DESCRIPTION section of the insert. **The firm is asked to include the components of the imprinting ink in the DESCRIPTION section of the insert.**

(b) (4)

| Ingredient | 20 mg (mg/Cap) | 40 mg (mg/Cap) | Wt/Wt (%) |
|---|---|---|---|

(b) (4)

(b) (4)

5. STORAGE AND DISPENSING STATEMENT:
   - RLD: Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Dispense in a tight container if the product package is subdivided.
   - ANDA:
     Insert and Bottles: Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Keep container tightly closed. Pharmacist: Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

     (b) (4)

6. PACKAGE CONFIGURATION:
   - RLD: Unit of use bottles of 30; Unit dose packages of 100; Bottles of 90 and 1000
   - ANDA: Bottles of 30, 90 and 1000; (b) (4)

7. CONTAINER/CLOSURE: (Volume 1.5; pages 3, 4, and 13)
   Container for 20 mg and 40 mg:

| Unit | Container | Closure |
|---|---|---|
| 30s | HDPE bottles | 33 mm CRC caps |
| 90s | HDPE bottles | 33 mm CRC caps |
| 1000s | HDPE bottles | 53 mm non-CRC caps |

(b) (4)

8. FINISHED DOSAGE FORM: (Volume 1.5; pages 341 and 343)
   - RLD:
     20 mg: opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and NEXIUM 20 mg in yellow on the body
     40 mg: opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and NEXIUM 40 mg in yellow on the body.
   - ANDA:
     20 mg: Hard gelatin size '4' capsules having light turquoise blue opaque cap and light turquoise blue opaque body with Ivax hour glass logo "⧖" and "6450" spin printed on cap in gold ink and "20 mg" spin printed in gold ink on the body containing off white to pale yellow coloured pellets.

     40 mg: Hard gelatin size '3' capsules having light turquoise blue opaque cap and light turquoise blue opaque body with Ivax hour glass logo "⧖" and "6451" spin printed on cap in gold ink and "40 mg" spin printed in gold ink on the body containing off white to pale yellow coloured pellets.

9. MANUFACTURER: (Volume 1.2, page 253)
Cipla Ltd.
Kurkumbh, India

Manufactured for TEVA Pharmaceuticals USA (Previously IVAX Pharmaceuticals, Inc.)

10. BIOAVAILABILITY/BIOEQUIVALENCE:
Firm submitted fasting and fed bio studies for the 40 mg strength.

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Primary Reviewer: Sarah Park Date:

Team Leader: Koung Lee Date:

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Review – NA2

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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.**

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/s/
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Soojung Sarah Park
11/24/2008 06:01:03 PM
LABELING REVIEWER

**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

---

| | |
|---|---|
| ANDA Number: | **78-003** |
| Date of Submission: | **November 23, 2005 (Original)** |
| Applicant's Name: | **IVAX Pharmaceuticals, Inc.** |
| Established Name: | **Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg** |
| Proprietary Name: | **None proposed** |

---

Labeling Deficiencies:

[redacted] (b) (4)

INSERT

GENERAL COMMENTS

a. Due to changes in the insert labeling for the reference listed drug, Nexium® Delayed-Release Capsules, NDA 21-153/S-027, approved April 27, 2007, please revise your labeling to be in accordance with the approved referenced listed drug labeling.

b. You should address all exclusivities and patents listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") and revise your insert labeling accordingly. Specifically, please address the following:

   i. The expiration date for Patent No. 4,738,974*PED has changed from "October 19, 2007" to "March 1, 2008". Please provide a revised patent certification.

   ii. You did not provide an Exclusivity Statement in your original ANDA submission dated November 23, 2005. Exclusivities I-484, I-504 and NPP are now listed in the Electronic Orange Book. Please provide an exclusivity statement.

c. You stated that the [redacted] (b) (4) However, you did not provide a quantitive composition of the gold ink. Please provide a quantitive composition of the gold ink. [redacted] (b) (4)

Please revise your labels and labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA. Please ensure that the electronic documents are printable.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by- side comparison of your proposed labeling with your last submission with all differences annotated and explained.

*{See appended electronic signature page}*

_____

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES AND QUESTIONS TO THE CHEMIST:

None

FOR THE RECORD:

1. MODEL LABELING: Nexium® Delayed-Release Capsules by AstraZeneca; NDA 21-153/S-027; approved April 27, 2007;

2. Esomeprazole is not the subject of a USP 29 Drug Product Monograph.

3. PATENTS/EXCLUSIVITIES: (Volume 1.1, page 17-19)

**Patent Data**

| Appl No | Prod No | Patent No | Patent Expiration | Certification | Labeling Impact | Patent Use Code |
|---|---|---|---|---|---|---|
| 021153 | 002 | 4738974 | SEP 01,2007 | III* | none | U-635 |
| 021153 | 002 | 4738974 | SEP 01,2007 | III* | none | U-373 |
| 021153 | 002 | 4738974 | SEP 01,2007 | III* | none | U-770 |
| 021153 | 002 | 4738974*PED | MAR 01,2008 | III* | none | U-373 |
| 021153 | 002 | 4786505 | APR 20,2007 | III | none | U-373 |
| 021153 | 002 | 4786505 | APR 20,2007 | III | none | U-729 |
| 021153 | 002 | 4786505 | APR 20,2007 | III | none | U-770 |
| 021153 | 002 | 4786505*PED | OCT 20,2007 | III | none | U-373 |
| 021153 | 002 | 4853230 | APR 20,2007 | III | none | U-373 |
| 021153 | 002 | 4853230 | APR 20,2007 | III | none | U-729 |
| 021153 | 002 | 4853230 | APR 20,2007 | III | none | U-770 |
| 021153 | 002 | 4853230*PED | OCT 20,2007 | III | none | U-373 |
| 021153 | 002 | 5690960 | NOV 25,2014 | IV | none | U-729 |
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| 021153 | 002 | 5690960 | NOV 25,2014 | IV | none | U-770 |
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| 021153 | 002 | 5714504 | FEB 03,2015 | IV | none | U-373 |
| 021153 | 002 | 5714504 | FEB 03,2015 | IV | none | U-729 |
| 021153 | 002 | 5714504 | FEB 03,2015 | IV | none | U-770 |
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| 021153 | 002 | 5877192 | MAY 27,2014 | IV | none | U-373 |
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| 021153 | 002 | 5877192 | MAY 27,2014 | IV | none | U-770 |
| 021153 | 002 | 5877192*PED | NOV 27,2014 | IV | none | U-373 |
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| 021153 | 002 | 5900424 | MAY 04,2016 | IV | none | U-770 |
| 021153 | 002 | 5900424 | MAY 04,2016 | IV | none | U-729 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 021153 | 002 | 5900424*PED | NOV 04,2016 | IV | none | U-373 |
| 021153 | 002 | 6147103 | OCT 09,2018 | IV | none | |
| 021153 | 002 | 6147103*PED | APR 09,2019 | IV | none | |
| 021153 | 002 | 6166213 | OCT 09,2018 | IV | none | |
| 021153 | 002 | 6166213*PED | APR 09,2019 | IV | none | |
| 021153 | 002 | 6191148 | OCT 09,2018 | IV | none | |
| 021153 | 002 | 6191148*PED | APR 09,2019 | IV | none | |
| 021153 | 002 | 6369085 | MAY 25,2018 | IV | none | U-770 |
| 021153 | 002 | 6369085 | MAY 25,2018 | IV | none | U-729 |
| 021153 | 002 | 6369085*PED | NOV 25,2018 | IV | none | |
| 021153 | 002 | 6428810 | NOV 03,2019 | IV | none | U-469 |
| 021153 | 002 | 6428810 | NOV 03,2019 | IV | none | U-729 |
| 021153 | 002 | 6428810 | NOV 03,2019 | IV | none | U-770 |
| 021153 | 002 | 6428810*PED | MAY 03,2020 | IV | none | U-469 |
| 021153 | 002 | 6875872 | MAY 27,2014 | IV | none | |
| 021153 | 002 | 6875872*PED | NOV 27,2014 | IV | none | |

**Exclusivity Data**

| Appl No | Prod No | Exclusivity Code | Exclusivity Expiration | Labeling Impact |
|---|---|---|---|---|
| 021153 | 002 | I-484 | NOV 24,2007 | See note below** |
| 021153 | 002 | I-504 | OCT 11,2009 | See note below** |
| 021153 | 002 | NPP | APR 28,2009 | See note below** |

| Code | Definition |
|---|---|
| U-635 | TREATMENT OF GERD, MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS AND RISK REDUCTION OF NSAID ASSOCIATED GASTRIC ULCERS |
| U-373 | GENERAL USE CLAIM SUBMITTED FOR 12 NEXIUM PATIENTS STATING "PERTINENT TO THE CAPSULE FORMULATION FOR NEXIUM AND ITS INDICATIONS FOR THE TREATMENT OF GERD AND ERADICATION OF H.PYLORI TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U-770 | LONG-TERM TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS |
| U-729 | TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD), RISK-REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER, H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE |
| U-469 | TREATMENT OF GASTROESOPHAGEAL REFLEX DISEASE (GERD) AND ERADICATION OF H.PYLORI TO REDUCE RISK OF DUODENAL ULCER RECURRENCE |
| I-484 | FOR THE RISK REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCERS |
| I-504 | TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS INCLUDING ZOLLINGER-ELLISON SYNDROME |
| NPP | NEW PATIENT POPULATION |

***The expiration date for Patent No. 4,738,974*PED has changed from "October 19, 2007" to "March 1, 2008". The firm is asked to provide a revised patent certification.**

****The firm did not provide an Exclusivity Statement. However, exclusivities I-484, I-504 and NPP are now listed in the Electronic Orange Book. The firm is asked to provide an exclusivity statement.**

4. INACTIVE INGREDIENTS: (Volume 1.1; page 25 and 548)
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, except as specified below.

(b) (4) **However, the quantitive composition of the gold ink is not provided. Firm is asked to provide a quantitive composition of the gold ink** (b) (4)

5. STORAGE AND DISPENSING STATEMENT:
   - RLD: Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Dispense in a tight container if the product package is subdivided.
   - ANDA:
     Bottles: Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Keep container tightly closed. Pharmacist: Dispense in a tight container as defined n the USP. Use child-resistant closure (as required).
     (b) (4)

6. PACKAGE CONFIGURATION:
   - RLD: Unit of use bottles of 30; Unit dose packages of 100; Bottles of 90 and 1000
   - ANDA: Bottles of 30, 90 and 1000; (b) (4)

7. CONTAINER/CLOSURE: (Volume 1.5; pages 3, 4, and 13)

| Strength | Unit | Container | Closure |
|---|---|---|---|
| 20 mg | 30s | 60 cc HDPE bottles | 33 mm CRC caps |
| | 90s | 60 cc HDPE bottles | 33 mm CRC caps |
| | 1000s | 750 cc HDPE bottles | 53 mm non-CRC caps |
| 40 mg | 30s | 60 cc HDPE bottles | 33 mm CRC caps |
| | 90s | 60 cc HDPE bottles | 33 mm CRC caps |
| | 1000s | 950 cc HDPE bottles | 53 mm non-CRC caps |

(b) (4)

(b) (4)

8. FINISHED DOSAGE FORM: (Volume 1.5; pages 341 and 343)

- RLD:
  - 20 mg: opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and NEXIUM 20 mg in yellow on the body
  - 40 mg: opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and NEXIUM 40 mg in yellow on the body.
- ANDA:
  - 20 mg: Hard gelatin size ‘4’ capsules having light turquoise blue opaque cap and light turquoise blue opaque body with Ivax hour glass logo “⧖” and “6450” spin printed on cap in gold ink and “20 mg” spin printed in gold ink on the body containing off white to pale yellow coloured pellets.

  - 40 mg: Hard gelatin size ‘3’ capsules having light turquoise blue opaque cap and light turquoise blue opaque body with Ivax hour glass logo “⧖” and “6451” spin printed on cap in gold ink and “40 mg” spin printed in gold ink on the body containing off white to pale yellow coloured pellets.

9. MANUFACTURER: (Volume 1.2, page 253)
Cipla Ltd.
Kurkumbh, India

Manufactured for IVAX Pharmaceuticals, Inc.

10. BIOAVAILABILITY/BIOEQUIVALENCE:
Firm submitted fasting and fed bio studies for the 40 mg strength.

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cc: ANDA: 78-003
DUP/DIVISION FILE

HFD-613/SPark
HFD-613/LGolson

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Review

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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.**

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/s/
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Soojung Sarah Park
5/9/2007 04:24:24 PM
MEDICAL OFFICER

Lillie Golson
5/11/2007 12:25:56 PM
MEDICAL OFFICER

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 78003

# CHEMISTRY REVIEWS

**Approval**

**Review #6a**

# ANDA 78003

## Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

**IVAX Pharmaceuticals, Inc.**
**(An indirect, wholly owned subsidiary of TEVA Pharmaceuticals USA)**

**Yanping Pan**
**Division of Chemistry II**

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**Chemistry Assessment** ..... Error! Bookmark not defined.

# Chemistry Review Data Sheet

1. ANDA 78003

2. REVIEW #6a

3. REVIEW DATE: November 13 , 2014/ December 1, 2014/ January 5, 2015

4. REVIEWER: Yanping Pan

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original | 11/23/05 |
| 1st Minor Amendment | 3/4/08 |
| 2nd Minor Amendment | 8/19/2011 |
| 3rd Minor Amendment (SD 16) | 9/20/2013 |
| 4rd Minor Amendment (SD 17) | 03/31/2014 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| 5rd Minor Amendment (SD 20) | 08/22/2014 |
| Facility withdraw (SD 21) | 11/5/2014 |
| Amendment (SD 23) | 12/12/2014 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Teva Pharmaceuticals |
| Address: | 425 Privet Road<br>Horsham, PA 19044 |
| Representative: | Scott Tomsky |
| Telephone: | 215-591-3142 |
| Fax: | 215-591-8812 |

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Esomeprazole Magnesium Delayed-release Capsules

9. LEGAL BASIS FOR SUBMISSION:
   Reference Listed drug product: Nexium® Capsule, Delayed-release pellets; Oral by Astrazeneca approved as NDA #21153 on Feb 20, 2001.

   Paragraph III certification:
   IVAX certifies that the following patent will expire on the specific date:

   US Patent 4,738,974-Expiry date: April 19, 2006
   Pediatric Exclusivity Date: October 19, 2006
   US Patent 4,786,505-Expiry date: April 20, 2007
   Pediatric Exclusivity Date: October 20, 2007
   US Patent 4,738,974-Expiry date: April 20, 2007
   Pediatric Exclusivity Date: October 20, 2007

   Paragraph IV Certification:
   IVAX certifies that the following patents listed for Nexium® are invalid, unenforceable, or will not be infringed by the manufacture, use or sale of IVAX's Esomeprazole Delayed-release Capsules 20 mg and 40 mg:

| | | |
|---|---|---|
| US. Patent 5,690,960 | Expiry: 11/25/14 | Ped. Expiry: 05/25/15 |
| US. Patent 5,714,504 | Expiry: 02/03/15 | Ped. Expiry: 08/03/15 |
| US. Patent 5,877,192 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |
| US. Patent 5,900,424 | Expiry: 05/04/16 | Ped. Expiry: 11/04/16 |
| US. Patent 6,147,103 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,166,213 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,191,148 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,369,085 | Expiry: 05/25/18 | Ped. Expiry: 11/25/18 |
| US. Patent 6,428,810 | Expiry: 11/03/19 | Ped. Expiry: 05/03/20 |
| US. Patent 6,875,872 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |

   There is no unexpired exclusivity for this product According to Orange Book.

10. PHARMACOL. CATEGORY: Treatment of Gastroesophageal Reflux Disease (GERD)

11. DOSAGE FORM: Delayed- Release Capsules

12. STRENGTH/POTENCY: 20 mg and 40 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:

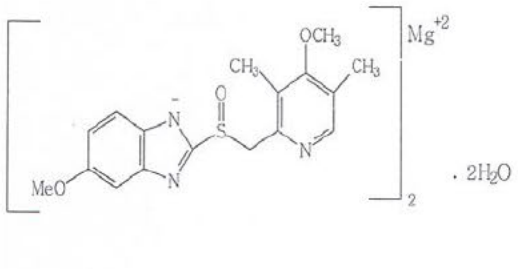
Chemical name: Di-[(s)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulphinyl]benzimidazole]magnesium dehydrate;

Molecular weight: 749.2 (Dihydrate)

Molecular weight: 713.1 (anhydrous)

Chemical Formula: $(C_{17}H_{18}N_3O_3S)_2Mg \cdot 2H_2O$

Chemical structure:



## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| **18821** | **II** | **Cipla** | **Esomeprazole magnesium Dihydrate** | **1** | **Adequate** | **1/5/2015** | **by Y. Pan** |
| (b) (4) | III | (b) (4) | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |

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

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

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| N/A | | |
| | | |

## 18. STATUS:

Chemistry Review Data Sheet

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Pending | 2/6/2014 | |
| Methods Validation | N/A | | |
| Labeling | Deficient | 04/29/2014 | S. Park |
| Bioequivalence | Deficient* | 9/19/2013 | L. Xia |
| EA | Waiver | | |
| Radiopharmaceutical | N/A | | |

* There is internal meeting minutes (pertaining to the in vitro NG tube tests) in DARRTS dated 04/30/2014.

## 19. ORDER OF REVIEW

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 78003

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Approvable (CMC)

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

N/A

## II. Summary of Chemistry Assessments

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

**Drug substance:** : Esomeprazole magnesium **dihydrate** (not compendial):
Please note Esomeprazle magnesium **trihydrate** is compendial.

RLD uses Esomeprazole magnesium trihydrate as API. They also claim that it is Esomeprazole magnesium trihydrate in their drug product according their labeling.

The existence of different drug substance polymorphs may affect bioequivalency of the drug product.

**Drug Product:** Esomeprazole Magnesium Delayed-release Capsules is not compendial.

The formulation for 20 mg and 40 mg are proportional.

Each esomeprazole magnesium delayed-release capsules, for oral administration, contains either 20 mg and 40 mg of esomeprazole in the form of enteric-coated pellets. In addition, each delayed-release capsule contains the following inactive ingredients: FD&C blue#1, gelatin, hypromellose, methacrylic acid copolymer dispersion, polysorbate 80, propylene glycol, sugar spheres, talc, titanium dioxide, triethyl citrate and yellow iron oxide.

Esomeprazole magnesium delayed-release capsules are packed in 30's and 1000's HDPE bottles (b) (4)

The manufacturing process is (b) (4)

Satisfactory 12 weeks accelerated and 24 months room temperature stability data are provided to support proposed 24 months expiration date.

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

MDD 240 mg

**C. Basis for Approvability or Not-Approval Recommendation**

CMC is approvable.

**Review Note:**

This ANDA is approvable per CR#5 on 6/12/2014. However, it was recently found (b) (4) [redacted] in ANDA 78003.

The following was sent to ANDA sponsor:

*DMF 18821 for esomeprazole magnesium is currently inadequate and the DMF holder has been notified. Please consult the DMF holder regarding the drug substance* (b) (4) [redacted]

(b) (4) [redacted]

Following this page, 2 Pages Withheld in Full as (b)(4)

(b) (4)

**-acceptable**

**ENDORSEMENT:**

Reviewer: Y. Pan/13-Nov-2014, 1-Dec-2014, 5-Jan-2015
Team Leader: D. Roselle/14-Nov-2014, 1-Dec-2014, 05-Jan-2015
Deputy Director: B. Wu for Glen Smith/05-Dec-2014; 05-Jan-2015
Project Manager: S. Khanna

**TYPE OF LETTER:** approvable

ECD

Review #5a (Addendum)

# ANDA 78003

## Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

IVAX Pharmaceuticals, Inc.
(An indirect, wholly owned subsidiary of TEVA Pharmaceuticals USA)

Yanping Pan
Division of Chemistry II

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A. Recommendation and Conclusion on Approvability ..... 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable ..... 8

II. Summary of Chemistry Assessments ..... 8

A. Description of the Drug Product(s) and Drug Substance(s) ..... 8

B. Description of How the Drug Product is Intended to be Used ..... 9

C. Basis for Approvability or Not-Approval Recommendation ..... 9

**Chemistry Assessment** ..... Error! Bookmark not defined.

# Chemistry Review Data Sheet

1. ANDA 78003

2. REVIEW #5a

3. REVIEW DATE: July 1, 2014

4. REVIEWER: Yanping Pan

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original | 11/23/05 |
| 1st Minor Amendment | 3/4/08 |
| 2nd Minor Amendment | 8/19/2011 |
| 3rd Minor Amendment (SD 16) | 9/20/2013 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| 4rd Minor Amendment (SD 17) | 03/31/2014 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Teva Pharmaceuticals |
| Address: | 425 Privet Road<br>Horsham, PA 19044 |
| Representative: | Scott Tomsky |
| Telephone: | 215-591-3142 |
| Fax: | 215-591-8812 |

8. DRUG PRODUCT NAME/CODE/TYPE:



Reference ID: 3539043

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Esomeprazole Magnesium Delayed-release Capsules

## 9. LEGAL BASIS FOR SUBMISSION:

Reference Listed drug product: Nexium® Capsule, Delayed-release pellets; Oral by Astrazeneca approved as NDA #21153 on Feb 20, 2001.

Paragraph III certification:
IVAX certifies that the following patent will expire on the specific date:

US Patent 4,738,974-Expiry date: April 19, 2006
Pediatric Exclusivity Date: October 19, 2006
US Patent 4,786,505-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007
US Patent 4,738,974-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007

Paragraph IV Certification:
IVAX certifies that the following patents listed for Nexium® are invalid, unenforceable, or will not be infringed by the manufacture, use or sale of IVAX's Esomeprazole Delayed-release Capsules 20 mg and 40 mg:

| | | |
|---|---|---|
| US. Patent 5,690,960 | Expiry: 11/25/14 | Ped. Expiry: 05/25/15 |
| US. Patent 5,714,504 | Expiry: 02/03/15 | Ped. Expiry: 08/03/15 |
| US. Patent 5,877,192 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |
| US. Patent 5,900,424 | Expiry: 05/04/16 | Ped. Expiry: 11/04/16 |
| US. Patent 6,147,103 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,166,213 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,191,148 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,369,085 | Expiry: 05/25/18 | Ped. Expiry: 11/25/18 |
| US. Patent 6,428,810 | Expiry: 11/03/19 | Ped. Expiry: 05/03/20 |
| US. Patent 6,875,872 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |

There is no unexpired exclusivity for this product According to Orange Book.

## 10. PHARMACOL. CATEGORY: Treatment of Gastroesophageal Reflux Disease (GERD)

## 11. DOSAGE FORM: Delayed- Release Capsules

## 12. STRENGTH/POTENCY: 20 mg and 40 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:

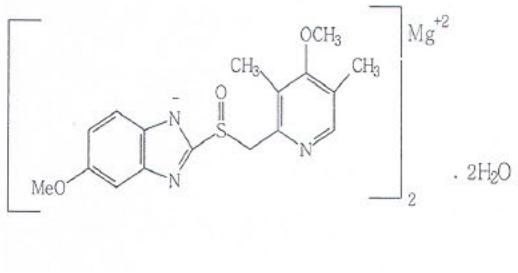
Chemical name: Di-[(s)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulphinyl]benzimidazole]magnesium dehydrate;

Molecular weight: 749.2 (Dihydrate)

Molecular weight: 713.1 (anhydrous)

Chemical Formula: $(C_{17}H_{18}N_3O_3S)_2Mg \cdot 2H_2O$

Chemical structure:






Reference ID: 3539043

## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| **18821** | **II** | **Cipla** | **Esomeprazole magnesium Dihydrate** | **1** | **Inadequate** | **07/01/2014** | **by Y. Pan** |
| (b) (4) | III | | (b) (4) | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |

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

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

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| N/A | | |
| | | |

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Pending | 2/6/2014 | |
| Methods Validation | N/A | | |
| Labeling | Deficient | 04/29/2014 | S. Park |
| Bioequivalence | Deficient* | 9/19/2013 | L. Xia |
| EA | Waiver | | |
| Radiopharmaceutical | N/A | | |

* There is internal meeting minutes (pertaining to the in vitro NG tube tests) in DARRTS dated 04/30/2014.

## 19. ORDER OF REVIEW

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 78003

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Not Approvable (ECD)

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

N/A

## II. Summary of Chemistry Assessments

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

**Drug substance:** : Esomeprazole magnesium **dihydrate** (not compendial):
Please note Esomeprazle magnesium **trihydrate** is compendial.

RLD uses Esomeprazole magnesium trihydrate as API. They also claim that it is Esomeprazole magnesium trihydrate in their drug product according their labeling.

The existence of different drug substance polymorphs may affect bioequivalency of the drug product.

**Drug Product:** Esomeprazole Magnesium Delayed-release Capsules is not compendial.

The formulation for 20 mg and 40 mg are proportional.

Each esomeprazole magnesium delayed-release capsules, for oral administration, contains either 20 mg and 40 mg of esomeprazole in the form of enteric-coated pellets. In addition, each delayed-release capsule contains the following inactive ingredients: FD&C blue#1, gelatin, hypromellose, methacrylic acid copolymer dispersion, polysorbate 80, propylene glycol, sugar spheres, talc, titanium dioxide, triethyl citrate and yellow iron oxide.

Esomeprazole magnesium delayed-release capsules are packed in 30's and 1000's HDPE bottles (b) (4)

The manufacturing process is (b) (4)

Satisfactory 12 weeks accelerated and 24 months room temperature stability data are provided to support proposed 24 months expiration date.

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

Esomeprazole magnesium delayed-release capsules are indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8-week course of esomeprazole may be considered. Maximum daily dose is 40 mg.

**C. Basis for Approvability or Not-Approval Recommendation**

ECD

Chemistry Assessment Section

**Review Note:**

This ANDA is approvable per CR#5 on 6/12/2014. However, it was recently found (b) (4) [redacted] in ANDA 78003.

The following ECD will be sent to ANDA sponsor:

*DMF 18821 for esomeprazole magnesium is currently inadequate and the DMF holder has been notified. Please consult the DMF holder regarding the drug substance* (b) (4) [redacted]



Reference ID: 3539043

**CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 078003

APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg

A. The deficiencies presented below represent minor deficiencies.

DMF 18821 for esomeprazole magnesium is currently inadequate and the DMF holder has been notified. Please consult the DMF holder regarding the drug substance

(b) (4)

Sincerely yours,

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

**ENDORSEMENT:**

Reviewer: Y. Pan/July 1, 2014
Team Leader: P. Simamora for P. Capella/2-JUL-2014
Deputy Director: Bing Wu for S. Rosencrance/3-Jul-2014
Project Manager: F. Nice/7/8/14

**TYPE OF LETTER: CR**



Reference ID: 3539043

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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.**

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/s/

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YANPING PAN
07/08/2014

FRANK J NICE
07/09/2014

PAHALA SIMAMORA` on behalf of PETER CAPELLA
07/09/2014

PETER CAPELLA on behalf of SUSAN M ROSENCRANCE
07/09/2014

**Approvable**

**Review #5**

# ANDA 78003

## Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

**IVAX Pharmaceuticals, Inc.**
**(An indirect, wholly owned subsidiary of TEVA Pharmaceuticals USA)**

**Yanping Pan**
**Division of Chemistry II**

# Table of Contents

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B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable ..... 8

II. Summary of Chemistry Assessments ..... 8

A. Description of the Drug Product(s) and Drug Substance(s) ..... 8

B. Description of How the Drug Product is Intended to be Used ..... 9

C. Basis for Approvability or Not-Approval Recommendation ..... 9

**Chemistry Assessment** ..... **10**

# Chemistry Review Data Sheet

1. ANDA 78003

2. REVIEW #5

3. REVIEW DATE: 05/23/2014

4. REVIEWER: Yanping Pan

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original | 11/23/05 |
| 1st Minor Amendment | 3/4/08 |
| 2nd Minor Amendment | 8/19/2011 |
| 3rd Minor Amendment (SD 16) | 9/20/2013 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| 4rd Minor Amendment (SD 17) | 03/31/2014 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Teva Pharmaceuticals |
| Address: | 425 Privet Road<br>Horsham, PA 19044 |
| Representative: | Scott Tomsky |
| Telephone: | 215-591-3142 |
| Fax: | 215-591-8812 |

8. DRUG PRODUCT NAME/CODE/TYPE:



Reference ID: 3522210

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Esomeprazole Magnesium Delayed-release Capsules

## 9. LEGAL BASIS FOR SUBMISSION:

Reference Listed drug product: Nexium® Capsule, Delayed-release pellets; Oral by Astrazeneca approved as NDA #21153 on Feb 20, 2001.

Paragraph III certification:
IVAX certifies that the following patent will expire on the specific date:

US Patent 4,738,974-Expiry date: April 19, 2006
Pediatric Exclusivity Date: October 19, 2006
US Patent 4,786,505-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007
US Patent 4,738,974-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007

Paragraph IV Certification:
IVAX certifies that the following patents listed for Nexium® are invalid, unenforceable, or will not be infringed by the manufacture, use or sale of IVAX's Esomeprazole Delayed-release Capsules 20 mg and 40 mg:

| | | |
|---|---|---|
| US. Patent 5,690,960 | Expiry: 11/25/14 | Ped. Expiry: 05/25/15 |
| US. Patent 5,714,504 | Expiry: 02/03/15 | Ped. Expiry: 08/03/15 |
| US. Patent 5,877,192 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |
| US. Patent 5,900,424 | Expiry: 05/04/16 | Ped. Expiry: 11/04/16 |
| US. Patent 6,147,103 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,166,213 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,191,148 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,369,085 | Expiry: 05/25/18 | Ped. Expiry: 11/25/18 |
| US. Patent 6,428,810 | Expiry: 11/03/19 | Ped. Expiry: 05/03/20 |
| US. Patent 6,875,872 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |

There is no unexpired exclusivity for this product According to Orange Book.

## 10. PHARMACOL. CATEGORY: Treatment of Gastroesophageal Reflux Disease (GERD)

## 11. DOSAGE FORM: Delayed- Release Capsules

## 12. STRENGTH/POTENCY: 20 mg and 40 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:

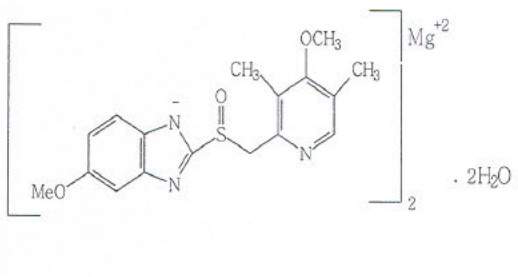
Chemical name: Di-[(s)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulphinyl]benzimidazole]magnesium dehydrate;

Molecular weight: 749.2 (Dihydrate)

Molecular weight: 713.1 (anhydrous)

Chemical Formula: $(C_{17}H_{18}N_3O_3S)_2Mg \cdot 2H_2O$

Chemical structure:



## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| 18821 | II | Cipla | Esomeprazole magnesium Dihydrate | 1 | Adequate | 05/21/2014 | by Y. Pan |
| (b) (4) | III | (b) (4) | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |

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

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

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| N/A | | |
| | | |

## 18. STATUS:

Chemistry Review Data Sheet

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Pending | 2/6/14 | |
| Methods Validation | N/A | | |
| Labeling | Deficient | 04/29/2014 | S. Park |
| Bioequivalence | Deficient* | 9/19/2013 | L. Xia |
| EA | Waiver | | |
| Radiopharmaceutical | N/A | | |

* There is internal meeting minutes (pertaining to the in vitro NG tube tests) in DARRTS dated 04/30/2014.

## 19. ORDER OF REVIEW

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:



Reference ID: 3522210

# The Chemistry Review for ANDA 78003

## *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

N/A

## II. Summary of Chemistry Assessments

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

**Drug substance:** : Esomeprazole magnesium **dihydrate** (not compendial):
Please note Esomeprazle magnesium **trihydrate** is compendial.

RLD uses Esomeprazole magnesium trihydrate as API. They also claim that it is Esomeprazole magnesium trihydrate in their drug product according their labeling.

The existence of different drug substance polymorphs may affect bioequivalency of the drug product.

The drug substance Esomeprazole magnesium (dihydrate) is manufactured by Cipla (DMF 18821). The amendments for DMF has been reviewed and found adequate on 5/21/2014 by Y. Pan.

**Drug Product:** Esomeprazole Magnesium Delayed-release Capsules is not compendial.

The formulation for 20 mg and 40 mg are proportional.

Each esomeprazole magnesium delayed-release capsules, for oral administration, contains either 20 mg and 40 mg of esomeprazole in the form of enteric-coated pellets. In addition, each delayed-release capsule contains the following inactive ingredients: FD&C blue#1, gelatin, hypromellose, methacrylic acid copolymer dispersion, polysorbate 80, propylene glycol, sugar spheres, talc, titanium dioxide, triethyl citrate and yellow iron oxide.

Esomeprazole magnesium delayed-release capsules are packed in 30's and 1000's HDPE bottles (b) (4)

The manufacturing process is (b) (4)

Satisfactory 12 weeks accelerated and 24 months room temperature stability data are provided to support proposed 24 months expiration date.

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

Esomeprazole magnesium delayed-release capsules are indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8-week course of esomeprazole may be considered. Maximum daily dose is 40 mg.

**C. Basis for Approvability or Not-Approval Recommendation**

Approvable (all CMC issues are resolved).

Director's Note: Pending Bioequivalence.



Following this page, 80 Pages Withheld in Full as (b)(4)

**ENDORSEMENT:**

Reviewer/Date: Y. Pan/23-May-2014
Team Leader/Date: P. Capella/P. Simamora for P.C./28-May-2014
Deputy Division Director/Date: G. Smith/4-June-2014
Project Manager/Date: FNice/6/10/14

**TYPE OF LETTER:** APPROVABLE

---

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

---

/s/

---

YANPING PAN
06/10/2014

FRANK J NICE
06/11/2014

PAHALA SIMAMORA` on behalf of PETER CAPELLA
06/11/2014

GLEN J SMITH
06/12/2014

**Not-Approvable / Minor**

**Review #4**

# ANDA 78003

## Esomeprazole Magnesium Delayed- release Capsules, 20 mg and 40 mg

**IVAX Pharmaceuticals, Inc.**
**(An indirect, wholly owned subsidiary of TEVA Pharmaceuticals USA)**

**Yanping Pan**
**Division of Chemistry II**

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C. Basis for Approvability or Not-Approval Recommendation ..... 9

**Chemistry Assessment** ..... **10**

# Chemistry Review Data Sheet

1. ANDA 78003

2. REVIEW #4

3. REVIEW DATE: 10/31/2013

4. REVIEWER: Yanping Pan

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original | 11/23/05 |
| 1st Minor Amendment | 3/4/08 |
| 2nd Minor Amendment | 8/19/2011 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| 3rd Minor Amendment (SD 16) | 9/20/2013 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | IVAX Pharmaceuticals, Inc. |
| Address: | 400 Chestnut Ridge Road<br>Woodcliff Lake, NJ 07677 |
| Representative: | Robert S. Vincent |
| Telephone: | 201-930-3610 |
| Fax: | 201-489-1403 |

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A



Reference ID: 3449723

b) Non-Proprietary Name (USAN): Esomeprazole Magnesium Delayed-release Capsules

9. LEGAL BASIS FOR SUBMISSION:
Reference Listed drug product: Nexium® Capsule, Delayed-release pellets; Oral by Astrazeneca approved as NDA #21153 on Feb 20, 2001.

Paragraph III certification:
IVAX certifies that the following patent will expire on the specific date:

US Patent 4,738,974-Expiry date: April 19, 2006
Pediatric Exclusivity Date: October 19, 2006
US Patent 4,786,505-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007
US Patent 4,738,974-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007

Paragraph IV Certification:
IVAX certifies that the following patents listed for Nexium® are invalid, unenforceable, or will not be infringed by the manufacture, use or sale of IVAX's Esomeprazole Delayed-release Capsules 20 mg and 40 mg:

| | | |
|---|---|---|
| US. Patent 5,690,960 | Expiry: 11/25/14 | Ped. Expiry: 05/25/15 |
| US. Patent 5,714,504 | Expiry: 02/03/15 | Ped. Expiry: 08/03/15 |
| US. Patent 5,877,192 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |
| US. Patent 5,900,424 | Expiry: 05/04/16 | Ped. Expiry: 11/04/16 |
| US. Patent 6,147,103 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,166,213 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,191,148 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,369,085 | Expiry: 05/25/18 | Ped. Expiry: 11/25/18 |
| US. Patent 6,428,810 | Expiry: 11/03/19 | Ped. Expiry: 05/03/20 |
| US. Patent 6,875,872 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |

There is no unexpired exclusivity for this product According to Orange Book.

10. PHARMACOL. CATEGORY: Treatment of Gastroesophageal Reflux Disease (GERD)

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 20 mg and 40 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:

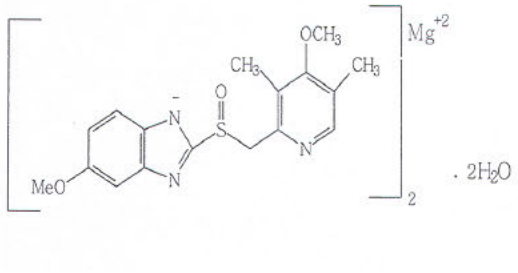
Chemical name: Di-[(s)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulphinyl]benzimidazole]magnesium dehydrate;

Molecular weight: 749.2 (Dihydrate)

Molecular weight: 713.1 (anhydrous)

Chemical Formula: $(C_{17}H_{18}N_3O_3S)_2Mg \cdot 2H_2O$

Chemical structure:






Reference ID: 3449723

## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| 18821 | II | Cipla | Esomeprazole magnesium Dihydrate | 1 | Inadequate | 10/24/2013 | by Y. Pan |
| (b) (4) | III | (b) (4) | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |

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

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

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| N/A | | |
| | | |

## 18. STATUS:



Reference ID: 3449723

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Acceptable | 12/7/2006 | S. Ferguson |
| Methods Validation | N/A | | |
| Labeling | Deficiency | 10/18/2012 | S. Park |
| Bioequivalence | Deficiency | 9/19/2013 | P. Chandaroy |
| EA | Waiver | | |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

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 78003

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Not Approvable (MINOR)

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

N/A

## II. Summary of Chemistry Assessments

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

**Drug substance:** : Esomeprazole magnesium **dihydrate** (not compendial):
Please note Esomeprazle magnesium **trihydrate** is compendial.

RLD uses Esomeprazole magnesium trihydrate as API. They also claim that it is Esomeprazole magnesium trihydrate in their drug product according their labeling.

The existence of different drug substance polymorphs may affect bioequivalency of the drug product.

The drug substance Esomeprazole magnesium (dihydrate) is manufactured by Cipla (DMF 18821). The amendments for DMF has been reviewed and found inadequate on 1/20/2012 by Y. Pan.

**Drug Product:** Esomeprazole Magnesium Delayed-release Capsules is not compendial.

The formulation for 20 mg and 40 mg are proportional.

Each esomeprazole magnesium delayed-release capsules, for oral administration, contains either 20 mg and 40 mg of esomeprazole in the form of enteric-coated pellets. In addition, each delayed-release capsule contains the following inactive ingredients: FD&C blue#1, gelatin, hypromellose, methacrylic acid copolymer dispersion, polysorbate 80, propylene glycol, sugar spheres, talc, titanium dioxide, triethyl citrate and yellow iron oxide.

Esomeprazole magnesium delayed-release capsules are packed in 30's and 1000's HDPE bottles (b) (4)

The manufacturing process is (b) (4)

Satisfactory 12 weeks accelerated and 24 months room temperature stability data are provided to support proposed 24 months expiration date.

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

Esomeprazole magnesium delayed-release capsules are indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8-week course of esomeprazole may be considered. Maximum daily dose is 40 mg.

**C. Basis for Approvability or Not-Approval Recommendation**

See deficiency letter in section 36 of this review



Following this page, 77 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

**30. MICROBIOLOGY**

N/A

**31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS – N/A**

**32. LABELING – Deficiency**

**33. ESTABLISHMENT INSPECTION – Pending**

**34. BIOEQUIVALENCE – Deficiency**

**35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION N/A**

**CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 078003 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg

A. The deficiencies presented below represent MINOR deficiencies.

1. The amendment for the DMF 18821 has been reviewed and found inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has responded to the deficiencies.

2. (b) (4)

3.

4.

5.

6.

Sincerely yours,

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

**ENDORSEMENT:**

Reviewer/Date: Y. Pan/31-Oct-2013
Team Leader/Date: P. Capella/P. Simamora for P.C./30-Jan-2014
Deputy Division Director/Date: S. Rosencrance/Peter Capella for S. Rosencrance/06-Feb-2014
Project Manager/Date: F. Nice/2/6/14

**TYPE OF LETTER:** NOT APPROVABLE - MINOR



Reference ID: 3449723

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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.**

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/s/

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YANPING PAN
02/06/2014

FRANK J NICE
02/07/2014

PAHALA SIMAMORA` on behalf of PETER CAPELLA
02/07/2014

PETER CAPELLA on behalf of SUSAN M ROSENCRANCE
02/07/2014

# ANDA 78-003

## Esomeprazole Magnesium Delayed- release Capsules, 20 mg and 40 mg

**IVAX Pharmaceuticals, Inc.**
**(An indirect, wholly owned subsidiary of TEVA Pharmaceuticals USA)**

**Yanping Pan**
**Division of Chemistry II**

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B. Description of How the Drug Product is Intended to be Used ..... 9

C. Basis for Approvability or Not-Approval Recommendation ..... 9

**Chemistry Assessment** ..... **10**

# Chemistry Review Data Sheet

1. ANDA 78-003

2. REVIEW #3

3. REVIEW DATE: 1/20/2012

4. REVIEWER: Yanping Pan

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original | 11/23/05 |
| 1st Minor Amendment | 3/4/08 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| 2nd Minor Amendment | 8/19/2011 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | IVAX Pharmaceuticals, Inc. |
| Address: | 400 Chestnut Ridge Road<br>Woodcliff Lake, NJ 07677 |
| Representative: | Robert S. Vincent |
| Telephone: | 201-930-3610 |
| Fax: | 201-489-1403 |

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Esomeprazole Magnesium Delayed-release Capsules

9. LEGAL BASIS FOR SUBMISSION:
Reference Listed drug product: Nexium® Capsule, Delayed-release pellets; Oral by Astrazeneca approved as NDA #21153 on Feb 20, 2001.

Paragraph III certification:
IVAX certifies that the following patent will expire on the specific date:

US Patent 4,738,974-Expiry date: April 19, 2006
Pediatric Exclusivity Date: October 19, 2006
US Patent 4,786,505-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007
US Patent 4,738,974-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007

Paragraph IV Certification:
IVAX certifies that the following patents listed for Nexium® are invalid, unenforceable, or will not be infringed by the manufacture, use or sale of IVAX's Esomeprazole Delayed-release Capsules 20 mg and 40 mg:

| | | |
|---|---|---|
| US. Patent 5,690,960 | Expiry: 11/25/14 | Ped. Expiry: 05/25/15 |
| US. Patent 5,714,504 | Expiry: 02/03/15 | Ped. Expiry: 08/03/15 |
| US. Patent 5,877,192 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |
| US. Patent 5,900,424 | Expiry: 05/04/16 | Ped. Expiry: 11/04/16 |
| US. Patent 6,147,103 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,166,213 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,191,148 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,369,085 | Expiry: 05/25/18 | Ped. Expiry: 11/25/18 |
| US. Patent 6,428,810 | Expiry: 11/03/19 | Ped. Expiry: 05/03/20 |
| US. Patent 6,875,872 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |

There is no unexpired exclusivity for this product According to Orange Book.

10. PHARMACOL. CATEGORY: Treatment of Gastroesophageal Reflux Disease (GERD)

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 20 mg and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

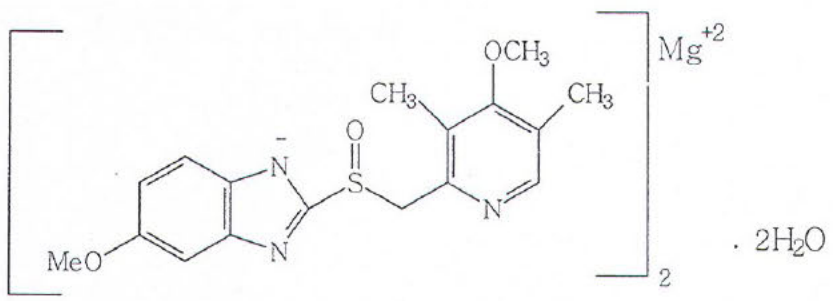
14. Rx/OTC DISPENSED: _x_Rx ___OTC

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: Di-[(s)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulphinyl]benzimidazole]magnesium dehydrate;
Molecular weight: 749.2 (Dihydrate)
Molecular weight: 713.1 (anhydrous)
Chemical Formula: $(C_{17}H_{18}N_3O_3S)_2Mg \cdot 2H_2O$
Chemical structure:






Reference ID: 3098183

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| 18821 | II | Cipla | Esomeprazole magnesium Dihydrate | 1 | **Inadequate** | **1/20/2012 (by Y. Pan)** | |
| (b) (4) | III | (b) (4) | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |

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

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

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| N/A | | |
| | | |

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Acceptable | 12/7/2006 | Fergusons |
| Methods Validation | N/A | | |
| Labeling | Deficiency | 11/24/2011 | S. Park |
| Bioequivalence | Deficiency | 1/10/2007 | P. Chandaroy |
| EA | Waiver | | |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

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 78-003

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Not Approvable (MINOR)

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

N/A

## II. Summary of Chemistry Assessments

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

**Drug substance:** : Esomeprazole magnesium **dihydrate** (not compendial):
Please note Esomeprazle magnesium **trihydrate** is compendial.

RLD uses Esomeprazole magnesium trihydrate as API. They also claim that it is Esomeprazole magnesium trihydrate in their drug product according their labeling.

The existence of different drug substance polymorphs may affect bioequivalency of the drug product.

The drug substance Esomeprazole magnesium (dihydrate) is manufactured by Cipla (DMF 18821). The amendments for DMF has been reviewed and found inadequate on 1/20/2012 by Y. Pan.

**Drug Product:** Esomeprazole Magnesium Delayed-release Capsules is not compendial.

The formulation for 20 mg and 40 mg are proportional.

Each esomeprazole magnesium delayed-release capsules, for oral administration, contains either 20 mg and 40 mg of esomeprazole in the form of enteric-coated pellets. In addition, each delayed-release capsule contains the following inactive ingredients: FD&C blue#1, gelatin, hypromellose, methacrylic acid copolymer dispersion, polysorbate 80, propylene glycol, sugar spheres, talc, titanium dioxide, triethyl citrate and yellow iron oxide.

Esomeprazole magnesium delayed-release capsules are packed in 30's and 1000's HDPE bottles (b) (4)

The manufacturing process is (b) (4)

Satisfactory 12 weeks accelerated and 24 months room temperature stability data are provided to support proposed 24 months expiration date.

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

Esomeprazole magnesium delayed-release capsules are indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8-week course of esomeprazole may be considered. Maximum daily dose is 40 mg.

**C. Basis for Approvability or Not-Approval Recommendation**

See deficiency letter in section 36 this review



Following this page, 42 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

**30. MICROBIOLOGY**

N/A

**31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS – N/A**

**32. LABELING – Deficiency**

**33. ESTABLISHMENT INSPECTION – Pending**

**34. BIOEQUIVALENCE – deficiency**

## 35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION N/A

APPEARS THIS WAY ON ORIGINAL

**CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 078003

APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-release Capsules,
20 mg and 40 mg

A. The deficiencies presented below represent Minor deficiencies.

1. The amendment for the DMF 18821 has been reviewed and found inadequate. The DMF holder has been notified.

(b) (4)

2.

3.

4.

5.

6.

7.

8.

(b) (4)

9.

10.

11.

12.

13.

Sincerely yours,

{See appended electronic signature}

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



Reference ID: 3098183

cc: ANDA 78-003
ANDA DUP
DIV FILE
Field Copy

Endorsements

HFD-645/YPan/1/20/2012;3/1/2012

HFD-645/RRajagopalan/2/28/2012; 3/6/2012

HFD-617/FNice/3/7/12

F/T by

**TYPE OF LETTER:** NOT APPROVABLE - MINOR



Reference ID: 3098183

---

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

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/s/

---

YANPING PAN
03/07/2012

FRANK J NICE
03/07/2012

RADHIKA RAJAGOPALAN
03/07/2012

# ANDA 78-003

## Esomeprazole Magnesium Delayed- release Capsules, 20 mg and 40 mg

**IVAX Pharmaceuticals, Inc.**
**(An indirect, wholly owned subsidiary of TEVA Pharmaceuticals USA)**

**Yanping Pan**
**Division of Chemistry II**

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C. Basis for Approvability or Not-Approval Recommendation ..... 9

**Chemistry Assessment** ..... 10

# Chemistry Review Data Sheet

1. ANDA 78-003

2. REVIEW #2

3. REVIEW DATE: 7/2/08

4. REVIEWER: Yanping Pan

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original | 11/23/05 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| 1st Minor Amendment | 3/4/08 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | IVAX Pharmaceuticals, Inc. |
| Address: | Two University Plaza, suite 220<br>Hackensack, NJ -7601 |
| Representative: | Patricia Jaworski, Director, Regulatory Affairs |
| Telephone: | 215-293-6150 |
| Fax: | 201-489-1403 |

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Esomeprazole Magnesium Delayed-release Capsules

9. LEGAL BASIS FOR SUBMISSION:
Reference Listed drug product: Nexium® Capsule, Delayed-release pellets; Oral by Astrazeneca approved as NDA #21153 on Feb 20, 2001.

Paragraph III certification:
IVAX certifies that the following patent will expire on the specific date:

US Patent 4,738,974-Expiry date: April 19, 2006
Pediatric Exclusivity Date: October 19, 2006
US Patent 4,786,505-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007
US Patent 4,738,974-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007

Paragraph IV Certification:
IVAX certifies that the following patents listed for Nexium® are invalid, unenforceable, or will not be infringed by the manufacture, use or sale of IVAX's Esomeprazole Delayed-release Capsules 20 mg and 40 mg:

| | | |
|---|---|---|
| US. Patent 5,690,960 | Expiry: 11/25/14 | Ped. Expiry: 05/25/15 |
| US. Patent 5,714,504 | Expiry: 02/03/15 | Ped. Expiry: 08/03/15 |
| US. Patent 5,877,192 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |
| US. Patent 5,900,424 | Expiry: 05/04/16 | Ped. Expiry: 11/04/16 |
| US. Patent 6,147,103 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,166,213 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,191,148 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,369,085 | Expiry: 05/25/18 | Ped. Expiry: 11/25/18 |
| US. Patent 6,428,810 | Expiry: 11/03/19 | Ped. Expiry: 05/03/20 |
| US. Patent 6,875,872 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |

There is no unexpired exclusivity for this product According to Orange Book.

10. PHARMACOL. CATEGORY: Treatment of Gastroesophageal Reflux Disease (GERD)

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 20 mg and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

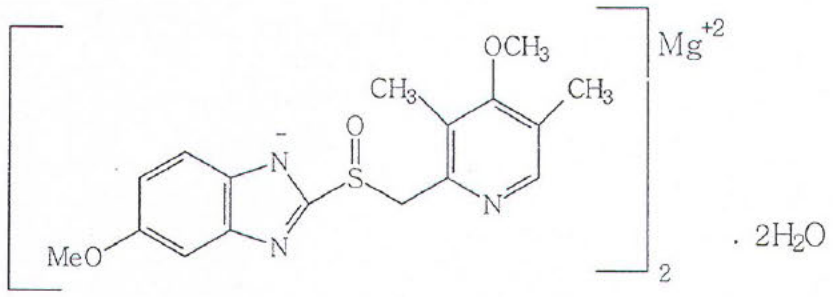
14. Rx/OTC DISPENSED: _x_Rx ___OTC

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: Di-[(s)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulphinyl]benzimidazole]magnesium dehydrate;
Molecular weight: 749.2 (Dihydrate)
Molecular weight: 713.1 (anhydrous)
Chemical Formula: $(C_{17}H_{18}N_3O_3S)_2Mg \cdot 2H_2O$
Chemical structure:



## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| 18821 | II | Cipla | Esomeprazole magnesium Dihydrate | 1 | **Inadequate** | **6/27/08 (by Y. Pan)** | |
| (b) (4) | III | (b) (4) | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |

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

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

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| N/A | | |
| | | |

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Acceptable | 12/7/06 | |
| Methods Validation | N/A | | |
| Labeling | Pending | | |
| Bioequivalence | Pending | | |
| EA | Waiver | | |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

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 78-003

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Not Approvable (MINOR)

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

N/A

## II. Summary of Chemistry Assessments

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

**Drug substance:** : Esomeprazle magnesium dihydrate (not compendial):
According to raw material and components and composition statement sections in this application, the following statement is provided:

The active ingredient in Esomeprazole magnesium delayed-release capsules is bis (5-methoxy-2-[(s)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl-1H-benzimidazole-1-yl] magnesium dihydrate. Esomeprazole is the S-isomer of omeprazole, which is a mixture of S- and R- isomers. Its empirical formula is $(C_{17}H_{18}N_3O_3S)_2$. Mg x 2 $H_2O$ with molecular weight of 749.1 as dihydrate and 713.1 on an anhydrous basis.

However, according to proposed labeling on page 107, vol, 1, the API is esomeprazole magnesium [redacted] (b) (4) during the manufacturing process. The firm will be asked to clarify.

RLD uses Esomeprazole magnesium trihydrate as API. They also claim that it is Esomeprazole magnesium trihydrate in their drug product according their labeling.

The existence of different drug substance polymorphs may affect bioequivalency of the drug product. The firm did not address this issue.

The drug substance Esomeprazole magnesium is manufactured by Cipla (DMF 18821). The DMF has been reviewed and found inadequate on 6/27/08 by Y. Pan.

**Drug Product:** Esomeprazole Magnesium Delayed-release Capsules is not compendial.

The formulation for 20 mg and 40 mg are proportional.

Each esomeprazole magnesium delayed-release capsules, for oral administration, contains either 20 mg and 40 mg of esomeprazole in the form of enteric-coated pellets. In addition, each delayed-release capsule contains the following inactive ingredients: FD&C blue#1, gelatin, hypromellose, methacrylic acid copolymer dispersion, polysorbate 80, propylene glycol, sugar spheres, talc, titanium dioxide, triethyl citrate and yellow iron oxide.

Esomeprazole magnesium delayed-release capsules are packed in 30's and 1000's HDPE bottles (b) (4)

The manufacturing process is (b) (4)

Satisfactory 12 weeks accelerated and room temperature stability data are provided to support proposed 24 months expiration date.

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

Esomeprazole magnesium delayed-release capsules are indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8-week course of esomeprazole may be considered. Maximum daily dose is 40 mg.

**C. Basis for Approvability or Not-Approval Recommendation**

See deficiency letter in section 36 this review



Following this page, 32 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

**30. MICROBIOLOGY**

N/A

**31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS – N/A**

Methods validation will not be requested based on the new Office Policy.

**32. LABELING – pending**

**33. ESTABLISHMENT INSPECTION – Acceptable 12/7/06**

**34. BIOEQUIVALENCE – pending**

**35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION N/A**

**CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 78-003 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg

A. The deficiencies presented below represent Minor deficiencies.

(b) (4)

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5.

6.

(b) (4)

7.

8

9.

Sincerely yours,

***{electronic signature on file}***

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

cc: ANDA 78-003
ANDA DUP
DIV FILE
Field Copy

Endorsements

HFD-645/YPan/6/30/08

HFD-645/DMaldonado/ 7/29/08.

HFD-617/TLiu/7/30/08

F/T by

**TYPE OF LETTER:** NOT APPROVABLE - MINOR

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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.**

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/s/
---
Shanaz Read
8/4/2008 03:21:52 PM
CHEMIST
Entered for Y Pan

Theresa Liu
8/5/2008 09:50:20 AM
CSO

Damaris Maldonado
8/5/2008 12:08:48 PM
CHEMIST

# ANDA 78-003

## Esomeprazole Magnesium Delayed- release Capsules, 20 mg and 40 mg

## IVAX Pharmaceuticals, Inc.

**Yanping Pan**
**Division of Chemistry II**

# Table of Contents

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# Chemistry Review Data Sheet

1. ANDA 78-003

2. REVIEW #1

3. REVIEW DATE: 3/24/06

4. REVIEWER: Yanping Pan

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| N/A | |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 11/23/05 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | IVAX Pharmaceuticals, Inc. |
| Address: | 125 Wells Avenue<br>Congers, NY 10920 |
| Representative: | Patricia Jaworski, Director, Regulatory Affairs |
| Telephone: | 845-267-2444 (Ext. 201 or 200) |
| Fax: | 845-268-0117 |

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Esomeprazole Magnesium Delayed-release Capsules

9. LEGAL BASIS FOR SUBMISSION:
Reference Listed drug product: Nexium® Capsule, Delayed-release pellets; Oral by Astrazeneca approved as NDA #21153 on Feb 20, 2001.

Paragraph III certification:
IVAX certifies that the following patent will expire on the specific date:

US Patent 4,738,974-Expiry date: April 19, 2006
Pediatric Exclusivity Date: October 19, 2006
US Patent 4,786,505-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007
US Patent 4,738,974-Expiry date: April 20, 2007
Pediatric Exclusivity Date: October 20, 2007

Paragraph IV Certification:
IVAX certifies that the following patents listed for Nexium® are invalid, unenforceable, or will not be infringed by the manufacture, use or sale of IVAX's Esomeprazole Delayed-release Capsules 20 mg and 40 mg:

| | | |
|---|---|---|
| US. Patent 5,690,960 | Expiry: 11/25/14 | Ped. Expiry: 05/25/15 |
| US. Patent 5,714,504 | Expiry: 02/03/15 | Ped. Expiry: 08/03/15 |
| US. Patent 5,877,192 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |
| US. Patent 5,900,424 | Expiry: 05/04/16 | Ped. Expiry: 11/04/16 |
| US. Patent 6,147,103 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,166,213 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,191,148 | Expiry: 10/09/18 | Ped. Expiry: 04/09/19 |
| US. Patent 6,369,085 | Expiry: 05/25/18 | Ped. Expiry: 11/25/18 |
| US. Patent 6,428,810 | Expiry: 11/03/19 | Ped. Expiry: 05/03/20 |
| US. Patent 6,875,872 | Expiry: 05/27/14 | Ped. Expiry: 11/27/14 |

There is no unexpired exclusivity for this product According to Orange Book.

10. PHARMACOL. CATEGORY: Treatment of Gastroesophageal Reflux Disease (GERD)

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 20 mg and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

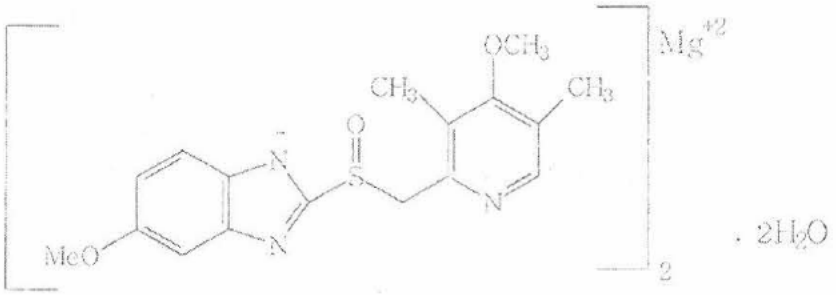
14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

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: Di-[(s)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulphinyl]benzimidazole]magnesium dehydrate;
Molecular weight: 749.2 (Dihydrate)
Molecular weight: 713.1 (anhydrous)
Chemical Formula: $(C_{17}H_{18}N_3O_3S)_2Mg \cdot 2H_2O$
Chemical structure:



## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE [1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| 18821 | II | Cipla | Esomeprazole magnesium Dihydrate | 1 | Inadequate | 3/14/06 (by Y. Pan) | |
| (b) (4) | III | (b) (4) | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | | | | |

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

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

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| N/A | | |
| | | |

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Pending | | |
| Methods Validation | N/A | | |
| Labeling | Pending | | |
| Bioequivalence | Pending | | |
| EA | Waiver | | |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

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 78-003

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Not Approvable (MINOR)

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

N/A

## II. Summary of Chemistry Assessments

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

**Drug substance:** : Esomeprazle magnesium dihydrate (not compendial):
According to raw material and components and composition statement sections in this application, the following statement is provided:

The active ingredient in Esomeprazole magnesium delayed-release capsules is bis (5-methoxy-2-[(s)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl-1H-benzimidazole-1-yl] magnesium dihydrate. Esomeprazole is the S-isomer of omeprazole, which is a mixture of S- and R- isomers. Its empirical formula is $(C_{17}H_{18}N_3O_3S)_2$. Mg x 2 $H_2O$ with molecular weight of 749.1 as dihydrate and 713.1 on an anhydrous basis.

However, according to proposed labeling on page 107, vol, 1, the API is esomeprazole magnesium [redacted] (b) (4) during the manufacturing process. The firm will be asked to clarify.

RLD uses Esomeprazole magnesium trihydrate as API. They also claim that it is Esomeprazole magnesium trihydrate in their drug product according their labeling.

The existence of different drug substance polymorphs may affect bioequivalency of the drug product. The firm did not address this issue.

The drug substance Esomeprazole magnesium is manufactured by Cipla (DMF 18821). The DMF has been reviewed and found inadequate on 3/14/06 by Y. Pan.

**Drug Product:** Esomeprazole Magnesium Delayed-release Capsules is not compendial.

The formulation for 20 mg and 40 mg are proportional.

Each esomeprazole magnesium delayed-release capsules, for oral administration, contains either 20 mg and 40 mg of esomeprazole in the form of enteric-coated pellets. In addition, each delayed-release capsule contains the following inactive ingredients: FD&C blue#1, gelatin, hypromellose, methacrylic acid copolymer dispersion, polysorbate 80, propylene glycol, sugar spheres, talc, titanium dioxide, triethyl citrate and yellow iron oxide.

Esomeprazole magnesium delayed-release capsules are packed in 30's and 1000's HDPE bottles (b) (4)

The manufacturing process is (b) (4)

Satisfactory 12 weeks accelerated and room temperature stability data are provided to support proposed 24 months expiration date.

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

Esomeprazole magnesium delayed-release capsules are indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8-week course of esomeprazole may be considered. Maximum daily dose is 40 mg.

**C. Basis for Approvability or Not-Approval Recommendation**

Not Approvable (Minor) due to following section minor deficiencies: Components and composition, raw materials controls, container/closure, manufacturing process, container/closure, finished product and stability.



Following this page, 24 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

**30. MICROBIOLOGY**

N/A

**31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS – N/A**

Methods validation will not be requested based on the new Office Policy.

**32. LABELING – pending**

**33. ESTABLISHMENT INSPECTION - pending**

**34. BIOEQUIVALENCE – pending**

**35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION N/A**

## CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-003 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg

A. The deficiencies presented below represent Minor deficiencies.

(b) (4)

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7. It is noted that the analytical method and methods validation data for the drug substance provided in this ANDA application is the same as that provided in DMF 18821. We have

provided our concerns in DMF 18821 regarding the analytical methods and the method validation package. Please also address these concerns here and provide updated data as appropriate.

(b) (4)

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B. In addition to responding to the deficiencies presented above, please note and acknowledge the following:

1. DMF 18821, Esomeprazole magnesium dihydrate has been reviewed and found inadequate. The DMF holder has been informed. Please indicate in your response that the holder has responded to the deficiencies.

2. Please provide updated data from your on-going stability study.

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

4. A satisfactory CGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

Sincerely yours,

N. Scott Dorsey for

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

cc: ANDA 78-003
ANDA DUP
DIV FILE
Field Copy

Endorsements

HFD-645/YPan/3/24/06 Yapi Pan 4/10/06

HFD-645/SFurness/4/6/06 N. Stockman 4/11/06

HFD-617/YKong/4/10/06 YK 4/11/06

F/T by rad4/10/06

V:\FIRMSNZ\IVAXPharm\LTRS&REV\78003.R01.doc

**TYPE OF LETTER:** NOT APPROVABLE - MINOR

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 78003

# BIOEQUIVALENCE REVIEWS

# DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 078003 |
| **Drug Product Name** | Esomeprazole Magnesium Delayed-Release Capsules, USP |
| **Strength(s)** | Eq. 20 mg and 40 mg base |
| **Applicant Name** | IVAX Pharmaceuticals, Inc.,<br>(An indirect and wholly owned subsidiary of Teva Pharmaceuticals USA) |
| **Address** | 425 Privet Road<br>Horsham, PA, 19044 |
| **Applicant's Point of Contact** | Scott D. Tomsky, Vice President, N.A. Generics Regulatory Affairs<br>Scott.Tomsky@tevapharm.com |
| **Contact's Telephone Number** | 215-591-3142 |
| **Contact's Fax Number** | 215-591-8812 |
| **Submission Dates of Original Application and Previous Amendments** | November 23, 2005<br>November 13, 2006 (study amendment)<br>April 25, 2013 (In vitro NG tube study)<br>March 31, 2014 (In vitro NG tube study) |
| **Submission Date of Amendment Under Review** | **August 22, 2014 (In vitro NG Tube Study)** |
| **Reviewer** | Zhuojun Zhao, Ph.D. |

| | | | |
|---|---|---|---|
| **Study Number (s)** | P1BD05001 | P1BD05002 | P1BD05010 |
| **Study Type (s)** | Fasting | Fed | Sprinkled Fasting |
| **Strength (s)** | eq. to 40 mg base | eq. to 40 mg base | eq. to 40 mg base |
| **Clinical Site** | Allied Research International Inc. | | |
| **Clinical Site Address** | 4520 Dixie Road, Mississauga, Ontario, Canada L4W 1N2 | | |
| **Analytical Site** | (b) (4) | | |
| **Analytical Site Address** | | | |

| | | | |
|---|---|---|---|
| **OVERALL REVIEW RESULT** | **Adequate** | | |
| **OSI REPORT RESULT** | **Adequate** | | |
| **BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #** | **STUDY/TEST TYPE** | **STRENGTH** | **REVIEW RESULT** |
| **1** | **Dissolution** | **20 mg and 40 mg** | **Adequate** |
| **1** | **Fasting study** | **40 mg** | **Adequate** |
| **1** | **Fed study** | **40 mg** | **Adequate** |
| **1** | **Sprinkled Fasting Study** | **40 mg** | **Adequate** |
| **1** | **Biowaiver Request** | **20 mg** | **Adequate** |
| **1** | **NG Tube Test** | **20 mg and 40 mg** | **Adequate** |

**Review of a Study Amendment**

## 1 EXECUTIVE SUMMARY

This is a review of a study amendment.

IVAX Pharmaceuticals, Inc. previously submitted an application (11/23/2005) consisting of three bioequivalence (BE) studies comparing its test product, Esomeprazole Magnesium Delayed-Release (DR) Capsules, 40 mg, to the corresponding reference product, AstraZeneca's NEXIUM® (Esomeprazole Magnesium) DR Capsules, 40 mg, under fasting, fed, and fasting "sprinkled" conditions. Firm's fasting, fed and fasting sprinkled BE studies were found acceptable; the dissolution testing conducted using the FDA-recommended method was also acceptable[1,2].

Since Esomeprazole Magnesium DR Capsules include an alternate administration method through a nasogastric (NG) tube per the approved labeling of the reference product, the DB II issued a deficiency letter on 09/26/2012 to request the firm perform the comparative *in vitro* tests (sedimentation testing, particle size distribution study, recovery testing, and acid resistance stability testing) to compare the performance of its test product to that of the reference product for both strengths, 20 mg and 40 mg, under NG tube administration conditions[3].

In the firm's amendment dated 4/25/2013, the firm submitted the results of in vitro NG tube studies. The results for sedimentation testing and recovery testing were acceptable. However, due to its improper sample preparation for particle size analysis, the firm did not determine the particle size distribution on test and reference products before delivery (in syringe) and after delivery through the combination of syringe and NG tube. In addition, firm's acid resistance stability testing is incomplete. Due to the concerns that the process of dispersing a test product in an oral syringe and/or an oral syringe with an NG tube might adversely impact the integrity of the enteric coating, the firm was requested to demonstrate the stability of the dispersed granules in different pH of water (e.g. 6, 7 and 8) with different soak time (e.g. 15, 30 and 60 min) prior to performing the acid resistance testing[2].

In the firm's amendment dated 03/31/2014, the firm repeated particle size distribution study and acid resistance testing in water with pHs of 5.4, 5.9 and 6.4 at 0, 15, 30 and 60 minutes, instead of water with pH 6, 7, and 8 which was previously recommended by the DB. The firm stated that the chosen pHs best represent water conditions in a hospital setting. The DB disagrees with the firm's statement. Since the tab water may be used to deliver the medicine in hospital and its pH of tap water may vary between 6.5 to 8.5, as per the control correspondence #140139[4], the current FDA guidance on Esomeprazole

[1] DARRTS: REV-BIOEQ-01(General Review) for ANDA 078003, final date 01/04/2007.
[2] DARRTS: REV-BIOEQ-21(Primary Review) for ANDA 078003, final date 09/19/2013.
[3] DARRTS: REV-BIOEQ-01(General Review) for ANDA 078003, final date 09/26/2012.
[4] V:\FIRMSAM\DBE\Esomeprazole\140139P0414

Magnesium DR Capsules recommends in vitro NG tube studies using water with different pH (pH 5.5, 6.5, and 7.5) with soak times of 0 minute and 15 minutes[5].

In the firm's amendment dated March 31, 2014, the firm's particle size analysis on the granules delivered through syringe and NG tube using microscopy was deemed not accurate and not suitable for particle size distribution (D10, D50 and D90). The results from the firm's acid resistance testing show that less than (b) (4)% of Esomeprazole for 20 mg and 40 mg strengths of the test product releases in the acidic medium after soaking in water (pH 5.4, 5.9 and 6.4) for 0, 15, 30 and 60 minutes[6]. Per internal meeting minutes dated 4/11/2014 (Section 4.2.6), the laser diffraction method for measuring particle size in lieu of microscopy was recommended in the OGD's Complete Response (CR) dated 07/11/2014. Therefore, the firm was requested to 1) repeat the particle size distribution study (using laser diffraction method) and acid resistance test in pH 7.5 water with soak times of 0 minute and 15 minutes, and 2) to conduct comparative recovery studies on the granule dispersion in water with different pH (pH 5.5, 6.5, and 7.5) and soak times (0 min and 15 min) per bio-management meeting dated 05/13/2014[10].

In the current amendment dated August 22, 2014, the firm provided the acid resistance study using pH 7.5 water by same procedures submitted in its amendment dated March 31, 2014. The results in the acid resistance testing show that the test product collected from NG tube retained (b) (4)% (20 mg) and (b) (4)% (40 mg) esomeprazole in pH 7.5 water and the mean of the amount released in acid medium meet the specification of NMT (b) (4)% drug released in acid stage for both strengths of the test products. The firm's acid resistance stability study showed that the study result for both strengths of the test product is acceptable with water pH at 7.5. The study is now acceptable.

The firm also repeated its comparative recovery studies of the dispersed granules for both 20 mg and 40 mg strengths using the 8 French nasogastric tubes in 50 ml water with different pH (5.5, 6.5, and 7.5) at 0 minute and 15 minutes. The 90% confidence intervals for the recovery study for both 20 mg and 40 mg with 0 and 15 minutes soaking calculated by the reviewer were in agreement with the values reported by the firm. The point estimate and 90% CI for the least squares geometric means of the recovery of Esomeprazole at 0 min and 15 min meet the 90% CI criteria of 80-125% for the recovery testing. The study is now acceptable.

In addition, the firm provided its particle size distribution study using 3 different pHs (5.5, 6.5 and 7.5) of water and soaked the dispersed granules with different soaking times (0 and 15 minutes) and it measured the particle size distribution at D10, D50 and D90 using the validated laser diffraction method as required in CR dated 07/11/2014. All the data of D10, D50 for both strengths (40 mg and 20 mg) in all three pH water failed to meet the limit of acceptance criteria for 90% CI (80%-125%), except for some data of D-span. However, the study is deemed acceptable based on the acceptable comparative

[5] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086251.pdf (Recommended May 2008; Revised March, 2011, July 2014)
[6] DARRTS:REV-BIOEQ-21 (Primary Review), final date 06/15/2014

recovery study and acid resistance testing (please see the current OGD discussion in (Section 4.2.9).

The 20 mg strength is proportionally formulated to the 40 mg strength. The DB deems the 20 mg strength of the test product to be bioequivalent to the 20 mg strength of the reference product based on CFR 320.24(b)(6).

No Office of Scientific Investigations (OSI) inspection is pending or necessary.

The application is **acceptable.**

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# 3 SUBMISSION SUMMARY

## 3.1 Drug Product Information

| | |
|---|---|
| **Test Product** | Esomeprazole Magnesium Delayed-Release capsules, 20 mg and 40 mg |
| **Reference Product** | NEXIUM® (Esomeprazole magnesium) Delayed-Release capsules, 20 mg and 40 mg |
| **RLD Manufacturer** | AstraZeneca |
| **NDA No.** | 021153 |

| RLD Approval Date | Feb 20, 2001 |
|---|---|
| Indication | Treatment of Gastroesophageal Reflux Disease (GERD), Maintenance of Healing of Erosive Esophagitis, Symptomatic Gastroesophageal Reflux Disease, Risk Reduction of NSAID-Associated Gastric Ulcer, H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence, Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome. |

## 3.2 Contents of Current Submission

| Study Types | Yes/No? | How many? |
|---|---|---|
| Single-dose fasting | No | 0 |
| Single-dose fed | No | 0 |
| Single-dose sprinkled fasting | No | 0 |
| In vitro NG tube study | Yes | 3 tests for 20 mg<br>3 tests for 40 mg |
| In vitro dissolution | No | 0 |
| Waiver requests | No | 0 |
| BCS Waivers | No | N/A |
| Clinical Endpoints | No | N/A |
| Amendments | Yes | 1 |

## 3.3 Review of Submission

In response to the 2nd complete response letter from the FDA dated July 11, 2014. Teva Pharmaceuticals USA submitted its current amendment dated 08/22/2014. The responses to DB II deficiencies related to In vitro test for Nasogastric (NG) Tube administrations are evaluated in this review as follows.

### 3.3.1 Deficiency #1 (Particle Size Distribution Study):

*We acknowledge that you conducted particle size distribution study after delivery through syringe and NG tube using water with different pH (5.4, 5.9 and 6.4) and different soak times (0, 15, 30 and 60 minutes). However, your particle size distribution analysis using microscopy may not be suitable to determine particle size distribution (D10, D50 and D90), therefore it is not acceptable.*

*In addition, since a tap water with pH varying between 6.5 to 8.5 may be possibly used to deliver the medicine to hospitably patients, please determine the comparative particle size of granule dispersion using 12 units each strength of the test and the reference products in pH 7.5 water with soak times of 0 and 15 minutes. Please follow the procedure described in the deficiency letter (deficiency #2) issued by the DB II on 9/26/2012.*

*Please provide the particle size data at the D10, D50, and D90 levels using laser diffraction method. Please also provide validation reports for particle size distribution study.*

**Firm's Response:**
As per Agency's request the comparative particle size of granule dispersion using 12 units each strength of the test and the reference products in pH 5.5, 6.5 and 7.5 at 0 minute and 15 minutes was performed.

As recommended by the Agency, analytical method using laser diffraction was developed and validated. The method was validated for analytical parameters such as precisionrepeatability, precision- intermediate precision (ruggedness), stability in dispersion and robustness.

A summary of particle size distribution of pellets is provided below.

**Summary of Mean Pellet Size for Test Product***

| Strength | pH | Initial (size in µm) | | | 0 Minute Soak (size in µm) | | | 15 Minute Soak (size in µm) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 20 mg | 5.5 | | | | | | | | | (b) (4) |
| | 6.5 | | | | | | | | | |
| | 7.5 | | | | | | | | | |
| 40 mg | 5.5 | | | | | | | | | |
| | 6.5 | | | | | | | | | |
| | 7.5 | | | | | | | | | |

*Esomeprazole Magnesium Delayed Release capsules 20mg, Batch no.Y31825, Expiry: 06/2015
*Esomeprazole Magnesium Delayed Release capsules 40mg, Batch no.Y31828, Expiry: 06/2015

**Summary of Mean Pellet Size for Reference Product****

| Strength | pH | Initial (size in µm) | | | 0 Minute Soak (size in µm) | | | 15 Minute Soak (size in µm) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 20 mg | 5.5 | | | | | | | | | (b) (4) |
| | 6.5 | | | | | | | | | |
| | 7.5 | | | | | | | | | |
| 40 mg | 5.5 | | | | | | | | | |
| | 6.5 | | | | | | | | | |
| | 7.5 | | | | | | | | | |

**Esomeprazole Magnesium Delayed Release capsules 20mg, Batch no.K005263, Expiry: Dec 2016
**Esomeprazole Magnesium Delayed Release capsules 40mg, Batch no.K003153, Expiry: Dec 2016

Please refer to Module 3.2.P.2 for particle size determination protocol including method, validation report and study report.

**Reviewer's Comments:**
In the current amendment, the firm provided it new product development report in Module 3.2, which contains reports for all three required studies, Particle Size Determination, Acid Resistance Stability Study and Assay Recovery Study.

**Particle Size Determination Report:**

**A. Materials used in the study**

| | |
|---|---|
| Test Product | Sample Analyzed:<br>• Esomeprazole Magnesium Delayed Release capsules 20mg<br>Sample Batch no.Y31825<br>Mfg date: 07/2013<br>Expiry date: 06/2015<br>Manufacturer Cipla.<br>• Esomeprazole Magnesium Delayed Release capsules 40mg<br>Sample Batch no.Y31828<br>Mfg date: 07/2013<br>Expiry: 06/2015<br>Manufacturer Cipla.<br>• Esomeprazole Magnesium Delayed Release capsules 20mg<br>Sample Batch no.K005263<br>Expiry: Dec 2016<br>Manufacturer AstraZeneca.<br>• Esomeprazole Magnesium Delayed Release capsules 40mg<br>Sample Batch no.K003153<br>Manufacturer AstraZeneca.<br>Expiry: Dec 2016 |
| RLD Product | |
| NG Feeding Tube | 8 French tube of material PVC manufactured by Kendall Argyle |
| Syringe | **50 ml syringe:-** BD syringe 60 ml capacity (BD 50 ml Precise syringe) Luer-Lok Tip Latex Free sterile syringe |
| Reagent | (b) (4) |

**B. Instrument used in the study**

(b) (4)

**C. Particle Size Distribution Study Procedure**

(b) (4)

**Same procedures were repeated for testing in Water about pH 6.5 and pH 7.5 and 40 mg strength in all three pH water.**

**D. Review of Firm's Data:**

The firm's result of particle size distribution study results and photographs are attached in Section 4.21 and Section 4.2.2, respectively.

The reviewer's calculated Arithmetic Mean for the firm's particle size distribution study is shown below for Syringe and Tube Combination:

**Table 1 Particle size distribution in combination of syringe and NG tube for 20 mg at 0 min**

| Testing Condition | Formulation | Product ID \ Batch No. | Dosage Strength & Form | No. of Dosage Units | | Syringes and NG tube for 20 mg at 0 min | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | D10 (µm) | D50 (µm) | D90 (µm) | D-span* |
| pH 5.5 | Test | Batch # Y31825 Manufacturing Date: 07/2013 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 4.67 | 2.07 | 4.74 | 10.45 |
| | Reference | Nexium®, Batch # K005263 Expiry Date: Dec 2016 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 2.68 | 1.60 | 2.11 | 4.00 |
| pH 6.5 | Test | Batch # Y31825 Manufacturing Date: 07/2013 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 3.11 | 2.38 | 2.63 | 3.38 |
| | Reference | Nexium®, Batch # K005263 Expiry Date: Dec 2016 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 2.79 | 1.81 | 2.58 | 6.65 |
| pH 7.5 | Test | Batch # Y31825 Manufacturing Date: 07/2013 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 3.52 | 2.73 | 2.87 | 3.22 |
| | Reference | Nexium®, Batch # K005263 Expiry Date: Dec 2016 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 4.93 | 2.33 | 2.77 | 4.60 |

*Span = (D90-D10)/D50

**Table 2 Particle size distribution in combination of syringe and NG tube for 20 mg at 15 min**

| Testing Condition | Formulation | Product ID \ Batch No. | Dosage Strength & Form | No. of Dosage Units | | Syringes and NG tube for 20 mg at 0 min | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | D10 (µm) | D50 (µm) | D90 (µm) | D-span* |
| pH 5.5 | Test | Batch # Y31825 Manufacturing Date: 07/2013 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 3.32 | 2.76 | 4.10 | 6.90 |
| | Reference | Nexium®, Batch # K005263 Expiry Date: Dec 2016 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 4.14 | 1.33 | 2.58 | 7.50 |
| pH 6.5 | Test | Batch # Y31825 Manufacturing Date: 07/2013 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 2.14 | 1.36 | 1.68 | 4.39 |
| | Reference | Nexium®, Batch # K005263 Expiry Date: Dec 2016 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 4.70 | 2.10 | 2.86 | 8.42 |
| pH 7.5 | Test | Batch # Y31825 Manufacturing Date: 07/2013 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 1.76 | 1.78 | 2.56 | 3.30 |
| | Reference | Nexium®, Batch # K005263 Expiry Date: Dec 2016 | 20 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 4.71 | 1.21 | 1.50 | 6.36 |

**Table 3 Particle size distribution in combination of syringe and NG tube for 40 mg at 0 min**

| Testing Condition | Formulation | Product ID \ Batch No. | Dosage Strength & Form | No. of Dosage Units | | Syringes and NG tube for 40 mg at 0 min | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | D10 (µm) | D50 (µm) | D90 (µm) | D-span* |
| pH 5.5 | Test | Batch # Y31828 Manufacturing | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Date: 07/2013 | | | %CV | 1.35 | 1.37 | 1.53 | 0.69 |
| | Reference | Nexium®, Batch # K003153 Expiry Date: Dec 2016 | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 2.42 | 1.64 | 2.43 | 5.39 |
| pH 6.5 | Test | Batch # Y31828 Manufacturing Date: 07/2013 | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 1.16 | 1.19 | 1.39 | 0.59 |
| | Reference | Nexium®, Batch # K003153 Expiry Date: Dec 2016 | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 4.21 | 1.64 | 2.14 | 5.89 |
| pH 7.5 | Test | Batch # Y31828 Manufacturing Date: 07/2013 | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 1.35 | 1.41 | 1.91 | 2.28 |
| | Reference | Nexium®, Batch # K003153 Expiry Date: Dec 2016 | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 1.92 | 1.51 | 2.01 | 3.15 |

**Table 4 Particle size distribution in combination of syringe and NG tube for 40 mg at 15 min**

| Testing Condition | Formulation | Product ID \ Batch No. | Dosage Strength & Form | No. of Dosage Units | | Syringes and NG tube for 40 mg at 0 min | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | D10 (µm) | D50 (µm) | D90 (µm) | D-span* |
| pH 5.5 | Test | Batch # Y31828 Manufacturing Date: 07/2013 | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 4.10 | 1.49 | 2.82 | 9.41 |
| | Reference | Nexium®, Batch # K003153 Expiry Date: Dec 2016 | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 72.70 | 1.48 | 1.14 | 28.79 |
| pH 6.5 | Test | Batch # Y31828 Manufacturing | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Date: 07/2013 | | | %CV | 1.40 | 1.66 | 1.90 | 0.90 |
| | Reference | Nexium®, Batch # K003153 Expiry Date: Dec 2016 | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 74.92 | 1.45 | 2.41 | 32.82 |
| pH 7.5 | Test | Batch # Y31828 Manufacturing Date: 07/2013 | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 1.60 | 1.49 | 1.45 | 0.92 |
| | Reference | Nexium®, Batch # K003153 Expiry Date: Dec 2016 | 40 mg Capsule | 12 | Mean | (b) (4) | | | |
| | | | | | Min | | | | |
| | | | | | Max | | | | |
| | | | | | %CV | 2.99 | 1.77 | 3.16 | 6.71 |

**Table 5. Statistical Summary of the Particle Size Distribution Studies:**

| **Method: PBE for Particle Size Study<br>Combination of syringe and NG tube for 20 mg<br>Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **ABE[7]** | | | | | | **PBE[8]** | | | |
| **Time (min)** | **Parameter** | **Test** | **Reference** | **Ratio** | **90% C.I.** | **Sigma R** | **95% upper confidence bound** | ***Method Used** | **Outcome** |
| **pH 5.5** | | | | | | | | | |

[7] Average Bioequivalence (ABE): The ABE approach is used to calculate point estimate and 90% confidence intervals for D10, D50, D90 and D-span. The acceptance criteria are 80%-125%.

[8] The Population Bioequivalence (PBE): Mixed scaling approaches of PBE are employed for in vitro particle size distribution studies according to ***Statistical Information for In Vitro Bioequivalence Data Posted on August 18, 1999***. When reference product variance is greater than the scaling variance, $\sigma_{T0}^2$ ($\sigma_{T0}$ = 0.10), the reference-scaling approach is used to calculate a 95% upper bound for D10, D50, D90, and D-span as below:

$$\frac{(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)}{\sigma_R^2} \leq 0$$

when this variance in the study is less than the scaling variance, the population BE criterion should be modified to its constant-scaled form (see below):

$$\frac{(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)}{\sigma_{T0}^2} \leq \theta$$

If this upper bound is less than or equal to the upper limit, θ, the test product may be judged to be bioequivalent to the reference product at the 5 percent level.

At the present time CDER recommends that the limit not be larger than 90/111 (i.e., the ratio of geometric means would fall within 0.90 and 1.11). This value should be used in calculating the population BE limit according to **Statistical Information for In Vitro Bioequivalence Data Posted on August 18, 1999**.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 0 min | D10 | (b) (4) | 128.58 | 125.1 | 132.2 | 0.027 | 0.0780 | C | Fail |
| | D50 | | 134.17 | 132.4 | 135.9 | 0.016 | 0.0938 | C | Fail |
| | D90 | | 141.12 | 137.6 | 144.8 | 0.021 | 0.1176 | C | Fail |
| | D-span | | 115.41 | 109.5 | 121.6 | 0.040 | 0.0277 | C | Fail |
| 15 min | D10 | | 133.80 | 130.2 | 137.4 | 0.043 | 0.0794 | C | Fail |
| | D50 | | 134.59 | 132.5 | 136.7 | 0.013 | 0.0775 | C | Fail |
| | D90 | | 139.56 | 136.3 | 142.9 | 0.025 | 0.1075 | C | Fail |
| | D-span | | 108.52 | 103.3 | 114.0 | 0.074 | -010041 | C | Pass |
| **pH 6.5** | | | | | | | | | |
| 0 min | D10 | (b) (4) | 133.80 | 131.0 | 136.7 | 0.028 | 0.0768 | C | Fail |
| | D50 | | 135.71 | 133.7 | 137.7 | 0.018 | 0.0819 | C | Fail |
| | D90 | | 140.55 | 138.0 | 143.1 | 0.026 | 0.1076 | C | Fail |
| | D-span | | 109.35 | 105.5 | 113.4 | 0.064 | -0.0081 | C | Pass |
| 15 min | D10 | | 135.72 | 132.2 | 139.4 | 0.048 | 0.0872 | C | Fail |
| | D50 | | 136.12 | 134.4 | 137.8 | 0.021 | 0.0818 | C | Fail |
| | D90 | | 142.60 | 140.3 | 145.0 | 0.029 | 0.1165 | C | Fail |
| | D-span | | 110.64 | 105.6 | 115.9 | 0.082 | -0.0039 | C | Pass |
| **pH 7.5** | | | | | | | | | |
| 0 min | D10 | (b) (4) | 133.95 | 129.9 | 138.1 | 0.050 | 0.0819 | C | Fail |
| | D50 | | 133.02 | 130.7 | 135.4 | 0.023 | 0.0711 | C | Fail |
| | D90 | | 136.95 | 134.3 | 139.7 | 0.028 | 0.0907 | C | Fail |
| | D-span | | 105.51 | 102.6 | 108.5 | 0.046 | -0.0153 | C | Pass |
| 15 min | D10 | | 138.53 | 134.9 | 142.2 | 0.048 | 0.1009 | C | Fail |
| | D50 | | 136.80 | 135.3 | 138.3 | 0.012 | 0.0843 | C | Fail |
| | D90 | | 141.27 | 139.2 | 143.4 | 0.015 | 0.1093 | C | Fail |
| | D-span | | 105.64 | 101.9 | 109.5 | 0.064 | -0.0155 | C | Pass |

***C: Constant-scale**

| **Method: PBE for Particle Size Study<br>Combination of syringe and NG tube for 40 mg<br>Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **ABE** | | | | | | **PBE** | | | |
| **Time (min)** | **Parameter** | **Test** | **Reference** | **Ratio** | **90% C.I.** | **Sigma R** | **95% upper confidence bound** | ***Method Used** | **Outcome** |
| **pH 5.5** | | | | | | | | | |
| 0 min | D10 | (b) (4) | | 136.88 | 135.0 | 138.8 | 0.025 | 0.0862 | C | Fail |
| | D50 | | | 137.64 | 136.2 | 139.1 | 0.016 | 0.0879 | C | Fail |
| | D90 | | | 142.51 | 140.5 | 144.6 | 0.024 | 0.1145 | C | Fail |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | D-span | (b) (4) [redacted] | 108.48 | 105.6 | 111.4 | 0.052 | -0.0118 | C | Pass |
| 15 min | D10 | [redacted] | 374.13 | 216.7 | 645.8 | 1.052 | 2.3393 | R | Fail |
| | D50 | [redacted] | 134.61 | 133.2 | 136.0 | 0.015 | 0.0737 | C | Fail |
| | D90 | [redacted] | 137.52 | 135.4 | 139.6 | 0.011 | 0.0912 | C | Fail |
| | D-span | [redacted] | 71.83 | 61.4 | 84.1 | 0.295 | 0.1364 | R | Fail |
| **pH 6.5** | | | | | | | | | |
| 0 min | D10 | (b) (4) [redacted] | 137.42 | 134.2 | 140.7 | 0.044 | 0.0937 | C | Fail |
| | D50 | [redacted] | 137.90 | 136.5 | 139.3 | 0.016 | 0.0887 | C | Fail |
| | D90 | [redacted] | 143.37 | 141.6 | 145.2 | 0.021 | 0.1179 | C | Fail |
| | D-span | [redacted] | 109.24 | 106.1 | 112.5 | 0.056 | -0.0103 | C | Pass |
| 15 min | D10 | [redacted] | 420.11 | 215.5 | 818.8 | 1.287 | 2.7348 | C | Fail |
| | D50 | [redacted] | 137.19 | 135.7 | 138.7 | 0.015 | 0.0861 | C | Fail |
| | D90 | [redacted] | 139.38 | 137.3 | 141.5 | 0.024 | 0.0994 | C | Fail |
| | D-span | [redacted] | 73.21 | 61.7 | 86.8 | 0.329 | 0.1041 | R | Fail |
| **pH 7.5** | | | | | | | | | |
| 0 min | D10 | (b) (4) [redacted] | 133.10 | 131.5 | 134.7 | 0.019 | 0.0675 | C | Fail |
| | D50 | [redacted] | 136.28 | 134.9 | 137.7 | 0.015 | 0.0813 | C | Fail |
| | D90 | [redacted] | 141.69 | 139.8 | 143.7 | 0.020 | 0.1103 | C | Fail |
| | D-span | [redacted] | 111.47 | 109.4 | 113.6 | 0.031 | -0.0051 | C | Pass |
| 15 min | D10 | [redacted] | 141.71 | 139.3 | 144.2 | 0.030 | 0.1122 | C | Fail |
| | D50 | [redacted] | 139.45 | 137.9 | 141.1 | 0.018 | 0.0973 | C | Fail |
| | D90 | [redacted] | 141.22 | 138.8 | 143.7 | 0.031 | 0.1098 | C | Fail |
| | D-span | [redacted] | 101.13 | 97.6 | 104.7 | 0.067 | -0.0226 | R | Pass |

**Reviewer's Comments on particle size distribution:**

In its current amendment, the firm conducted particle size distribution study using 3 different pHs (5.5, 6.5 and 7.5) of water and soaked the dispersed granules with different soaking times (0 and 15 minutes). The firm did not conduct particle size study in syringe only but conducted the particle size distribution study after delivery through the combination of NG tube and syringe. This is acceptable as the particle size at tube exit (without particle size at syringe) provides sufficient information to support NG tube administration. The sampling preparation procedure was correct. As required, the firm measured the particle size distribution at D10, D50 and D90 using the validated laser diffraction method.

As shown in table 5, all the data of D10, D50 for both strengths (40 mg and 20 mg) in all three pH water failed to meet the limit of acceptance criteria for 90% CI (80%-125%), except for some data of D-span. This is mainly due to the greater size of the test product compared to the reference product as shown in table 1 and 2. Based on the OGD Internal meeting dated April, 11, 2014 (Section 4.2.6), slightly greater particle size (Section 4.1) is acceptable as long as the test product passes the recovery test. The firm's comparative recovery Test results (in Section 3.3.3) are acceptable and thus the particle size in the test

product is deemed acceptable per OGD discussion regarding to NG tube study (Section 4.2.9). In addition, the CMC reviewer accepts the particle size distribution of the test product from (b) (4)[9]. Such slightly difference in particle size is also observed in ANDA 202784 (as shown in table below), in which the difference did not impact the study acceptance.

The reviewer summaries particle distribution data and the result of recovery testing in the following table:

| Combination of syringe and NG tube 8-F (20 mg and 40 mg) | | | | | |
|---|---|---|---|---|---|
| **ANDA No.** | **Sponsor** | **Particle Size D50 (mm)** | **Particle 90% CI** | **Recovery Testing** | **Comments** |
| 078003 | IVAX | (b) (4) | Failed | Passed | Acceptable |
| 078279 | Dr. Reddy's | | Passed | Passed | Minor deficiency for NG tube study |
| 78936 | Mylan | | Passed | Passed | Minor deficiency |
| (b) (4) | | | | | |
| 202784 | Hetero | (b) (4) | Possible Passed | Passed | Pending method validation report |

The firm's response is satisfactory.

### 3.3.2 Deficiency #2 (Acid Resistance Stability Study):

*We acknowledge that you have conducted acid resistance stability testing for both 20 mg and 40 mg strengths after recovery through a combination of oral syringe and 8 French NG tube in water with different pH (5.4, 5.9, and 6.4) at 0, 15, 30 and 60 minutes. For the same reason mentioned above in deficiency 1, please repeat comparative acid resistance stability testing for both strengths using 12 units of the test and the reference products* ***in pH 7.5 water at 0 minute and 15 minutes.*** *Please follow the procedure described in the deficiency letter (deficiency #4) issued by the DB II on 9/26/2012.*

**Firm's Response:**
As per Agency's request the comparative acid resistance stability testing for both strengths using 12 units of the test and the reference products in pH 7.5 water at 0 minute and 15 minutes was performed.

The table below provides a summary of the Acid Resistant Study Summary Results using 8.0 French NG Tube at pH 7.5.

[9] DARRTS: REV-QUALITY-21 (Primary Review), final date 06/12/2014

| Test Product | | | | | | Reference Product | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Soaking Time (minutes) | Initial HPLC Assay % | % Assay of pellets after Acid Treatment | | | | Soaking Time (minutes | Initial HPLC Assay % | % Assay of pellets after Acid Treatment | | | |
| | | Mean | Min | Max | %RSD | | | Mean | Min | Max | %RSD |
| **Esomeprazole Magnesium Delayed-Release Capsules USP, 20 mg** | | | | | | | | | | | |
| 0 | 102.6 | 100.0 | (b) (4) | | 2.4 | 0 | 100.9 | 98.5 | (b) (4) | | 0.7 |
| 15 | 102.6 | 98.7 | | | 1.2 | 15 | 100.9 | 96.8 | | | 2.5 |
| **Esomeprazole Magnesium Delayed-Release Capsules USP, 40 mg,** | | | | | | | | | | | |
| 0 | 99.7 | 98.7 | (b) (4) | | 1.3 | 0 | 100.6 | 90.8 | (b) (4) | | 8.5 |
| 15 | 99.7 | 97.1 | | | 1.8 | 15 | 100.6 | 21.6 | | | 57.6 |

The tubing and the syringe were inspected for any aggregation, adherence or clogging of granules. It was observed that no aggregation, adherence or clogging of granules were found for both Test (Cipla) and RLD product.

Please refer to **Module 3.2.P.2** product development report for complete study report and photographs of pellets taken at different stages (syringe with capsule's content, NG tube with capsule content, pellets in beaker after exiting NG Tube and pellets after two hours of acid treatment.).

**Reviewer's Comment:**
In the firm's previous amendment dated March 31, 2014, it conducted the acid resistance testing using water with pHs of 5.4, 5.9 and 6.4. The study results show that less than 4% of Esomeprazole for 20 mg (CV% < 3) and less than or equal to10.1% of Esomeprazole for 40 mg (CV% <6) DR granules of the test product collected from NG tube releases in the acidic medium at all three water pHs with all soaking times (0, 15, 30 and 60 minutes). Mean of the amount released in acid medium meet the specification of NMT (b) (4)% drug released in acid stage for both strengths of the test products. Based on the bio-meeting minute dated April 11, 2014 (in Section 4.2.6), the DB accepts the firm's acid resistance test with water pH 5.4 and 6.4 since the test product release less than the RLD. However, the firm was requested to conduct the test with water pH 7.5[10].

In the current amendment, the firm conducted the required acid resistance testing using the water pH 7.5 as shown below:

**Particle Size Determination Report:**
**A. Materials used in the study**

| | |
|---|---|
| Test Product | Sample Analyzed:<br>• Esomeprazole Magnesium Delayed Release capsules<br>Sample Batch no.Y31825<br>Mfg date: 07/2013<br>Expiry date: 06/2015<br>Manufacturer Cipla.<br>• Esomeprazole Magnesium Delayed Release capsules<br>Sample Batch no.Y31828<br>Mfg date: 07/2013<br>Expiry: 06/2015<br>Manufacturer Cipla. |

[10] DARRTS: REV-BIOEQ-21 (Primary Review), final date 06/15/2014

| | |
|---|---|
| RLD Product | |
| NG Feeding Tube | 8 French tube of material PVC manufactured by Kendall Argyle |
| Syringe | **50 ml syringe:-** BD syringe 60 ml capacity (BD 50 ml Precise syringe) Luer-Lok Tip Latex Free sterile syringe |
| Reagent | (b) (4) |

**B. Instrument used in the study**

**Chromatographic system:**

(b) (4)

**C. Acid Resistance Study Procedure**

(b) (4)



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(b) (4)

**D. Review of Firm's Data:**
Based on the data in Section 4.2.3, the reviewer summarized the firm's results as shown in the following Table 6:

**Table 6: Acid resistance stability data**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Dissolution Conditions** | | | **Apparatus:** | USP Apparatus II (Paddle) | | | |
| | | | **Speed of Rotation:** | 100 RPM | | | |
| | | | **Medium:** | Acid stage: 0.1N HCl | | | |
| | | | **Volume:** | 300 mL | | | |
| | | | **Temperature:** | 37 ± 0.5° C | | | |
| **Firm's Proposed Specifications** | | | Acid stage: Not more than (b) (4)% in 120 min | | | | |
| **Water pH** | **Soaking Time** | **No. of Dosage Units** | | **% Labeled amount of Esomeprazole** | | | |
| | | | | **20 mg** | | **40 mg** | |
| | | | | **Test (Batch Y31825 )** | **RLD (Batch #K005263)** | **Test (Batch #Y31828 )** | **RLD (Batch #K003153)** |
| 7.5 | 0 min | 12 | Mean | 100.0 | 98.5 | 98.7 | 90.8 |
| | | | Range | (b) (4) | | | |
| | | | %CV | 2.4 | 0.7 | 1.3 | 8.5 |
| | 15 min | 12 | Mean | 98.7 | 96.8 | 97.1 | 21.6 |
| | | | Range | (b) (4) | | | |
| | | | %CV | 1.2 | 2.5 | 1.8 | 57.6 |

1. Esomeprazole is acid labile drug substance. The firm conducted the acid resistance study using pH 7.5 water by same procedures submitted in its amendment dated March 31, 2014, in which the firm measured esomeprazole retained in the pellets not in the dissolution medium[10].

2. The results in the acid resistance testing show that the test product collected from NG tube retained (b) (4)% (20 mg) and (b) (4)% (40 mg) esomeprazole in pH 7.5 water and the mean of the amount released in acid medium meet the specification of NMT (b) (4)% drug released in acid stage for both strengths of the test products. In contrast, the 40 mg reference drug released up to (b) (4)% of Esomeprazole with 15 minutes pretreated in pH 7.5 water. Comparing with the acid resistance data with 0 minute soaking time (immediate delivery), it indicates that the enteric coating of the reference product 40 mg is damaged by 15 minutes pH 7.5 water pretreatment. This was also observed in the acid resistance testing with water pH 5.4, 5.9 and 6.4 in the previous amendment dated March 31, 2014[10].

3. The reviewer compiled the acid resistance data which are available from our in house ANDAs as below:

**Summary of Acid Resistance Stability Data in ANDAs**

| ANDA # | NG tube information | | % Released in the Acid Stage for 2 hours | | | |
|---|---|---|---|---|---|---|
| | Time | Water pH | 20 mg | | 40 mg | |
| | | | Test | RLD | Test | RLD |
| | | | | | | (b) (4) |
| **078279** | 15 min | No define | 6.1 | 11.8 | 5.6 | 2.3 |
| **078936** | 15 min | No define | 2.6 | 3.2 | 2.7 | 1.0 |
| **202784** | 15 min | No define | 5.5 (94.5%) | 6.2 (93.8%) | 6.7 (93.3%) | 7.7 (92.3%) |
| **078003** | 0 min | **5.4** | 3 | 6.2 | 8.8 | 7.9 |
| | 15 min | | 3.5 | 6.5 | 8.6 | 86.6 |
| | 0 min | **5.9** | 0 | 6.9 | 2.3 | 8.3 |
| | 15 min | | -0.7 | 9.6 | 2.9 | 97.1 |
| | 0 min | **6.4** | 1.0 | 4.8 | 0.5 | 1.9 |
| | 15 min | | 1.5 | 5.3 | 0.9 | 98.2 |
| | 0 min | **7.5** | 0 | 1.5 | 1.3 | 9.2 |
| | 15 min | | 1.3 | 3.2 | 2.9 | 78.4 |
| **202784** | 15 min | No define | 5.5 (94.5%) | 6.2 (93.8%) | 6.7 (93.3%) | 7.7 (92.3%) |
| | | | | | | (b) (4) |

As shown above, it has been observed in several ANDAs the RLD products failed the OGD's proposed acid resistance test after soaking in water for 15 minutes. The issue was discussed in Bio II Internal meeting dated April 11, 2014, FDA lab has been requested to investigate this issue (see Section 4.2.4 and Section 4.2.10).

Based on the current DB II agreement, i.e. the test product will be accepted if it does not release more than the RLD, the firm's acid resistance stability test with water pH @ 5.4, 6.4 and 7.5 is **acceptable**.

### 3.3.3 Deficiency #3 (Comparative Recovery Testing):

*We acknowledge that you had conducted comparative recovery testing in your previous amendment dated 04/25/2013, where the pH of water used in the recovery test was not defined. To ensure that the test product has the same recovery as that of the RLD using different pH of water (5.5, 6.5 and 7.5), please repeat the comparative recovery studies of the dispersed granules for both 20 mg and 40 mg strengths using the 8 French nasogastric tubes in 50 ml water* ***with different pH (5.5, 6.5, and 7.5) at 0 minute and 15 minutes****. Please use 12 units of the test and the reference products and follow the procedure described in previous deficiency letter (deficiency #3) issued by the DB II on 9/26/2012.*

**Firm's Response:**
As per Agency's request, the comparative recovery studies of the dispersed granules for both 20 mg and 40 mg strengths using the 8 French nasogastric tubes in 50 ml water with different pH (5.5, 6.5, and 7.5) at 0 minute and 15 minutes was repeated.

The table below provides a summary of the comparative assay recovery study results.

| Strength | pH | Soak Time (min) | % Initial Assay | Mean % Assay | % RSD | % Initial Assay | Mean % Assay | % RSD | Mean T/R | 90% CI Range |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Test | | | RLD | | | | |
| 20 mg | 5.5 | 0 | 102.6 | 99.5 | 1.6 | 100.9 | 99.6 | 1.9 | 1.00 | 98.70 - 101.19 |
| | | 15 | | 99.6 | 2.7 | | 99.7 | 2.5 | 1.00 | 98.07 - 101.72 |
| | 6.5 | 0 | | 102.2 | 0.7 | | 99.7 | 0.8 | 1.03 | 101.90 - 103.02 |
| | | 15 | | 100.7 | 0.9 | | 100.1 | 1.3 | 1.01 | 99.86 - 101.40 |
| | 7.5 | 0 | | 99.9 | 1.8 | | 100.2 | 1.3 | 1.00 | 98.55 - 100.74 |
| | | 15 | | 100.4 | 1.4 | | 99.8 | 1.5 | 1.01 | 99.58 - 101.67 |
| 40 mg | 5.5 | 0 | 99.7 | 98.0 | 1.6 | 100.6 | 97.6 | 1.1 | 1.01 | 99.47 - 101.36 |
| | | 15 | | 98.1 | 1.5 | | 97.3 | 1.1 | 1.01 | 99.82 - 101.71 |
| | 6.5 | 0 | | 97.7 | 1.1 | | 97.8 | 1.0 | 1.00 | 99.13 - 100.61 |
| | | 15 | | 98.1 | 1.5 | | 97.9 | 1.2 | 1.00 | 99.22 - 101.10 |
| | 7.5 | 0 | | 98.1 | 1.3 | | 96.9 | 0.7 | 1.01 | 100.50 - 101.96 |
| | | 15 | | 98.5 | 0.9 | | 98.3 | 1.1 | 1.00 | 99.50 - 100.91 |

Please refer to **Module 3.2.P.2** product development report for complete study report.

**Reviewer's Comment:**
The firm had conducted comparative recovery testing in its amendment dated 04/25/2013 and the study was found acceptable[11]. However, it was noted that the pH of water used in the recovery test was not reported[10]. Therefore, in the OGD's Complete Response dated 07/11/2014, the firm was requested to repeat the comparative recovery studies of the dispersed granules for both 20 mg and 40 mg strengths using the 8 French nasogastric tubes with different pH (5.5, 6.5, and 7.5) at 0 minute and 15 minutes.

In the current amendment, the firm conducted the required the comparative recovery testing as shown below:

**A. Materials used in the study**
Same as those used in the Acid Resistance Study in Section 3.3.2

**B. Instrument used in the study**
Same as the one used in the Acid Resistance Study in Section 3.3.2

**C. Comparative Recovery Study Procedure (Through catheter tipped syringe in combination with nasogastric feeding tube)**

[11] DARRTS: REV-BIOEQ-21 (Primary Review), final date 09/19/2013



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(b) (4)

**D. Review of Firm's Data:**

The firm provided representative Photographs in the amendment. The photographs are attached in Section 4.2.5[12]. The firm did not provide its conclusion on its observation. As shown in the photographs, no aggregation or adherence was observed.

Based on the data in Section 4.2.4, the reviewer analyzed the firm's results of comparative Recovery study using syringe and NG tube combination as shown in the following Table 7 and 8:

[12] Some photographs (e.g. RLD 20 mg at pH 7.5) are with too low resolution to observe the study results. However, based on the firm's study data, the reviewer will not request the firm to resubmit the photographs.

**Table 7: Comparative Recovery Study Using Syringe and NG Tube**

| Test Condition | Formulation | Strength | No. of Dosage Units | | Time | |
|---|---|---|---|---|---|---|
| | | | | | 0 min | 15 min |
| pH 5.5 | Test, Batch # Y31825 Manufacturing Date: 07/2013 | 20 mg Capsule | 12 | Mean | 99.5 | 99.6 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |
| | | | | %CV | 1.6 | 1.9 |
| | Nexium®, Batch # K005263 Expiry Date: Dec 2016 | 20 mg Capsule | 12 | Mean | 99.6 | 99.7 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |
| | | | | %CV | 1.9 | 2.5 |
| | Test, Batch # Y31828 Manufacturing Date: 07/2013 | 40 mg Capsule | 12 | Mean | 98.1 | 97.7 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |
| | | | | %CV | 1.5 | 1.1 |
| | Nexium®, Batch # K003153 Expiry Date: Dec 2016 | 40 mg Capsule | 12 | Mean | 97.7 | 97.3 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |
| | | | | %CV | 1.1 | 1.1 |
| pH 6.5 | Test, Batch # Y31825 Manufacturing Date: 07/2013 | 20 mg Capsule | 12 | Mean | 102.16 | 99.71 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |
| | | | | %CV | 0.75 | 0.83 |
| | Nexium®, Batch # K005263 Expiry Date: Dec 2016 | 20 mg Capsule | 12 | Mean | 99.71 | 100.05 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |
| | | | | %CV | 0.83 | 1.24 |
| | Test, Batch # Y31828 Manufacturing Date: 07/2013 | 40 mg Capsule | 12 | Mean | 97.69 | 97.82 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |
| | | | | %CV | 1.11 | 0.96 |
| | Nexium®, Batch # K003153 Expiry Date: Dec 2016 | 40 mg Capsule | 12 | Mean | 97.82 | 97.96 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |
| | | | | %CV | 0.96 | 1.17 |
| pH 7.5 | Test, Batch # Y31825 Manufacturing Date: 07/2013 | 20 mg Capsule | 12 | Mean | 99.88 | 100.24 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | %CV | 1.83 | 1.28 |
| | Nexium®, Batch # K005263 Expiry Date: Dec 2016 | 20 mg Capsule | 12 | Mean | 100.24 | 99.79 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |
| | | | | %CV | 1.28 | 1.51 |
| | Test, Batch # Y31828 Manufacturing Date: 07/2013 | 40 mg Capsule | 12 | Mean | 98.07 | 96.88 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |
| | | | | %CV | 1.27 | 0.65 |
| | Nexium®, Batch # K003153 Expiry Date: Dec 2016 | 40 mg Capsule | 12 | Mean | 96.88 | 98.27 |
| | | | | Min | (b) (4) | |
| | | | | Max | | |
| | | | | %CV | 0.65 | 1.05 |

**Table 8: Geometric Means and 90% Confidence Intervals - Reviewer Calculated**

| Esomeprazole DR Capsules, 20 mg and 40 mg<br>Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals | | | | | | | |
|---|---|---|---|---|---|---|---|
| Comparative Recovery Testing | | | | | | | |
| Water pH | Strength | Time | Test | Reference | Ratio | 90% C.I. | |
| 5.5 | 20 mg | 0 min | 99.52924 | 99.59195809 | 0.99937 | 98.7014 | 101.188 |
| | | 15 min | 99.50945 | 99.6286595 | 0.998803 | 98.0720 | 101.722 |
| | 40 mg | 0 min | 98.04755 | 97.64463349 | 1.004126 | 99.4741 | 101.360 |
| | | 15 min | 98.04803 | 97.31090503 | 1.007575 | 99.8176 | 101.706 |
| 6.5 | 20 mg | 0 min | 102.1558 | 99.70514986 | 1.024579 | 101.896 | 103.023 |
| | | 15 min | 100.6712 | 100.0429415 | 1.006279 | 99.8627 | 101.399 |
| | 40 mg | 0 min | 97.68594 | 97.81233455 | 0.998708 | 99.1321 | 100.615 |
| | | 15 min | 98.10695 | 97.95192325 | 1.001583 | 99.2224 | 101.103 |
| 7.5 | 20 mg | 0 min | 99.86812 | 100.2341831 | 0.996348 | 98.5434 | 100.738 |
| | | 15 min | 100.3988 | 99.78114117 | 1.00619 | 99.5818 | 101.667 |
| | 40 mg | 0 min | 98.05917 | 96.87302295 | 1.012244 | 100.498 | 101.956 |
| | | 15 min | 98.46274 | 98.26150363 | 1.002048 | 99.5022 | 100.912 |

The 90% confidence intervals for the recovery study in various pH media for both 20 mg and 40 mg with 0 and 15 minutes soaking calculated by the reviewer were in agreement with the values reported by the firm. As, shown in table 8 above, the point estimate and 90% CI for the least squares geometric means of the recovery of Esomeprazole at 0 min and 15 min meet the 90% CI criteria of 80-125% for the recovery testing.

The recovery testing for the strengths of 20 mg and 40 mg test product at 0 min and 15 min with water pH 5.5, 6.5 and 7.5 is acceptable. The firm's response is satisfactory.

### 3.3.4 Deficiency #4:

*Please provide the expiration date for the reference listed product (20 mg: batch #J014509; 40 mg: batch# J012025) and testing dates for your particle size distribution study and acid resistance testing submitted in your current amendment dated 3/31/2014.*

**Firm's Response:**
Please find below the requested information:

The expiration date for the reference listed product 20 mg, batch # J014509 is May 2016.

The expiration date for the reference listed product 40 mg, batch # J012025 is July 2016.

Testing completion date for particle size distribution study submitted in amendment dated March 31, 2014 is March 25, 2014.

Testing Completion date for acid resistance study submitted in amendment dated March 31, 2014 is March 23, 2014.

**Reviewer's Comments:**
The firm's response is satisfactory.

## 3.4 Deficiency Comments

None.

## 3.5 Recommendations

1. The single-dose, *in vivo* **fasting** bioequivalence study (#P1BD05001) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable.**

2. The single-dose, *in vivo* **fed** bioequivalence study (#P1BD05002) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable**.

3. The single-dose, *in vivo* **sprinkled fasting** bioequivalence study (#P1BD05010) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable**.

4. The *in vitro* dissolution testing conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 20 mg (Lot #Y51231) and 40 mg (Lot # Y51232, same as Lot#Y51286 used in the *in vivo* bioequivalence studies, but different package number), comparing to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 20 mg (Lot#P4879) and 40 mg (Lot #N5819), is **acceptable**.

   The dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b)(4)% in 120 minutes<br>Buffer stage: NLT (b)(4)% in 30 minutes |

5. The firm's in vitro comparative nasogastric (NG tube) studies are now acceptable.

6. The 20 mg strength is proportionally formulated to the 40 mg strength. The DB deems the 20 mg strength of the test product to be bioequivalent to the 20 mg strength of the reference product based on CFR 320.24(b)(6).

# 4 APPENDIX

## 4.1 Formulation Data

### Test Product[13]

| Ingredient | 20 mg (mg/Capsule) | wt/wt (%) 20 mg | 40 mg (mg/Capsule) | wt/wt (%) (40 mg) |
|---|---|---|---|---|
| [redacted] | | | | |

(b) (4)

### Reference Product[14]

| Composition of Nexium® Delayed-Release Capsules | | |
|---|---|---|
| **Component** | **EQ. 20.00 mg Base strength (mg)** | **EQ. 40.00 mg Base strength (mg)** |
| Esomeprazole as Magnesium Trihydrate | 22.30 | 44.50 |
| Glyceryl monostearate (b) (4) | [redacted] | (b) (4) |
| Hydroxypropyl Cellulose | | |
| Magnesium Stearate | | |
| Methacrylic Acid Copolymer Type C | | |

[13] v:\Firmsam\IvaxPharm\ltrs&rev\78003N1105.doc

[14] Control Document # 03-165; Esomeprazole Magnesium Delayed-Release Capsules.

| | | | |
|---|---|---|---|
| Polysorbate 80 | | (b) (4) | |
| Sugar spheres (b) (4) | | | |
| Talc | | | |
| Hard gelatin capsules | | | |

**Formulation Data**

| | RLD | IVAX |
|---|---|---|
| (b) (4) | | |

Diameter of Size of feeding tube (1 French unit=0.33 millimeters):
16 French = 5.28 mm
8 French =2.666 mm

## 4.2 Attachments

### 4.2.1 Particle Size Distribution Data

**STUDY SUMMARY**

**Product** : Esomeprazole Magnesium Delayed Release capsules 20 mg & 40mg.

**Method** : Particle size distribution of pellets by Laser diffraction

**A.R. No.** : T14080604



**VII. STUDY RESULT:**

**Cipla Product - 20mg strength at pH 5.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 11.1 | 14.4 | 22.0 | 26.5 | 16.7 | 55.3 | 19.6 | 22.7 | 48.2 |
| %RSD | 1.9 | 1.8 | 1.9 | 4.7 | 2.1 | 4.7 | 3.3 | 2.8 | 4.1 |

**Cipla Product - 20mg strength at pH 6.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 11.1 | 14.4 | 22.0 | 18.2 | 19.3 | 30.4 | 12.6 | 11.2 | 20.0 |
| %RSD | 1.9 | 1.8 | 1.9 | 3.1 | 2.4 | 2.6 | 2.1 | 1.4 | 1.7 |

**Cipla Product - 20mg strength at pH 7.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 11.1 | 14.4 | 22.0 | 20.4 | 21.9 | 32.7 | 10.4 | 14.7 | 30.1 |
| %RSD | 1.9 | 1.8 | 1.9 | 3.5 | 2.7 | 2.9 | 1.8 | 1.8 | 2.6 |

**VII. STUDY RESULT (Contd .....) :**

**Cipla Product - 40mg strength at pH 5.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 6.1 | 7.8 | 13.3 | 8.1 | 11.4 | 17.8 | 24.7 | 12.4 | 33.4 |
| %RSD | 1.0 | 1.0 | 1.2 | 1.3 | 1.4 | 1.5 | 4.1 | 1.5 | 2.8 |

**Cipla Product - 40mg strength at pH 6.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 6.1 | 7.8 | 13.3 | 7.0 | 9.9 | 16.3 | 8.6 | 14.0 | 22.7 |
| %RSD | 1.0 | 1.0 | 1.2 | 1.2 | 1.2 | 1.4 | 1.4 | 1.7 | 1.9 |

**Cipla Product - 40mg strength at pH 7.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 6.1 | 7.8 | 13.3 | 8.0 | 11.6 | 22.3 | 9.9 | 12.7 | 17.3 |
| %RSD | 1.0 | 1.0 | 1.2 | 1.4 | 1.4 | 1.9 | 1.6 | 1.5 | 1.4 |

**Reference Product - 20mg strength at pH 5.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 9.3 | 7.6 | 14.4 | 11.8 | 9.6 | 17.4 | 18.3 | 8.2 | 21.8 |
| %RSD | 2.2 | 1.3 | 1.8 | 2.7 | 1.6 | 2.1 | 4.1 | 1.3 | 2.6 |

**Reference Product - 20mg strength at pH 6.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 9.3 | 7.6 | 14.4 | 12.2 | 10.8 | 21.2 | 20.5 | 12.8 | 23.9 |
| %RSD | 2.2 | 1.3 | 1.8 | 2.8 | 1.8 | 2.6 | 4.7 | 2.1 | 2.9 |

**Reference Product - 20mg strength at pH 7.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 9.3 | 7.6 | 14.4 | 21.3 | 14.1 | 23.0 | 20.1 | 7.3 | 12.5 |
| %RSD | 2.2 | 1.3 | 1.8 | 4.9 | 2.3 | 2.8 | 4.7 | 1.2 | 1.5 |

**Reference Product - 40mg strength at pH 5.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 9.9 | 15.1 | 29.2 | 10.7 | 9.9 | 20.0 | 172.3 | 9.2 | 9.8 |
| %RSD | 2.3 | 2.6 | 3.7 | 2.4 | 1.6 | 2.4 | 72.7 | 1.5 | 1.1 |

**Reference Product - 40mg strength at pH 6.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 9.9 | 15.1 | 29.2 | 18.5 | 9.9 | 17.6 | 187.5 | 8.9 | 20.7 |
| %RSD | 2.3 | 2.6 | 3.7 | 4.2 | 1.6 | 2.1 | 74.9 | 1.4 | 2.4 |

**Reference Product - 40mg strength at pH 7.5**

| Sr. No | Initial (µm) | | | 0 Minute Soak (µm) | | | 15 Minutes Soak (µm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | D10 | D50 | D90 | D10 | D50 | D90 | D10 | D50 | D90 |
| 1 | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| Mean | | | | | | | | | |
| SD | 9.9 | 15.1 | 29.2 | 8.6 | 9.1 | 16.6 | 13.0 | 10.8 | 26.8 |
| %RSD | 2.3 | 2.6 | 3.7 | 1.9 | 1.5 | 2.0 | 3.0 | 1.8 | 3.2 |

### 4.2.2 Particle Size Distribution Representative Photographs

| Strength | | 0 min | 0 min in Beaker | 15 mins | 15 mins in beaker |
|---|---|---|---|---|---|
| 20 mg Test | pH 5.5 | (b) (4) | | | |
| | pH 6.5 | | | | |
| | pH 7.5 | | | | |

| | | |
|---|---|---|
| 40 mg Test | pH 5.5 | (b) (4) |
| | pH 6.5 | |
| | pH 7.5 | |
| 20 mg RLD | pH 5.5 | |

| | | |
|---|---|---|
| | pH 6.5 | (b) (4) |
| | pH 7.5 | |
| 40 mg RLD | pH 5.5 | |
| | pH 6.5 | |

| | | |
|---|---|---|
| | pH 7.5 | (b) (4) |

### 4.2.3 Acid Resistance Study Data

**A) % RELEASE IN ACID STAGE (ACID RESISTANCE STABILITY) THROUGH CATHETER TIPPED SYRINGE IN COMBINATION WITH 8.0 FRENCH NASOGASTRIC FEEDING TUBE OF MATERIAL PVC MANUFACTURED BY KENDALL ARGYLE**

| CIPLA (8.0 FRENCH) WATER pH 7.5 (0 minutes soak) | | | | | | |
|---|---|---|---|---|---|---|
| | For 20mg | | | For 40mg | | |
| Sr. No. | Assay mean (%LC) | Content of Esomeprazole after acid stage (mg/cap) | % Assay after acid treatment | Assay mean (%LC) | Content of Esomeprazole after acid stage (mg/cap) | % Assay after acid treatment |
| 1 | 102.6 | (b) (4) | | 99.7 | (b) (4) | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | | 20.01 | 100.0 | | 39.46 | 98.7 |
| Minimum | | (b) (4) | | | (b) (4) | |
| Maximum | | | | | | |
| SD | | 0.473 | 2.365 | | 0.507 | 1.268 |
| % RSD | | 2.4 | 2.4 | | 1.3 | 1.3 |

| CIPLA (8.0 FRENCH) WATER pH 7.5 (15 minutes soak) | | | | | | |
|---|---|---|---|---|---|---|
| | For 20mg | | | For 40mg | | |
| Sr. No. | Assay mean (%LC) | Content of Esomeprazole after acid stage (mg/cap) | % Assay after acid treatment | Assay mean (%LC) | Content of Esomeprazole after acid stage (mg/cap) | % Assay after acid treatment |
| 1 | 102.6 | (b) (4) | | 99.7 | (b) (4) | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | | 19.73 | 98.7 | | 38.86 | 97.1 |
| Minimum | | (b) (4) | | | (b) (4) | |
| Maximum | | | | | | |
| SD | | 0.229 | 1.144 | | 0.718 | 1.794 |
| % RSD | | 1.2 | 1.2 | | 1.8 | 1.8 |

| REFERENCE PRODUCT (8.0 FRENCH) WATER pH 7.5 (0 minutes soak) | | | | | | |
|---|---|---|---|---|---|---|
| Sr. No. | For 20mg | | | For 40mg | | |
| | Assay mean (%LC) | Content of Esomeprazole after acid stage (mg/cap) | % Assay after acid treatment | Assay mean (%LC) | Content of Esomeprazole after acid stage (mg/cap) | % Assay after acid treatment |
| 1 | 100.9 | (b) (4) | | 100.6 | (b) (4) | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | | 19.71 | 98.5 | | 36.30 | 90.8 |
| Minimum | | (b) (4) | | | (b) (4) | |
| Maximum | | | | | | |
| SD | | 0.138 | 0.691 | | 3.080 | 7.700 |
| % RSD | | 0.7 | 0.7 | | 8.5 | 8.5 |

| REFERENCE PRODUCT (8.0 FRENCH) WATER pH 7.5 (15 minutes soak) | | | | | | |
|---|---|---|---|---|---|---|
| Sr. No. | For 20mg | | | For 40mg | | |
| | Assay mean (%LC) | Content of Esomeprazole after acid stage (mg/cap) | % Assay after acid treatment | Assay mean (%LC) | Content of Esomeprazole after acid stage (mg/cap) | % Assay after acid treatment |
| 1 | 100.9 | (b) (4) | | 100.6 | (b) (4) | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | | 19.37 | 96.8 | | 8.65 | 21.6 |
| Minimum | | (b) (4) | | | (b) (4) | |
| Maximum | | | | | | |
| SD | | 0.478 | 2.390 | | 4.979 | 12.448 |
| % RSD | | 2.5 | 2.5 | | 57.6 | 57.6 |

### 4.2.4 Comparative Recovery Study Data (Catheter Tipped Syringe in combination with 8.0 French NG tube)

| SAMPLE | FOR 20 MG [at 0 minutes] pH 5.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay = 102.6 | | % Initial Assay = 100.9 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | (b) (4) |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 19.91 | 99.5 | 19.92 | 99.6 | 1.00 | 1.00 |
| Minimum | | | | | | (b) (4) |
| Maximum | | | | | | |
| SD | 0.328 | 1.641 | 0.380 | 1.902 | 0.022 | 0.022 |
| % RSD | 1.6 | 1.6 | 1.9 | 1.9 | 2.2 | 2.2 |
| 90%CI – Upper Level | mg/cap =101.20<br>% LC = 101.19 | | | | | |
| 90%CI – Lower Level | mg/cap = 98.70<br>% LC = 98.70 | | | | | |

| SAMPLE | FOR 20 MG [at 15 minutes] pH 5.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay = 102.6 | | % Initial Assay = 100.9 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | (b) (4) |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 19.91 | 99.6 | 19.93 | 99.7 | 1.00 | 1.00 |
| Minimum | | | | | | (b) (4) |
| Maximum | | | | | | |
| SD | 0.530 | 2.649 | 0.505 | 2.523 | 0.031 | 0.031 |
| % RSD | 2.7 | 2.7 | 2.5 | 2.5 | 3.1 | 3.1 |
| 90%CI – Upper Level | mg/cap =101.73<br>% LC = 101.72 | | | | | |
| 90%CI – Lower Level | mg/cap = 98.09<br>% LC = 98.07 | | | | | |

| SAMPLE | FOR 40 MG [at 0 minutes] pH 5.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay = 99.7 | | % Initial Assay = 100.6 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | (b) (4) |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 39.22 | 98.0 | 39.06 | 97.6 | 1.01 | 1.01 |
| Minimum | | | | | | (b) (4) |
| Maximum | | | | | | |
| SD | 0.610 | 1.524 | 0.428 | 1.069 | 0.017 | 0.017 |
| % RSD | 1.6 | 1.6 | 1.1 | 1.1 | 1.7 | 1.7 |
| 90%CI – Upper Level | mg/cap =101.35<br>% LC = 101.36 | | | | | |
| 90%CI – Lower Level | mg/cap = 99.48<br>% LC = 99.47 | | | | | |

| SAMPLE | FOR 40 MG [at 15 minutes] pH 5.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay = 99.7 | | % Initial Assay = 100.6 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | (b) (4) |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 39.23 | 98.1 | 38.93 | 97.3 | 1.01 | 1.01 |
| Minimum | | | | | | (b) (4) |
| Maximum | | | | | | |
| SD | 0.602 | 1.506 | 0.439 | 1.099 | 0.018 | 0.018 |
| % RSD | 1.5 | 1.5 | 1.1 | 1.1 | 1.8 | 1.8 |
| 90%CI – Upper Level | mg/cap = 101.73<br>% LC = 101.71 | | | | | |
| 90%CI – Lower Level | mg/cap = 99.83<br>% LC = 99.82 | | | | | |

| SAMPLE | FOR 20 MG [at 0 minutes] pH 6.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay = 102.6 | | % Initial Assay = 100.9 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 20.43 | 102.2 | 19.94 | 99.7 | 1.03 | 1.03 |
| Minimum | | | | | | |
| Maximum | | | | | | |
| SD | 0.147 | 0.737 | 0.166 | 0.831 | 0.014 | 0.014 |
| % RSD | 0.7 | 0.7 | 0.8 | 0.8 | 1.3 | 1.4 |
| 90%CI – Upper Level | mg/cap =103.03<br>% LC = 103.02 | | | | | |
| 90%CI – Lower Level | mg/cap = 101.92<br>% LC = 101.90 | | | | | |

(b) (4)

| SAMPLE | FOR 20 MG [at 15 minutes] pH 6.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay = 102.6 | | % Initial Assay = 100.9 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 20.14 | 100.7 | 20.01 | 100.1 | 1.01 | 1.01 |
| Minimum | | | | | | |
| Maximum | | | | | | |
| SD | 0.183 | 0.914 | 0.251 | 1.254 | 0.014 | 0.014 |
| % RSD | 0.9 | 0.9 | 1.3 | 1.3 | 1.3 | 1.3 |
| 90%CI – Upper Level | mg/cap =101.41<br>% LC = 101.40 | | | | | |
| 90%CI – Lower Level | mg/cap = 99.86<br>% LC = 99.86 | | | | | |

(b) (4)

| SAMPLE | FOR 40 MG [at 0 minutes] pH 6.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay = 99.7 | | % Initial Assay = 100.6 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | (b) (4) |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 39.08 | 97.7 | 39.13 | 97.8 | 1.00 | 1.00 |
| Minimum | | | | | | (b) (4) |
| Maximum | | | | | | |
| SD | 0.440 | 1.099 | 0.388 | 0.971 | 0.014 | 0.014 |
| % RSD | 1.1 | 1.1 | 1.0 | 1.0 | 1.4 | 1.4 |
| 90%CI – Upper Level | mg/cap =100.62<br>% LC = 100.61 | | | | | |
| 90%CI – Lower Level | mg/cap = 99.14<br>% LC = 99.13 | | | | | |

| SAMPLE | FOR 40 MG [at 15 minutes] pH 6.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay = 99.7 | | % Initial Assay = 100.6 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | (b) (4) |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 39.24 | 98.1 | 39.18 | 97.9 | 1.00 | 1.00 |
| Minimum | | | | | | (b) (4) |
| Maximum | | | | | | |
| SD | 0.574 | 1.435 | 0.469 | 1.172 | 0.021 | 0.021 |
| % RSD | 1.5 | 1.5 | 1.2 | 1.2 | 2.1 | 2.1 |
| 90%CI – Upper Level | mg/cap = 101.10<br>% LC = 101.10 | | | | | |
| 90%CI – Lower Level | mg/cap = 99.23<br>% LC = 99.22 | | | | | |

| SAMPLE | FOR 20 MG [at 0 minutes] pH 7.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay = 102.6 | | % Initial Assay = 100.9 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 19.98 | 99.9 | 20.05 | 100.2 | 1.00 | 1.00 |
| Minimum | | | | | | |
| Maximum | | | | | | |
| SD | 0.366 | 1.831 | 0.253 | 1.264 | 0.024 | 0.024 |
| % RSD | 1.8 | 1.8 | 1.3 | 1.3 | 2.4 | 2.4 |
| 90%CI – Upper Level | mg/cap =100.75<br>% LC = 100.74 | | | | | |
| 90%CI – Lower Level | mg/cap = 98.56<br>% LC = 98.55 | | | | | |

(b) (4)

| SAMPLE | FOR 20 MG [at 15 minutes] pH 7.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay =102.6 | | % Initial Assay = 100.9 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 20.08 | 100.4 | 19.96 | 99.8 | 1.01 | 1.01 |
| Minimum | | | | | | |
| Maximum | | | | | | |
| SD | 0.287 | 1.437 | 0.302 | 1.512 | 0.015 | 0.016 |
| % RSD | 1.4 | 1.4 | 1.5 | 1.5 | 1.5 | 1.6 |
| 90%CI – Upper Level | mg/cap =101.67<br>% LC = 101.67 | | | | | |
| 90%CI – Lower Level | mg/cap = 99.59<br>% LC = 99.58 | | | | | |

(b) (4)

| SAMPLE | FOR 40 MG [at 0 minutes] pH 7.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay = 99.7 | | % Initial Assay = 100.6 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 39.23 | 98.1 | 38.75 | 96.9 | 1.01 | 1.01 |
| Minimum | | | | | | |
| Maximum | | | | | | |
| SD | 0.505 | 1.263 | 0.261 | 0.653 | 0.017 | 0.017 |
| % RSD | 1.3 | 1.3 | 0.7 | 0.7 | 1.7 | 1.7 |
| 90%CI – Upper Level | mg/cap =101.97<br>% LC = 101.96 | | | | | |
| 90%CI – Lower Level | mg/cap = 100.52<br>% LC = 100.50 | | | | | |

(b) (4)

(b) (4)

| SAMPLE | FOR 40 MG [at 15 minutes] pH 7.5 | | | | | |
|---|---|---|---|---|---|---|
| | CIPLA | | REFERENCE PRODUCT | | T / R RATIO | |
| | % Initial Assay = 99.7 | | % Initial Assay = 100.6 | | | |
| | mg/Cap | % LC | mg/Cap | % LC | mg/Cap | % LC |
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | 39.39 | 98.5 | 39.31 | 98.3 | 1.00 | 1.00 |
| Minimum | | | | | | |
| Maximum | | | | | | |
| SD | 0.373 | 0.932 | 0.416 | 1.041 | 0.016 | 0.015 |
| % RSD | 0.9 | 0.9 | 1.1 | 1.1 | 1.6 | 1.5 |
| 90%CI – Upper Level | mg/cap = 100.92<br>% LC = 100.91 | | | | | |
| 90%CI – Lower Level | mg/cap = 99.51<br>% LC = 99.50 | | | | | |

(b) (4)

(b) (4)

### 4.2.5 Comparative Recovery Study Photographs (Catheter Tipped Syringe in combination with 8.0 French NG tube)[15]

| Strength | | 0 min | 0 min in Beaker | 15 mins | 15 mins in beaker |
|---|---|---|---|---|---|
| 20 mg Test | pH 5.5 | (b) (4) | | | |
| | pH 6.5 | | | | |

[15] The firm also provided the pellets in NG tube in the current amendment. However, those pictures can not represent clearly the pellets and thus the reviewer did not attach those in the review.

| | | |
|---|---|---|
| | pH 7.5 | (b) (4) |
| 40 mg Test | pH 5.5 | |

| | | |
|---|---|---|
| | pH 6.5 | (b) (4) |
| | pH 7.5 | |
| 20 mg RLD | pH 5.5 | |

| | | |
|---|---|---|
| | pH 6.5 | (b) (4) |
| | pH 7.5 | |
| 40 mg RLD | pH 5.5 | |

| | | |
|---|---|---|
| | pH 6.5 | (b) (4) |
| | pH 7.5 | |

### 4.2.6 Internal Meeting Minutes (04/11/2014)

**Internal Meeting Minutes**

| | |
|---|---|
| **Topic**: | Esomeprazole Delayed Release Capsules, 20 mg and 40 mg (Control 140139) |
| **Date:** | Friday, April 11th, 2014, 3:30 PM to 4:30 PM |
| **Meeting Location:** | MM2 Third Floor Room 373 |
| **FDA Attendees:** | John Peters, Ethan Stier, Xiaojian Jiang, Minglei Cui, Ping Ren, and Nabeel Babaa (meeting recorder) |

**Background Summary**

This meeting was arranged to discuss issues identified in several applications of the noted drug product and the impact of these findings to the current draft guidance. Control 140139 is intended to revise the current FDA guidance on Esomeprazole Magnesium and request comparative *in vitro* NG tube tests (sedimentation testing, particle size distribution study, recovery testing, and acid resistance stability testing) to compare the performance of the test product to that of the reference product under NG tube administration.

(b) (4) applications in house failed acid resistance test for the reference product. U. The failed acid resistance data from (b) (4) were summarized and referenced. The ultimate goal of the meeting was to finalize the guidance as there are (b) (4) ANDAs pending its completion, to discuss acid resistance testing condition, and to discuss the allowed difference in particle size between test and reference product if the recovery test passed.

**Discussion**

(b) (4)
(b) (4)
(b) (4).

**ANDA 078003:**

**Acid Resistance Test Data for** It was noted that the firm conducted the acid resistance test in water with pHs of 5.4, 5.9, and 6.4 instead of pH 6, 7 and 8 as recommended. The firm justified this by saying that the former pH values best represent water in hospital setting; however, no reference source for this assertion was provided. For the 20 mg strength, approximately 20% and 80% of reference drug were released from enteric coated pellets after soaking in water (pH 5.4, 5.9 and 6.4) for 30 and 60 minutes, respectively whereas less than (b) (4)% of test product was released under the same conditions. For the 40 mg strength, approximately 90% of reference product was released after soaking in the water for 15, 30 or 60 minutes, whereas less than (b) (4)% of the test product was released under the same treatment conditions.

**Particle Size Microscopy**: It was noted that in the case of the 20 mg and 40 strengths of the reference product, the pellets started to rupture, disintegrate, and were irregular in shape after 30 and 15 minutes of soaking time, respectively. In contrast, for the 20 mg and 40 mg strengths of the test product, the pellets remained intact throughout soaking and maintained their oval to circular shape. It was noted that if microscopy data is not accurate, particle size data can be measured using laser diffraction. It should be noted that the particle size of the test product is slightly larger than that of reference products based on Microscopy data (approximately $D_{50}$ 0.8 mm reference vs. 0.6 mm test).

(b) (4)

[redacted]

**Proposals:**

1. Based above ANDAs, we recommend the in vitro NG tube testing to be conducted in water with pH 5.5, 6.5, and 7.5 at soaking time 0 and 15 min (instead of previous 15, 30 and 60 min).

   Proposal #1 was agreed upon. It was noted that the pH of tap water ranges from 6.5 to 8.5, and the mean pH value of sterile water pH is 5.5.

2. Discuss with Division of New Drug on issues regarding failed acid resistance test of the RLD after soaking in water for a period of time, e.g. even for 15 min. (note: labeling does indicate immediate delivery)[16]

   Proposal #2 was dismissed. We do not need to discuss with Division of New Drug on issues regarding failed acid resistance test of the RLD after soaking in water for a period of time, e.g. even for 15 min since the RLD label indicates immediate delivery (the data show acceptable acid resistance at 0 min for the RLD). The in vitro data would be acceptable if the test product shows acid résistance no worse than that of the RLD.

3. How to evaluate acid resistance testing. Should the test be no worse than RLD in all pH, and 0 or 15 min?

   Proposal #3 pertaining to evaluating acid resistance testing was agreed upon.

4. Ask FDA lab to conduct the in vitro NG tube study for the reference product and some problematic test product. In history, generic firm submitted acceptable NG tube studies for its product (particle size different, but acceptable recovery and acid resistance test). However, the FDA's lab data showed failed results.

   Proposal #4 was agreed upon. It was agreed that the new guidance not be posted until after the FDA lab completes their analysis. The FDA lab can forward the data to the new drug division.

5. How to evaluate data if the firm does not conduct the pH we recommended for In vitro NG tube testing (such as 78003)

   a. Ask firm re-conduct the study in our recommended pH

   b. Further discussion on allowed difference on enteric coated particle size between the test and reference product (include Chemistry division) if recover test is passed.

   c. Studies on NG tube with different material?

Proposal #5 was agreed upon. We should ask the firm to re-conduct the study in our recommended pH. In this manner, we will accept the test product as long as it doesn't release more than the RLD, even if it technically fails the acid resistance test according to the less than (b) (4)% release criteria.

**Action Items**

1. Deficiency letter can be sent but hold off on posting the new guidance until after the FDA lab conducts its test, per Proposal #4. The new guidance will include our recommended pH values of 5.5, 6.5, and 7.5 for NG tube testing in water, as well as a soaking time of 0

[16] NDA chemistry indicated that the reference product is stable up to 30 min in tape water with pH 7.8.

min and 15 min. Note: the pH of tap water ranges from 6.5 to 8.5 and the mean pH value of sterile water is 5.5.

2. Ask FDA lab to conduct the in vitro NG tube study for the reference product and some test product, per Proposal #4. The DB should coordinate with science team on the testing.

3. The drug specific guidance should recommend the laser method for measuring particle size in lieu of microscopy. The DB can summarize the particle size method in lansoprazole and esomeprazole applications and reference the nasal guidance to determine the appropriate method.

4. For ANDA 78003, firm should conduct the study using our recommended pH. The particle size is acceptable. There is no need to ask the NG tube study with different materials. The criteria will be: if the test product doesn't release more than the RLD it will pass ( even if it technically fails the acid resistance test according to the less than (b) (4) % release criteria).

Draft by: Nabeel Babaa (04/16/2014)

Comments: Minglei Cui (04/18/2014)

Comments: Xiaojian Jiang (04/20/2014)

Comments: Ethan Stier (04/21/2014)

### 4.2.7 Internal Email Regarding the NG tube Study

**From:** Jiang, Xiaojian
**Sent:** Friday, May 09, 2014 9:39 AM
**To:** Lionberger, Robert
**Cc:** Stier, Ethan; Huang, Yih Chain; Peters, John (CDER); Cui, Minglei; Wen, Hong
**Subject:** RE: NG tube guidance for esomeprazole manesium DR capsule

Thanks, Rob
Yes, for the particle size, we do not require to pass the statistical analysis if the recover studies are fine.
Sedimentation volume is a test copied from the FDA lab when they did it for lansoprazole ODT (b) (4) It is measurement of the total mass settling in the syringe.
It seems useful only for lansoprazole ODT but not for beaded capsule because all the beads fall down in the bottom, volume is less than 1 ml.

Since we have detailed instruction how to measure the sedimentation in the guidance, the firm appears not having problem and it is pretty easy to measure.

"Sedimentation testing measures the settling of particle or floccules occur under gravitational force in liquid condition. Sedimentation velocity (v) is directly

proportional to the square of diameter of particle and inversely proportional to viscosity of dispersion medium. "

Will talk to Team leader and Reviewer to see if we can find simple word to explain sedimentation volume in the guidance..

Thanks a lot.
Xiaojian

**From:** Lionberger, Robert
**Sent:** Friday, May 09, 2014 8:39 AM
**To:** Jiang, Xiaojian
**Cc:** Stier, Ethan; Huang, Yih Chain; Peters, John (CDER); Cui, Minglei; Wen, Hong
**Subject:** RE: NG tube guidance for esomeprazole manesium DR capsule

In general, we agree with the proposed tests. I want to confirm that there is not an intention to require equivalence in the granule size distribution, if the recovery studies are acceptable. (This was my interpretation of the guidance)

I am not exactly sure what the sedimentation volume is, so probably need to describe it more in the guidance.

Rob

**From:** Jiang, Xiaojian
**Sent:** Tuesday, May 06, 2014 8:21 PM
**To:** Lionberger, Robert
**Cc:** Stier, Ethan; Huang, Yih Chain; Peters, John (CDER); Cui, Minglei
**Subject:** FW: NG tube guidance for esomeprazole manesium DR capsule

Dear Rob,

We have been working on the control to revise the draft guidance for Esomeprazole. The new guidance will include the NG tube requirements in addition to previous fasting, fed and fasting sprinkle studies. We have discussed the draft guidance with Dr. John Peters and would like you to take a look at the draft guidance before we post it as requested by John (see below email). Please find the attached control and draft guidance and let us know your concurrence if we can post the guidance by Friday, May 9, 2014). Thank you very much for your advice in advance.

The following are some background for NG tube project:
Nasogastric (NG) tubes are sometimes used to administer medication to patients who are unable to safely swallow or tolerate oral intake. One such product that can be administered in this manner is the Proton Pump Inhibitor (PPI), Lansoprazole,

esomeprazole, omeprazole, and lansoprazole delayed-release orally disintegrating tablets. We have TSI issue with Teva's now discontinued ANDA 078730, Lansoprazole Delayed-Release Orally Disintegrating Tablets (LODT).

Since 2011, through several internal meetings with chemistry, it was conclude that In vitro NG testing should be requested if a product is a solid oral dosage form and contains instructions for NG tube administration in the RLD labeling. So far we have sent the NG tube requirements to quite number of ANDAs mostly for PPI drug products (e.g. lansoprazole, esomeprazole, omeprazole, [redacted] (b) (4)) through deficiency letters. However, we believe that posting daft guidance immediately will benefit both FDA and generic companies the most due to the following reasons:

1. The current guidance do not have NG tube study requirement. The firm will only know NG tube requirement through our deficiency letter after their submission. We can refuse to file the applications with the new guidance. With GUDUFA deadline, this may help us to meet the 10 month deadline.

2. If the firm knows that NG tube requirement ahead of time, they will be more careful on particle size design. They will less likely fall in the situation in which fasting, fed and fasting sprinkle studies all passed 90% confidence acceptance criteria but they have to reformulate the test product due to failed recovery NG tube studies as the result of large particle size (which we saw in same cases now).

We also learn during our review of some NG tube studies submitted by the applicants, different pH of water can damage the enteric coating. So we asked the firm to conduct testing in different pH of water if the label indicates that water is the medium. In case where that apple juice is used for NG tube administration (e.g. lansoprazole DR capsule), there is no need to using different type of juice. We also had agreement with CMC division, they will also send out deficiencies asking in vitro study using different tube material etc. Bio will do statistical comparison while, CMC conducts qualitative evaluation for the comparison.

Sincerely,
Xiaojian

**From:** Peters, John (CDER)
**Sent:** Friday, May 02, 2014 10:54 AM
**To:** Jiang, Xiaojian
**Cc:** Cui, Minglei; Stier, Ethan
**Subject:** RE: NG tube guidance

Makes sense. When the draft is complete let's make sure that we have Rob's ok too. He was at the meetings so should be up to date on the content of the draft.

Tx

J

**From:** Jiang, Xiaojian
**Sent:** Thursday, May 01, 2014 10:25 AM
**To:** Peters, John (CDER)
**Cc:** Cui, Minglei; Stier, Ethan
**Subject:** NG tube guidance

Hi, John
At our last meeting (4/11/2014), we decided to postpone posting the draft guidance for Esomeprazole until FDA conduct and finish confirmative NG tube studies for reference and some test products for us. The new guidance will include the NG tube requirements in addition to previous fasting, fed and fasting sprinkle studies.
However after giving some more thought for GDUFA deadlines and the current guidance, we would like to suggest posting the draft guidance now instead of waiting for FDA's label results due to the following reasons:

1. The current guidance do not have NG tube study requirement. The firm will only know NG tube requirement through deficiency letter after their submission. With GUDUFA deadline, this may post a risk for us missing 10 month deadline.

2. If the firm knows that NG tube requirement ahead of time, they will be more careful on particle size design. They will less likely fall in the situation in which fasting, fed and fasting sprinkle studies all passed 90% confidence acceptance criteria but they have to reformulate the test product due to failed recovery NG tube studies as the result of large particle size (which we saw now).

3. The FDA lab studies may take a long time. The draft guidance can be changed anytime if the lab result indicates that change is necessary. However, because the guidance we proposed is using a very conservative method, it is less likely that more studies will be required based on the lab results (most likely reducing the amount of testing)

Based above rationale, we suggest posting guidance now and would like to get your approval on this decision.

Thanks,
Xiaojian

### 4.2.8 DB II Biomanagement Meeting Minutes (05/13/2014)

**DBII Bio Management Meeting Minutes**

**Meeting Date:** May 13, 2014
**Meeting Time:** 11:00 am – 12:00 pm
**Meeting Location:** Conference Room 255

**Attendees:** Ethan Stier, Xiaojian Jiang, Parthapratim Chandaroy, Moheb Makary, Svetlana Cherstniakova, Kuldeep Dhariwal, Chandra Chaurasia, Saied Raofi, Minglei Cui, Om Anand, Nabeel Babaa, Chitra Mahadevan, and Diane Nhu

Team 7 – Minglei Cui – please see Attachment 2 for additional data.

**Summary of key issues, background information discussed and discussion:**

| | |
|---|---|
| **OGD Control No./ANDAs** | 140139/ANDA 202784, (b) (4) 78003 |
| **Drug Product Name** | Esomeprazole Delayed Release Capsules |
| **Strength(s)** | 20 mg and 40 mg |

The Division of Bioequivalence (DB) recommendations for the In Vitro Comparative Nasogastric (NG) Tube Studies:

1. Sedimentation testing
2. Particle size distribution study
3. Recovery testing
4. Comparative acid resistance stability testing

As recommended in the approved RLD labeling for Esomeprazole Magnesium Delayed Release Capsules, the product may be administered by NG tube. Therefore, DBII requested sponsors for ANDA 202784, (b) (4) and 078003 to perform comparative in vitro tests to compare the performance of its test to the reference for both strengths (20 mg and 40 mg) under NG tube administration. The firms responded to the deficiency comments in the recent amendment and submitted the comparative in vitro tests using 12 units of both strengths of the test and the reference to compare the performance of its test product to the reference at 0 min and 15 min. Based on new criteria, the sedimentation testing, particle size distribution study, recovery testing are acceptable (reference product failed acid resistance test in some ANDAs).

Since the enteric coating of test product is dissolved at pH > 5.5 and the pH of the water may vary between 6.5 to 8.5, then there is a concern that the process of dispersing a test product in an oral syringe and/or an oral syringe with an NG tube might adversely impact the integrity of the enteric coating. To ensure consistent stability of the enteric coating in water between the test and reference product, the firm needs to conduct additional in vitro study to demonstrate the stability of the dispersed granules in different pH of water within different soak time prior to performing the acid resistance testing.

Issue: Whether recovery studies are needed in addition to acid resistance testing in water with different pH and soaking time. The reason for requesting additional recovery studies are following:

1) (b) (4) in-house (b) (4) showed failed Acid Resistance Test for the RLD under conditions that we previously recommended (different pH and soaking time)

2) DBII requested the firm to re-conduct acid resistance test in the water with different pH and soaking time even if both test and reference passed acid resistance test under certain pH (unknown).

**Question**:
Based on the information provided, the acid resistance may fail in water in different pH and different soaking time. In this case, DBII does not know whether recovery study would also fail in these conditions. Can DBII recommend the firm to re-do recovery studies using different pH of water (e.g. pH 5.5, 6.5 and 7.5) with different soak times in syringe (e.g. 0 and 15 min)?

**Team's proposal and rationale for the proposal:**

Team 7's proposal is to repeat recovery studies using different pH of water (e.g. pH 5.5, 6.5 and 7.5) with different soak times in syringe (e.g. 0 and 15 min) for ANDA 202784, (b) (4) and 78003 due to the following reasons:

1) If the firm measures the drug release in acid resistance test at isosbestic point (for parent drug and degradation) instead of from remaining tablets, we will not know whether the recovery study would fail or not under the same conditions.

2) Since DBII has decided that bioequivalence of particle size is not critical, recovery and acid resistance testing become key studies in NG tube testing.

3) The NG tube studies in updated guidance for Esomeprazole Delayed Release Capsules require the pre-treatment of the test and reference product in water with different pH and soaking time for four studies.

**Management Decision:**

*DBII management concurred with the team's proposal to ask the firm to repeat recovery studies using different pH of water (e.g. pH 5.5, 6.5 and 7.5) with different soak times in syringe (e.g. 0 and 15 min).*

### 4.2.9 Internal Email Regarding the NG tube Study

**From:** Jiang, Xiaojian
**Sent:** Friday, May 09, 2014 9:39 AM
**To:** Lionberger, Robert
**Cc:** Stier, Ethan; Huang, Yih Chain; Peters, John (CDER); Cui, Minglei; Wen, Hong
**Subject:** RE: NG tube guidance for esomeprazole manesium DR capsule

Thanks, Rob
Yes, for the particle size, we do not require to pass the statistical analysis if the recover studies are fine.
Sedimentation volume is a test copied from the FDA lab when they did it for lansoprazole ODT (b) (4) It is measurement of the total mass settling in the syringe.
It seems useful only for lansoprazole ODT but not for beaded capsule because all the beads fall down in the bottom, volume is less than 1 ml.

Since we have detailed instruction how to measure the sedimentation in the guidance, the firm appears not having problem and it is pretty easy to measure.

> "Sedimentation testing measures the settling of particle or floccules occur under gravitational force in liquid condition. Sedimentation velocity (v) is directly proportional to the square of diameter of particle and inversely proportional to viscosity of dispersion medium. "

Will talk to Team leader and Reviewer to see if we can find simple word to explain sedimentation volume in the guidance..

Thanks a lot.
Xiaojian

**From:** Lionberger, Robert
**Sent:** Friday, May 09, 2014 8:39 AM
**To:** Jiang, Xiaojian
**Cc:** Stier, Ethan; Huang, Yih Chain; Peters, John (CDER); Cui, Minglei; Wen, Hong
**Subject:** RE: NG tube guidance for esomeprazole manesium DR capsule

In general, we agree with the proposed tests. I want to confirm that there is not an intention to require equivalence in the granule size distribution, if the recovery studies are acceptable. (This was my interpretation of the guidance)

I am not exactly sure what the sedimentation volume is, so probably need to describe it more in the guidance.

Rob

**From:** Jiang, Xiaojian
**Sent:** Tuesday, May 06, 2014 8:21 PM
**To:** Lionberger, Robert
**Cc:** Stier, Ethan; Huang, Yih Chain; Peters, John (CDER); Cui, Minglei
**Subject:** FW: NG tube guidance for esomeprazole manesium DR capsule

Dear Rob,

We have been working on the control to revise the draft guidance for Esomeprazole. The new guidance will include the NG tube requirements in addition to previous fasting, fed and fasting sprinkle studies. We have discussed the draft guidance with Dr. John Peters and would like you to take a look at the draft guidance before we post it as requested by John (see below email). Please find the attached control and draft guidance and let us know your concurrence if we can post the guidance by Friday, May 9, 2014). Thank you very much for your advice in advance.

The following are some background for NG tube project:
Nasogastric (NG) tubes are sometimes used to administer medication to patients who are unable to safely swallow or tolerate oral intake. One such product that can be administered in this manner is the Proton Pump Inhibitor (PPI), Lansoprazole, esomeprazole, omeprazole, and lansoprazole delayed-release orally disintegrating tablets. We have TSI issue with Teva's now discontinued ANDA 078730, Lansoprazole Delayed-Release Orally Disintegrating Tablets (LODT).

Since 2011, through several internal meetings with chemistry, it was conclude that In vitro NG testing should be requested if a product is a solid oral dosage form and contains instructions for NG tube administration in the RLD labeling. So far we have sent the NG tube requirements to quite number of ANDAs mostly for PPI drug products (e.g. lansoprazole, esomeprazole, omeprazole, [redacted] (b) (4)) through deficiency letters. However, we believe that posting daft guidance immediately will benefit both FDA and generic companies the most due to the following reasons:

3. The current guidance do not have NG tube study requirement. The firm will only know NG tube requirement through our deficiency letter after their submission. We can refuse to file the applications with the new guidance. With GUDUFA deadline, this may help us to meet the 10 month deadline.

4. If the firm knows that NG tube requirement ahead of time, they will be more careful on particle size design. They will less likely fall in the situation in which fasting, fed and fasting sprinkle studies all passed 90% confidence acceptance criteria but they have to reformulate the test product due to failed recovery NG tube studies as the result of large particle size (which we saw in same cases now).

We also learn during our review of some NG tube studies submitted by the applicants, different pH of water can damage the enteric coating. So we asked the firm to conduct

testing in different pH of water if the label indicates that water is the medium. In case where that apple juice is used for NG tube administration (e.g. lansoprazole DR capsule), there is no need to using different type of juice. We also had agreement with CMC division, they will also send out deficiencies asking in vitro study using different tube material etc. Bio will do statistical comparison while, CMC conducts qualitative evaluation for the comparison.

Sincerely,
Xiaojian

**From:** Peters, John (CDER)
**Sent:** Friday, May 02, 2014 10:54 AM
**To:** Jiang, Xiaojian
**Cc:** Cui, Minglei; Stier, Ethan
**Subject:** RE: NG tube guidance

Makes sense. When the draft is complete let's make sure that we have Rob's ok too. He was at the meetings so should be up to date on the content of the draft.

Tx

J

**From:** Jiang, Xiaojian
**Sent:** Thursday, May 01, 2014 10:25 AM
**To:** Peters, John (CDER)
**Cc:** Cui, Minglei; Stier, Ethan
**Subject:** NG tube guidance

Hi, John
At our last meeting (4/11/2014), we decided to postpone posting the draft guidance for Esomeprazole until FDA conduct and finish confirmative NG tube studies for reference and some test products for us. The new guidance will include the NG tube requirements in addition to previous fasting, fed and fasting sprinkle studies.
However after giving some more thought for GDUFA deadlines and the current guidance, we would like to suggest posting the draft guidance now instead of waiting for FDA's label results due to the following reasons:

4. The current guidance do not have NG tube study requirement. The firm will only know NG tube requirement through deficiency letter after their submission. With GUDUFA deadline, this may post a risk for us missing 10 month deadline.

5. If the firm knows that NG tube requirement ahead of time, they will be more careful on particle size design. They will less likely fall in the situation in which fasting, fed and fasting sprinkle studies all passed 90% confidence acceptance criteria but they have to

reformulate the test product due to failed recovery NG tube studies as the result of large particle size (which we saw now).

6. The FDA lab studies may take a long time. The draft guidance can be changed anytime if the lab result indicates that change is necessary. However, because the guidance we proposed is using a very conservative method, it is less likely that more studies will be required based on the lab results (most likely reducing the amount of testing)

Based above rationale, we suggest posting guidance now and would like to get your approval on this decision.

Thanks,
Xiaojian

### 4.2.10 DB II NG Tube Study Request For FDA Lab: Acid Resistance test following the delivery of NEXIUM® (Esomeprazole Magnesium) DR Capsules through NG tube

**From:** Cui, Minglei
**Sent:** Wednesday, September 24, 2014 4:00 PM
**To:** Lionberger, Robert; Jiang, Wenlei
**Cc:** Cui, Minglei; Jiang, Xiaojian
**Subject:** RE: Study request for FDA lab: Acid Resistance test following the delivery of NEXIUM® (Esomeprazole Magnesium) DR Capsules through NG tube

Hi Rob,
We have already posted draft guidance for Esomeprazole Magnesium DR Capsules. Therefore, no discipline review dates or target action dates of ANDA reviews for this product will not be affected at this time. However, as indicated in the action item of the internal meeting (attached previously), the original decision of DB was to post the guidance after the FDA lab's test on the in vitro NG tube performance of the RLD. However, due to the pressure of reviewing all submitted ANDAs on time, we posted the guidance right away. But we would like to have the confirmatory results from FDA lab asap. Thank you.

Minglei

**From:** Lionberger, Robert
**Sent:** Wednesday, September 24, 2014 9:37 AM
**To:** Cui, Minglei; Jiang, Wenlei
**Subject:** RE: Study request for FDA lab: Acid Resistance test following the delivery of NEXIUM® (Esomeprazole Magnesium) DR Capsules through NG tube

What are the target action dates and discipline review dates for these ANDA or are these pending with the applicant?

**From:** Cui, Minglei
**Sent:** Wednesday, September 24, 2014 7:55 AM
**To:** Jiang, Wenlei; Lionberger, Robert
**Cc:** Stier, Ethan; Jiang, Xiaojian; Xia, Li; Cui, Minglei
**Subject:** RE: Study request for FDA lab: Acid Resistance test following the delivery of NEXIUM® (Esomeprazole Magnesium) DR Capsules through NG tube

Good morning Wenlei,
We prefer the study to be finished in 1-2 month. Thank you.
Minglei

**From:** Jiang, Wenlei
**Sent:** Tuesday, September 23, 2014 11:38 AM
**To:** Cui, Minglei; Lionberger, Robert
**Cc:** Stier, Ethan; Jiang, Xiaojian; Xia, Li
**Subject:** RE: Study request for FDA lab: Acid Resistance test following the delivery of NEXIUM® (Esomeprazole Magnesium) DR Capsules through NG tube

Minglei,
Thanks for the detailed summary about the issue.
Yes, ORS can coordinate with OTR lab about the testing and keep you posted about the progress.
In addition, what's the target action date for these ANDA reviews? So we can plan the activity accordingly.
Wenlei

**From:** Cui, Minglei
**Sent:** Monday, September 22, 2014 9:47 PM
**To:** Lionberger, Robert; Jiang, Wenlei
**Cc:** Stier, Ethan; Jiang, Xiaojian; Xia, Li
**Subject:** RE: Study request for FDA lab: Acid Resistance test following the delivery of NEXIUM® (Esomeprazole Magnesium) DR Capsules through NG tube

Please also see the attached Internal meeting minutes for your reference (Action Items).
Thanks
Minglei

**From:** Cui, Minglei
**Sent:** Monday, September 22, 2014 9:29 PM
**To:** Lionberger, Robert; Jiang, Wenlei
**Cc:** Stier, Ethan; Jiang, Xiaojian; Cui, Minglei (Minglei.Cui@fda.hhs.gov); Xia, Li
**Subject:** Study request for FDA lab: Acid Resistance test following the delivery of NEXIUM® (Esomeprazole Magnesium) DR Capsules through NG tube

Dear Rob and Wenlei,
We have some scientific issues regarding to the performance of the reference product NEXIUM® (Esomeprazole Magnesium) DR Capsules in acid resistance testing following the delivery of the drug through NG tube. Per our discussion with John Peter, Ethan and Xiaojian, we would like your help in requesting the FDA's lab to conduct in vitro NG tube test for us. The background information and request are the follows:

**Background:**

1. According to current draft Guidance for Esomeprazole Magnesium Delayed Release Capsules, as part of the NG tube study the firm is requested to conduct comparative acid resistance stability testing on both 20 mg and 40 mg strengths following the delivery through a combination of oral syringe and 8 French NG tube using 12 units of the test and the reference products in water with different pH (pH 5.5, 6.5, and 7.5) at 0 minutes and 15 minutes.

2. Based on our in house data, the % release of the reference drug product, AstraZeneca's NEXIUM® (Esomeprazole Magnesium) DR Capsules in (b) (4) applications was more than (b) (4) % after soaking in water from 15 min to 60 min (b) (4), see the table below). In ANDA 078003, the 40 mg reference drug released greater than 85% at 15 minutes and up to 99% of Esomeprazole at 60 minutes at water pHs of 5.4, 5.9 and 6.4. Comparing with the acid resistance data with 0 minute soaking time (b) (4) %), this

indicates that the enteric coating of the reference product is damaged by 15 and 30 minutes water pretreatment. The particle rupture of the reference drug product was also observed in ANDA 078003 from the soaking times of 15 min to 60 min with different water pHs. The soaking time seems to be more relevant to the rupture of pellet than water pH as long as it is above pH 5.5.

Comparing to the significant release from the reference drug in ANDA 078003, the 20 mg and 40 mg reference drug in ANDA 078279 (6/20/2014 amendment) released less than 15% at pH 6.0 and pH 8.0 with 30 minutes soaking time. The firm also investigated the performance of another batch of the RLD, it released 31.1% after soaking the RLD in pH 8.0 water for 30 min, which is comparable to those in ANDA (b) (4) This may be due to the variability of different lots of the reference product.
Except that the 20 mg and 40 mg test product released 12.2-14.8% with 30 minutes soaking time in ANDA 078279 amendment dated 6/20/2014, none of test drug products in other ANDAs has release over (b) (4)%.

**Summary of Acid Resistance Stability Data in ANDAs**

| | NG tube information (8F) | | % Released in the Acid Stage for 2 hours | | | |
|---|---|---|---|---|---|---|
| | Time | Water pH | 20 mg | | 40 mg | |
| | | | Test | RLD | Test | RLD |
| (b) (4) | | | | | | |
| **078279** | 15 min | No define | 6.1 | 11.8 | 5.6 | 2.3 |
| **078936** | 15 min | No define | 2.6 | 3.2 | 2.7 | 1.0 |
| **202784** | 15 min | No define | 5.5 (94.5%) | 6.2 (93.8%) | 6.7 (93.3%) | 7.7 (92.3%) |
| **78003** | 0 min | **5.4** | 3 | 6.2 | 8.8 | 7.9 |
| | 15 min | | 3.5 | 6.5 | 8.6 | 86.6 |
| | 30 min | | 3.4 | 26.5 | 8.7 | 97.9 |
| | 60 min | | 2.6 | 81 | 10.1 | 99 |
| | 0 min | **5.9** | 0 | 6.9 | 2.3 | 8.3 |
| | 15 min | | -0.7 | 9.6 | 2.9 | 97.1 |
| | 30 min | | 0.6 | 22.2 | 2.8 | 98.3 |
| | 60 min | | 0.7 | 81.9 | 5.5 | ND |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 0 min | | 1.0 | 4.8 | 0.5 | 1.9 |
| | 15 min | **6.4** | 1.5 | 5.3 | 0.9 | 98.2 |
| | 30 min | | 1.4 | 12.2 | 0.3 | 97.3 |
| | 60 min | | 1.6 | 81.9 | 0.6 | 98.6 |

(b) (4)

**Request:**

**Regarding the difference of esomeprazole release observed in the reference listed drug among different ANDAs, the DB II requests the FDA laboratory to conduct acid resistance testing for each strength of reference drug products with different soaking time (i.e., 0, 15 minutes) in water with different pH (pH 5.5, 6.5, and 7.5) for confirmation purpose.**

Please let us know if you need any additional information. Thank you very much!

Best Regards,

Minglei

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078003

APPLICANT: IVAX Pharmaceuticals, Inc.,
(subsidiary of Teva Pharmaceuticals USA)

DRUG PRODUCT: Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns 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}

Ethan Stier, Ph.D.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

## 5 OUTCOME

ANDA: 078003

**Enter Review Productivity and Generate Report**

**Reviewer:** Zhao, Joan

**Date Completed:**

**Verifier:** ,

**Date Verified:**

**Division:** Division of Bioequivalence

**Description:** Esomeprazole Magnesium Delayed-Release Capsules, Eq. 20 mg and 40 mg base - In Vitro NG tube study

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*Productivity:*

| ***ID*** | ***Letter Date*** | ***Productivity Category*** | ***Sub Category*** | ***Productivity*** | ***Subtotal*** |
|---|---|---|---|---|---|
| 24592 | 8/22/2014 | Bioequivalence Study (REGULAR) | In Vitro Study (Particle Size Study on 20 mg and 40 mg) | 2 | 2 |
| 24592 | 8/22/2014 | Bioequivalence Study (REGULAR) | In Vitro Study (Recovery Testing on 20 mg and 40 mg) | 2 | 2 |
| 24592 | 8/22/2014 | Bioequivalence Study (REGULAR) | In Vitro Study (Acid Resistance Study on 20 mg and 40 mg) | 2 | 2 |
| | | | | Total: | 6 |

# DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 078003 |
| **Drug Product Name** | Esomeprazole Magnesium Delayed-Release Capsules, USP |
| **Strength(s)** | Eq. 20 mg and 40 mg base |
| **Applicant Name** | IVAX Pharmaceuticals, Inc.,<br>(An indirect and wholly owned subsidiary of Teva Pharmaceuticals USA) |
| **Address** | 425 Privet Road<br>Horsham, PA, 19044 |
| **Applicant's Point of Contact** | Scott D. Tomsky, Vice President, N.A. Generics Regulatory Affairs<br>Scott.Tomsky@tevapharm.com |
| **Contact's Telephone Number** | 215-591-3142 |
| **Contact's Fax Number** | 215-591-8812 |
| **Submission Dates of Original Application and Previous Amendments** | November 23, 2005<br>November 13, 2006 (study amendment)<br>April 25, 2013 (In vitro NG tube study) |
| **Submission Date of Amendment Under Review** | **March 31, 2014 (In vitro NG tube study)** |
| **Reviewer** | Li Xia, Ph.D. |

| | | | |
|---|---|---|---|
| **Study Number (s)** | P1BD05001 | P1BD05002 | P1BD05010 |
| **Study Type (s)** | Fasting | Fed | Sprinkled Fasting |
| **Strength (s)** | eq. to 40 mg base | eq. to 40 mg base | eq. to 40 mg base |
| **Clinical Site** | Allied Research International Inc. | | |
| **Clinical Site Address** | 4520 Dixie Road, Mississauga, Ontario, Canada L4W 1N2 | | |
| **Analytical Site** | (b) (4) | | |
| **Analytical Site Address** | | | |

| | | | |
|---|---|---|---|
| **OVERALL REVIEW RESULT** | **Inadequate pending firm's response to deficiencies related to in vitro NG tube study** | | |
| **OSI REPORT RESULT** | **Adequate** | | |
| **BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #** | **STUDY/TEST TYPE** | **STRENGTH** | **REVIEW RESULT** |
| **1** | **Dissolution** | **20 mg and 40 mg** | **Adequate** |
| **1** | **Fasting study** | **40 mg** | **Adequate** |
| **1** | **Fed study** | **40 mg** | **Adequate** |
| **1** | **Sprinkled Fasting Study** | **40 mg** | **Adequate** |
| **1** | **Biowaiver Request** | **20 mg** | **Inadequate** |
| **1** | **NG Tube Test** | **20 mg and 40 mg** | **Inadequate** |

**Review of a Study Amendment**

# 1 EXECUTIVE SUMMARY

This is a review of a study amendment.

IVAX Pharmaceuticals, Inc. previously submitted an application (11/23/2005) consisting of three bioequivalence (BE) studies comparing its test product, Esomeprazole Magnesium Delayed-Release (DR) Capsules, 40 mg, to the corresponding reference product, AstraZeneca's NEXIUM® (Esomeprazole Magnesium) DR Capsules, 40 mg, under fasting, fed, and fasting "sprinkled" conditions. Firm's fasting, fed and fasting sprinkled BE studies were found acceptable; the dissolution testing conducted using the FDA-recommended method was also acceptable[1,2].

Since Esomeprazole Magnesium DR Capsules include an alternate administration method through a nasogastric (NG) tube per the approved labeling of the reference product, the DB II issued a deficiency letter on 09/26/2012 to request the firm perform the comparative *in vitro* tests (sedimentation testing, particle size distribution study, recovery testing, and acid resistance stability testing) to compare the performance of its test product to that of the reference product for both strengths, 20 mg and 40 mg, under NG tube administration conditions[3].

In its previous amendment dated 4/25/2013, the firm submitted the results of in vitro NG tube studies. The results for sedimentation testing and recovery testing were acceptable. However, due to its improper sample preparation for particle size analysis, the firm did not determine the particle size distribution on test and reference products before delivery (in syringe) and after delivery through the combination of syringe and NG tube. In addition, firm's acid resistance stability testing is incomplete. Due to the concerns that the process of dispersing a test product in an oral syringe and/or an oral syringe with an NG tube might adversely impact the integrity of the enteric coating, the firm was requested to demonstrate the stability of the dispersed granules in different pH of water (e.g. 6, 7 and 8) with different soak time (e.g. 15, 30 and 60 min) prior to performing the acid resistance testing[2].

In its current amendment dated 03/31/2014, the firm repeated particle size distribution study and acid resistance testing in water with pHs of 5.4, 5.9 and 6.4 at 0, 15, 30 and 60 minutes, instead of water with pH 6, 7, and 8 which was previously recommended by the DB. The firm stated that the chosen pHs best represent water conditions in a hospital setting. The DB disagrees with the firm's statement. Since the tab water may be used to deliver the medicine in hospital and its pH of tap water may vary between 6.5 to 8.5, as per the control correspondence #140139[4], the current FDA guidance on Esomeprazole Magnesium DR Capsules will be revised to recommend in vitro NG tube studies using

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[1] DARRTS: REV-BIOEQ-01(General Review) for ANDA 078003, final date 01/04/2007.
[2] DARRTS: REV-BIOEQ-21(Primary Review) for ANDA 078003, final date 09/19/2013.
[3] DARRTS: REV-BIOEQ-01(General Review) for ANDA 078003, final date 09/26/2012.
[4] V:\FIRMSAM\DBE\Esomeprazole\140139P0414

water with different pH (pH 5.5, 6.5, and 7.5) with soak times of 0 minute and 15 minutes.

In its current amendment, firm's particle size analysis on the granules delivered through syringe and NG tube using microscopy is not accurate and not suitable for particle size distribution (D10, D50 and D90), therefore it is not acceptable. Per internal meeting minutes dated 4/11/2014 (Attachment 4.2.2), the laser diffraction method for measuring particle size in lieu of microscopy should be recommended. Since the firm conducted particle size study in water pHs of 5.4 and 6.4, which are closed to the DB-recommended pHs of 5.5 and 6.5, and the morphology did not show much difference under the pHs tested, the firm is requested to repeat the particle size distribution study using pH 7.5 water with soak times of 0 minute and 15 minutes.

The results from acid resistance testing show that less than (b)(4)% of Esomeprazole for 20 mg and 40 mg strengths of the test product releases in the acidic medium after soaking in water (pH 5.4, 5.9 and 6.4) for 0, 15, 30 and 60 minutes. In contrast, under the same treatment conditions, the 20 mg reference drug released greater than (b)(4)% at 30 minutes and up to (b)(4)% of Esomeprazole at 60 minutes, and the 40 mg reference drug released greater than (b)(4)% at 15 minutes and up to (b)(4)% of Esomeprazole at 60 minutes. The acid resistance data are in agreement with the particle size morphology. The pellets from test product remain intact throughout the soaking stage at various pHs (5.4, 5.9 and 6.4) up to 60 minutes, whereas the pellets from the reference pellets begin to rupture, deteriorate, disintegrate and lose their shape at the same water pHs from 15 to 60 minutes soaking minutes. Since the firm conducted acid resistance testing in water pHs of 5.4 and 6.4, which are closed to the DB-recommended pHs of 5.5 and 6.5, the firm is requested to repeat the acid resistance stability testing using pH 7.5 water with soak times of 0 minute and 15 minutes.

Per bio-management meeting dated 05/13/2014[5] (Attachment 4.2.4), the firm is also recommended to conduct comparative recovery studies on the granule dispersion in water with different pH (pH 5.5, 6.5, and 7.5) and soak times (0 min and 15 min) even that the firm's previous recover study submitted in its 4/25/2013 amendment was acceptable in water (pH is not defined). This requirement is due to the concern that the different pH of water may damage the integrity of enteric coating of the drug product and increase the risk of the stickiness of the granules to the tube.

The 20 mg strength is proportionally formulated to the 40 mg strength. Yet, the DB can not deem the 20 mg strength to be bioequivalent to the 20 mg strength of the reference product based on CFR 320.24(b)(6) at this time due to deficiencies identified in the in vitro NG tube studies.

No Office of Scientific Investigations (OSI) inspection is pending or necessary.

The application is **incomplete** pending firm's response to deficiencies related to the in vitro NG tube studies.

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[5] V:\DIVISION\BIO\BIO2\BIO Management Meeting Minutes\2014 Meeting Minutes

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# 3 SUBMISSION SUMMARY

## 3.1 Drug Product Information

| | |
|---|---|
| **Test Product** | Esomeprazole Magnesium Delayed-Release capsules, 20 mg and 40 mg |
| **Reference Product** | NEXIUM® (Esomeprazole magnesium)<br>Delayed-Release capsules, 20 mg and 40 mg |
| **RLD Manufacturer** | AstraZeneca |
| **NDA No.** | 021153 |
| **RLD Approval Date** | Feb 20, 2001 |
| **Indication** | Treatment of Gastroesophageal Reflux Disease (GERD), Maintenance of Healing of Erosive Esophagitis, Symptomatic Gastroesophageal Reflux Disease, Risk Reduction of NSAID-Associated Gastric Ulcer, H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence, Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome. |

## 3.2 Contents of Current Submission

| Study Types | Yes/No? | How many? |
|---|---|---|
| **Single-dose fasting** | No | 0 |
| **Single-dose fed** | No | 0 |
| **Single-dose sprinkled fasting** | No | 0 |

| | | |
|---|---|---|
| **In vitro NG tube study** | Yes | 2 tests for 20 mg<br>2 tests for 40 mg |
| **In vitro dissolution** | No | 0 |
| **Waiver requests** | No | 0 |
| **BCS Waivers** | No | N/A |
| **Clinical Endpoints** | No | N/A |
| **Amendments** | Yes | 03/31/2014 amendment for in vitro NG tube studies |

## 3.3 Study for Nasogastric Tube Administration

### 3.3.1 Labeling of NEXIUM (Esomeprazole Magnesium) Delayed-Release Capsules[6]

**Dosage and administration**

NEXIUM Delayed-Release Capsules should be swallowed whole.

Alternatively, for patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the NEXIUM Delayed-Release Capsule can be opened, and the granules inside the capsule carefully emptied onto the applesauce. The granules should be mixed with the applesauce and then swallowed immediately: do not store for future use. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The granules should not be chewed or crushed. If the granules/applesauce mixture is not used in its entirety, the remaining mixture should be discarded immediately.

For patients who have a nasogastric tube in place, NEXIUM Delayed-Release Capsules can be opened and the intact granules emptied into a 60 mL catheter tipped syringe and mixed with 50 mL of water. It is important to only use a catheter tipped syringe when administering NEXIUM through a nasogastric tube. Replace the plunger and shake the syringe vigorously for 15 seconds. Hold the syringe with the tip up and check for granules remaining in the tip. Attach the syringe to a nasogastric tube and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the granules, the nasogastric tube should be flushed with additional water. Do not administer the granules if they have dissolved or disintegrated.

The mixture must be used immediately after preparation.

### 3.3.2 History of Nasogastric Tube Study for the Reference Listed Drug

**In vivo and In vitro studies**

[6] Labeling of Nexium at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f4853677-1622-4037-688b-fdf533a11d96#nlm34068-7

AstraZeneca submitted the supplement of NDA (021153), SLR-008 on October 24, 2002 to provide proposed revisions to the Dosage and Administration section of the package insert by adding information regarding the administration of the contents of Nexium® capsules through a nasogastric tube. The innovator submitted in vivo and in vitro NG tube studies in support of proposed revisions. A bioequivalence study (No. 313) demonstrated that the intact Nexium® capsule administered orally and a dispersion of the capsule contents in water administered via a NG tube have similar bioavailability throughout 5 days of QD dosing. Therefore, the dosing recommendations for administration of opened Nexium capsules through the NG tube should be the same as for the intact Nexium capsules[7].

In addition, the sponsor submitted an i*n vitro* study to evaluate the delivery of the contents of an esomeprazole capsule through NG tubes of various sizes. This study, "An *In Vitro* Study to Evaluate the Delivery of Esomeprazole Magnesium Enteric-Coated Pellets Dispersed in Water Through Small Caliber and Standard NG Tubes & Gastrostomy Tubes", revealed that the average recovery of pellets was >98% following the dispersion of pellets in 50 mL of tap water in a syringe. The recovery was 77.7% following the dispersion of the pellets in 25mL of tap water and followed by the washing of the syringe with an additional 25 mL of tap water which was injected into the tube.

The second *in vitro* study evaluated the integrity of the enteric-coated pellets following administration of the esomeprazole pellets through the NG tube. This study, An *In Vitro* Study to Evaluate the Delivery of Esomeprazole Magnesium Enteric-Coated Pellets Dispersed in Water Through Small Caliber and Standard NG Tubes & Gastrostomy Tubes", indicated that an average of 98.8-99.5% of the contents of the 20mg Nexium capsules and 98.7-99.3% of the contents of the 40mg Nexium capsules were retained following passage through the NG tube and subsequent acid exposure. Therefore, the administration of the esomeprazole pellets through the NG tube did not appear to affect the acid resistance of the pellets (i.e., the integrity of the enteric coating). Please note the dispersed pellets were injected into the NG tube without prior soaking in water in the syringe.

**<u>Stability of the pellets in water</u>**

Per CMC review[8], studies submitted in the original NDA (April 3, 2000 amendment (Page 004-001-013)) support the label statement: (b) (4)

These studies showed that the pellets (b) (4)

However, in the absence of data the label should state that the drug should be administered (b) (4)

[7] DARRTS: REV-CLINIPHARM-01 (General Review) NDA021153, final date: 04/16/2003
[8] DARRTS: REV-QUALITY-03(General Review) for NDA 021152, final date: 4/21/2003.

The Division of Gastrointestinal and Coagulation Drug Products took an approvable action on April 24, 2003[9]. Before the application may be approved, however, the firm was asked to address the following deficiency: "Provide studies to demonstrate the stability of the pellets in water for up to two hours as a function of pH, time and temperature. In the absence of such information, include a statement on the label that the granules should be delivered immediately."

In response to the approvable letter dated April 24, 2003, in its supplement dated July 8, 2003[10], the applicant had stated in the letter that they were not providing studies to demonstrate the stability of the pellets (b) (4). Since the innovator did not adequately address the stability of the suspension of these enteric coated pellets in (b) (4) water, i.e. it did not define the maximum time in which it must be delivered after preparation of the suspension. An addendum *"The suspension must be used immediately after preparation"* to the proposed labeling was recommended. The firm updated its drug product labeling in the DOSAGE AND ADMINISTRATION section of the package insert with the administration of NEXIUM® via NG tube on 01/08/2004.

### 3.3.3 DB Recommendation of NG Tube Study for Generic Product

Enteral feeding tubes are sometimes used to administer medication to patients who cannot safely swallow or unable to tolerate oral intake. Esomeprazole is indicated for treatment of GERD, risk reduction of NSAID-associated gastric ulcer, H. pylori eradication to reduce the risk of duodenal ulcer recurrence, and treatment of pathological hypersecretory conditions Including Zollinger-Ellison syndrome. According to the labeling, Esomeprazole Magnesium DR capsules include an alternate administration method through a combination of syringe and a nasogastric (NG) tube. Esomeprazole is a substituted benzimidazole, and inhibits gastric acid secretion by specific inhibition of the enzyme, H+K+-ATPase at the surface of the gastric parietal cells. Esomeprazole has the similar chemical structure and the same bio-function as Lansoprazole.

Several current FDA adverse event report indicates that Teva's Lansoprazole DR Orally Disintegrating Tablets when dosing the product using an oral syringe or feeding tube has clogged and blocked oral syringes and feeding tubes including both gastric and jejunostomy types. The tablets may not fully disintegrate when water is added to them and/or they may disintegrate but later form clumps. These clumps can adhere to the inside walls of oral syringes and feeding tubes. In some cases, patients have had to seek emergency medical assistance and their feeding tubes have had to be unclogged or removed and replaced. In addition, the laboratory results conducted by the Division of Pharmaceutical Analysis (DPA) dated 11 March 2011 demonstrated that there is a risk of clogging the NG tube when using the RLD and Teva's product for 15 min or longer[11].

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[9] DARRTS: COR-SNDAACTION-03 (Approvable) NDA 021153, final date: 04/24/2003

[10] DARRTS: REV-QUALITY-03(General Review) for NDA 021153, final date: 12/18/2003.

[11] Interim report from the Division of Pharmaceutical Analysis 03/11/2011: Interim report on Evaluation of Lansoprazole Orally Disintegrating tablets: Dosing with Oral Syringe, Phase 1 Part A and Part B.

The Office of Generic Drugs (OGD) is concerned about this issue and the potential for harm to patients and is seeking prompt correction of the problem. The successful delivery of test drug product through a combination of syringe and NG tube requires that all of the capsule's contents be able to safely pass through the feeding tube and not cause tube occlusions. Therefore, we request the firm to demonstrate that the generic product has a similar performance profile to the reference product during NG tube administration.

Based on the control correspondence # 140139[4], where the revised guidance will be developed, the DB recommends the following comparative *in vitro* test:

1. **Sedimentation testing**: Determine comparative sedimentation volume of granule dispersion using 12 units each of the test and the reference products, for the 20 mg and 40 mg strength, in 50 ml of water with different pH (pH 5.5, 6.5, and 7.5) at 0 min and 15 min.

2. **Particle size distribution study**: Determine the comparative particle size of granule dispersion in water with different pH (pH 5.5, 6.5, and 7.5) using 12 units each of the test and the reference products before and after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 min and 15 min. Provide all particle size data at D10, D50, and D90 level. Determine particle size using the method of laser diffraction or any method that is sufficiently reproducible and sensitive.

3. **Recovery testing**: Conduct the comparative recovery studies of the granule dispersion from a combination of oral syringe and 8 French nasogastric tube using at least 12 units of the test and the reference products in 50 ml water with different pH (pH 5.5, 6.5, and 7.5). Determine the percentage of Esomeprazole recovered at the NG tube exit relative to the initial dose for both the test and the reference products at 0 min and 15 min. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated.

4. **Comparative acid resistance stability testing**: Measure acid resistance on the granule dispersion in water with different pH (pH 5.5, 6.5, and 7.5) after recovery through a combination of oral syringe and 8 F NG tube at 0 min and 15 min. Evaluate the stability at least 12 units of the test and the reference products using acid resistance as stability indicator.

Note: In pediatric practice, the sizes of 8F to 16 F NG tubes are generally used for medication administration. Since the indication of Esomeprazole Magnesium DR Capsules is also for Pediatric GERD from age of 1 month to 17 year old, 8F NG tube size is required for the NG tube study of Esomeprazole Magnesium DR Capsules.

### 3.3.4 CMC Deficiency

CMC issued a deficiency regarding in vitro NG tube testing to the firm in deficiency letter dated 03/07/2012 as below.

(b) (4)

In its amendment dated 09/20/2013, the firm responded CMC regarding the deficiencies related to the NG tube study. (b) (4)

(b) (4)

Sedimentation study in water was performed using both 'vigorous shaking' and 'shake well' methods as per instructions in the RLD's full prescribing information section 2 DOSAGE AND ADMINISTRATION and the Medication Guide Instructions for Use, respectively. Teva provided comparative sedimentation rates and observations in Table below and provided photographs in Module 3.2.P.2. Similar photographs were provided to the Agency in Teva's April 25, 2013 Bioequivalence Amendment.

**Table 3. Comparative Sedimentation Rate Study**

| Product Sedimentation Rate | | | | | |
|---|---|---|---|---|---|
| | 20 mg strength | | 40 mg strength | | |
| **Shake Well Action** | **Teva (seconds)** | **Reference (seconds)** | **Teva (seconds)** | **Reference (seconds)** | **Observations** |
| **Mean** | **31** | **10** | **30** | **10** | Observed no floating, no aggregation, and no adhering of pellets to the wall. |
| **Minimum** | (b) (4) | | | | |
| **Maximum** | | | | | |
| **Std Deviation** | 1.6 | 1.5 | 1.5 | 1.3 | |
| **% RSD** | 5.3 | 14.0 | 4.8 | 12.5 | |
| **Vigorous Shaking Action** | **Teva (seconds)** | **Reference (seconds)** | **Teva (seconds)** | **Reference (seconds)** | **Observations** |
| **Mean** | **70** | **20** | **70** | **20** | Observed floating and aggregation of pellets for Teva samples; aggregates sunk immediately upon gentle tapping of the syringe. |
| **Minimum** | (b) (4) | | | | |
| **Maximum** | | | | | |
| **Std Deviation** | 1.7 | 1.5 | 1.4 | 1.2 | |
| **% RSD** | 2.4 | 7.2 | 2.0 | 6.3 | |

For the comparative recovery study, the mean percent of Esomeprazole recovered through the syringe and tubing is greater than 97% for each of the product strengths held at both vertical and s-shaped positions for all types of tubing size 8.0 and greater. Results are summarized in Table 4 below. Neither the RLD nor Teva products were able to pass through the size 6.5 tubing. This was the only clogging observed.

**Table 4. Comparative Recovery Study**

| Comparative Recovery Study | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nasogastric Feeding Tube | | | | 20 mg strength (% Labeled Claim) | | 40 mg strength (% Labeled Claim) | |
| Position | Size | Manufacturer | Material | Teva | Reference | Teva | Reference |
| Vertical | 6.5 | Covidien Kangaroo | PVC | Clogging observed | Clogging observed | Clogging observed | Clogging observed |
| | 8.0 | Kendall Argyle | PVC | 99.0 | 100.7 | 97.1 | 100.4 |
| | 8.0 | Covidien Kangaroo | Polyurethane | 97.4 | 100.5 | 97.8 | 101.4 |
| | 12.0 | Rusch | PVC | 98.4 | 99.3 | 99.6 | 100.7 |
| | 14.0 | Rusch ENfuse | Polyurethane | 101.3 | 101.2 | 98.8 | 100.7 |
| S-Shaped | 6.5 | Covidien Kangaroo | PVC | Clogging observed | Clogging observed | Clogging observed | Clogging observed |
| | 8.0 | Kendall Argyle | PVC | 100.7 | 99.9 | 98.6 | 100.9 |
| | 8.0 | Covidien Kangaroo | Polyurethane | 100.5 | 98.7 | 100.2 | 101.2 |
| | 12.0 | Rusch | PVC | 99.3 | 98.6 | 99.3 | 99.6 |
| | 14.0 | Rusch ENfuse | Polyurethane | 101.2 | 99.3 | 98.7 | 100.6 |

## 3.4 Review of Submission

In response to a complete response letter from the FDA dated February 10, 2014. Teva Pharmaceuticals USA submitted its current amendment dated 03/31/2014. The responses to DB II deficiencies related to In vitro test for Nasogastric (NG) Tube administrations are evaluated in this review as follows.

### 3.4.1 Deficiency #1 (Particle Size Distribution Study):

*Your sample preparation for particle size analysis by laser diffraction method is incorrect. Test procedure states that "Take out 10ml of the dispersion and proceed for particle size test at 0minutes/15minutes as mentioned in Section D particle size test". However, due to rapid sedimentation there is absence of particles remaining in solution per the observation. Instead of taking out 10ml of sample from the dispersion, collect the pellets in the container in order to determine the particle size distribution of the pellets.*

*Please determine the comparative particle size of granule dispersion using 12 units each of the test and reference products, for both 20mg and 40mg strengths, before (in syringe) and after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 and 15 min. Please collect the pellets in the container to determine the particle size distribution of the pellets.*

*Please provide all particle size data at D10, D50 and D90 levels. Please visually examine*

*the tubing and syringe for any aggregation, adherence, clogging, etc., and report all the observations and supporting photographs. Please take photos at different stages (syringe with capsule's content, attaching syringe to the NG tube, injecting water with pellets into the NG tube, flushing NG tube etc.).*

**Firm's Response:**

It's more appropriate to perform particle size by microscopy rather than by laser diffraction for this particular study. Therefore, a microscopy experiment was designed to measure the particle size (in microns) and morphology of the pellets. Specifically, the 20 mg and 40 mg strength capsules were tested under different soaking times (0, 15, 30 and 60 minutes) using 3 different water pHs: 5.4, 5.9 and 6.4 for each soaking time. The pH range was chosen to represent routine hospital water conditions.

The microscopy experiment was designed by [redacted] (b) (4) A summary of microscopy data is provided below with the final conclusion.

## 20 mg: Summary of Microscopy Data

| Test Product-Esomeprazole Magnesium Delayed-Release Capsules USP, 20 mg, | | | | | Reference Product Nexium Capsules 20 mg | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Soaking Time (minutes) | | Mean | SD | %RSD | Soaking Time (minutes | | Mean | SD | %RSD |
| **Water at pH 5.4** | | | | | | | | | |
| **Initial** | Min | (b) (4) | 29.80 | 4.3 | **Initial** | Min | (b) (4) | 23.75 | 5.3 |
| | Max | | 43.09 | 4.7 | | Max | | 74.93 | 10.4 |
| **0** | Min | | 42.41 | 5.9 | **0** | Min | | 35.57 | 7.2 |
| | Max | | 78.82 | 8.6 | | Max | | 50.50 | 7.8 |
| **15** | Min | | 38.43 | 5.0 | **15** | Min | | 36.50 | 6.7 |
| | Max | | 82.94 | 8.6 | | Max | | 62.33 | 9.5 |
| **30** | Min | | 58.87 | 8.1 | **30** | Min | | 32.22 | 6.3 |
| | Max | | 91.02 | 10.0 | | Max | | 24.18 | 3.4 |
| **60** | Min | | 58.87 | 8.1 | **60** | Min | | 60.46 | 10.3 |
| | Max | | 91.02 | 10.0 | | Max | | 58.72 | 8.1 |
| **Observation:** Pellets remained intact throughout and maintained their oval to circular shape. | | | | | **Observation:** After 30 minutes of soaking pellets started to rupture, disintegrate and were irregular in shape | | | | |
| **Water at pH 5.9** | | | | | | | | | |
| **Initial** | Min | (b) (4) | 29.8 | 4.3 | **Initial** | Min | (b) (4) | 23.75 | 5.3 |
| | Max | | 43.09 | 4.7 | | Max | | 74.93 | 10.4 |
| **0** | Min | | 58.46 | 7.6 | **0** | Min | | 99.23 | 14.2 |
| | Max | | 28.86 | 2.7 | | Max | | 105.42 | 12.7 |
| **15** | Min | | 53.39 | 6.9 | **15** | Min | | 36.40 | 6.8 |
| | Max | | 90.18 | 9.5 | | Max | | 61.57 | 8.9 |
| **30** | Min | | 23.92 | 3.2 | **30** | Min | | 70.35 | 10.7 |
| | Max | | 58.8 | 6.1 | | Max | | 103.19 | 11.9 |
| **60** | Min | | 38.65 | 5.4 | **60** | Min | | 156.94 | 28.8 |
| | Max | | 40.15 | 4.4 | | Max | | 53.53 | 7.5 |
| **Observation:** Pellets remained intact throughout and maintained their oval to circular shape. | | | | | **Observation:** After 30 minutes of soaking pellets started to rupture, disintegrate and were irregular in shape | | | | |
| **Water at pH 6.4** | | | | | | | | | |
| **Initial** | Min | (b) (4) | 29.80 | 4.3 | **Initial** | Min | (b) (4) | 23.75 | 5.3 |
| | Max | | 43.09 | 4.7 | | Max | | 74.93 | 10.4 |
| **0** | Min | | 59.60 | 8.4 | **0** | Min | | 28.52 | 5.3 |
| | Max | | 51.31 | 5.6 | | Max | | 49.08 | 6.8 |
| **15** | Min | | 79.71 | 10.4 | **15** | Min | | 32.72 | 6.0 |
| | Max | | 62.04 | 6.5 | | Max | | 92.62 | 13.1 |
| **30** | Min | | 44.43 | 5.9 | **30** | Min | | 34.42 | 6.4 |
| | Max | | 74.66 | 7.7 | | Max | | 48.96 | 6.6 |
| **60** | Min | | 64.03 | 8.7 | **60** | Min | | 40.98 | 7.4 |
| | Max | | 74.89 | 7.4 | | Max | | 57.16 | 8.1 |
| **Observation:** Pellets remained intact throughout and maintained their oval to circular shape. | | | | | **Observation:** After 30 minutes of soaking pellets started to rupture, disintegrate and were irregular in shape | | | | |

**40 mg: Summary of Microscopy Data**

| Test Product-Esomeprazole Magnesium Delayed-Release Capsules USP, 20 mg, | | | | | Reference Product Nexium Capsules 20 mg | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Soaking Time (minutes) | | Mean | SD | %RSD | Soaking Time (minutes | | Mean | SD | %RSD |
| **Water at pH 5.4** | | | | | | | | | |
| **Initial** | Min | (b) (4) | 39.98 | 5.7 | **Initial** | Min | (b) (4) | 22.24 | 4.9 |
| | Max | | 95.73 | 10.7 | | Max | | 77.98 | 10.8 |
| **0** | Min | | 49.51 | 6.9 | **0** | Min | | 30.12 | 6.1 |
| | Max | | 50.32 | 5.6 | | Max | | 51.84 | 7.8 |
| **15** | Min | | 50.86 | 7.2 | **15** | Min | | N/A | N/A |
| | Max | | 108.60 | 11.9 | | Max | | N/A | N/A |
| **30** | Min | | 53.56 | 7.7 | **30** | Min | | N/A | N/A |
| | Max | | 67.89 | 7.2 | | Max | | N/A | N/A |
| **60** | Min | | 48.35 | 6.7 | **60** | Min | | N/A | N/A |
| | Max | | 56.99 | 6.4 | | Max | | N/A | N/A |
| **Observation:** Pellets remained intact throughout and maintained their oval to circular shape. | | | | | **Observation:** After 15 minutes of soaking pellets started to rupture, disintegrate and were irregular in shape | | | | |
| **Water at pH 5.9** | | | | | | | | | |
| **Initial** | Min | (b) (4) | 39.98 | 5.7 | **Initial** | Min | (b) (4) | 22.24 | 4.9 |
| | Max | | 95.73 | 10.7 | | Max | | 77.98 | 10.8 |
| **0** | Min | | 34.8 | 4.8 | **0** | Min | | 38.09 | 7.7 |
| | Max | | 79.1 | 8.2 | | Max | | 61.56 | 9.2 |
| **15** | Min | | 44.98 | 6.3 | **15** | Min | | N/A | N/A |
| | Max | | 76.35 | 8.2 | | Max | | N/A | N/A |
| **30** | Min | | 67.9 | 10.7 | **30** | Min | | N/A | N/A |
| | Max | | 96.0 | 10.6 | | Max | | N/A | N/A |
| **60** | Min | | 45.2 | 6.8 | **60** | Min | | N/A | N/A |
| | Max | | 65.5 | 7.0 | | Max | | N/A | N/A |
| **Observation-** Pellets remained intact throughout and maintained their oval to circular shape. | | | | | **Observation -** After 15 minutes of soaking pellets started to rupture, disintegrate and were irregular in shape | | | | |
| **Water at pH 6.4** | | | | | | | | | |
| **Initial** | Min | (b) (4) | 39.98 | 5.7 | **Initial** | Min | (b) (4) | 22.24 | 4.9 |
| | Max | | 95.73 | 10.7 | | Max | | 77.98 | 10.8 |
| **0** | Min | | 42.26 | 5.9 | **0** | Min | | 33.34 | 6.6 |
| | Max | | 83.53 | 9.1 | | Max | | 31.64 | 5.1 |
| **15** | Min | | 43.12 | 6.0 | **15** | Min | | N/A | N/A |
| | Max | | 59.71 | 6.8 | | Max | | N/A | N/A |
| **30** | Min | | 56.67 | 7.9 | **30** | Min | | N/A | N/A |
| | Max | | 54.04 | 6.1 | | Max | | N/A | N/A |
| **60** | Min | | 40.22 | 5.8 | **60** | Min | | N/A | N/A |
| | Max | | 65.44 | 7.3 | | Max | | N/A | N/A |
| **Observation-** Pellets remained intact throughout and maintained their oval to circular shape. | | | | | **Observation-** After 15 minutes of soaking pellets started to rupture, disintegrate and were irregular in shape | | | | |

**Firm's Conclusion:**

Based on the above observations it can be concluded that the test product remains unchanged during soaking time up to 60 minutes at different water pH's whereas the RLD product tends to rupture or lose its shape at the soaking time up to 30 minutes and 60 minutes at different water pH's.

It was also observed that the aggregation, adherence or clogging of granules did not occur for both Test (Cipla) and RLD product. From the above observations it can be concluded that no tube blockage in-use can potentially occur with our pellet sizes. Photographs were taken at different soaking times (0, 15, 30 and 60 minutes) under 3 different water pHs: 5.4, 5.9 and 6.4. Please refer to **Module 3.2.P.2** product development report for complete study report and photographs.

**Review of the firm's data:**

In its current amendment dated 03/31/2014, the firm provided detailed method procedure and the results in Module 3.2.P.2**.**

**A. Materials and Instrument used in the study**

Test and reference products

| Strength | Test Product (batch No.) | Manufacturing / Expiry Date | RLD (batch No.) | Expiry |
|---|---|---|---|---|
| 20 mg | Y31825 | 07/2013 (Mfg date) 6/2015 (Expiry) | J014509 | Unknown |
| 40 mg | Y31828 | 07/2013 (Mfg date) 6/2015 (Expiry) | J012025 | Unknown |

**Reviewer's Notes:**

1. The test batches for particle size distribution study and acid resistance testing in current amendment are different from the exhibit batches used in the BE studies and dissolution testing in the original application (Test: 20 mg: # Y51231; 40 mg: # Y51286; RLD: 20 mg: #/ P4879; 40 mg: # N5819) because those exhibition batches were expired. Also the test and RLD batches are different from those used in NG tube studies submitted in 04/25/2013 amendment (Test: 20 mg: # Y21936; 40 mg: # Y21935; RLD: 20 mg: #H010166; 40 mg: # H005206).

   The firm is requested to provide the expiration date for the reference product (20 mg: #J014509; 40 mg: # H012025) used in the in vitro NG tube studies. The firm is also requested to provide the testing dates for the particle size distribution study and acid resistance testing.

2. In response to DB's deficiency #2, the firm provided information of syringe, NG tube and type of water used in the testing as follows:

   Nasogastric Tubing: 8.0 French tube of material PVC manufactured by Kendall Argyle.

   Syringe: 50 ml syringe, BD syringe 60 ml capacity (BD 50 ml precise syringe) Luer-Lok Tip Latex Free sterile syringe.

   The in vitro NG tube study was conducted using Millipore/SG purified water at pHs: 5.4, 5.9 and 6.4 throughout all stages of the in vitro NG tube study as well as the particle size study by microscopy.

**Instrument used:**

(b) (4)

## B. Particle Size Distribution Study Procedure

(b) (4)

(b) (4)

**Review of Firm's Data:**
In its current amendment dated 03/31/2014, the firm conducted particle size distribution study using 3 different pHs (5.4, 5.9 and 6.4) of water and soaked the dispersed granules with different soaking times (0, 15, 30 and 60 minutes). The firm did not conduct particle

size study in syringe only, which is before the delivery through the syringe and NG tube. The firm only conducted particle size distribution study after delivery through the combination of NG tube and syringe. The sampling preparation procedure was correct, [redacted] (b) (4)

Per firm's response, it's more appropriate to perform particle size by microscopy rather than by laser diffraction for this particular study. However, the firm did not provide any rationale for using microscopy instead of laser diffraction to measure the particle size in its current amendment. The firm used laser diffraction to measure the particle size in its previous amendment dated 4/25/2013, however, due to its improper sample preparation there were absence of particles in the 10 mL of sample, the firm actually did not determine the particle size distribution on test and reference products before delivery (in syringe) and after delivery through the combination of syringe and NG tube.

In its current amendment, the firm's particle size data measured by microscope did not precisely represent the size of the pellets in each sample preparation, especially do not show the distribution at D10, D50 and D90. Therefore, the particle size data analyzed by microscopy are not accurate and not acceptable. In this report the firm did not describe how the measurement was conducted using the microscope, it did not provide method validation for this method either. Per its response to deficiency #3, since the microscope is used as a measuring device, the validation was not conducted. At module 3.2.P.2, the firm provided the original data (Attachment 4.2.1) and microscopy scanning pictures. As shown in the representative table and pictures below, the firm [redacted] (b) (4) and only reported the minimum and maximum values from these pellets shown in the table below. The average of twelve minimum and twelve maximum values were reported in firm's summary table above.

**Cipla Product 20mg at pH 5.4**

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) |
| 1 | [redacted] (b) (4) | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 29.80 | 43.09 | 42.41 | 78.82 | 38.43 | 82.94 | 58.87 | 91.02 | 58.87 | 91.02 |
| %RSD | 4.3 | 4.7 | 5.9 | 8.6 | 5.0 | 8.6 | 8.1 | 10.0 | 8.1 | 10.0 |

**Sample preparation from capsule #1** (20 mg Test product at pH 5.4 at 0 minute)

(b) (4)

**Sample preparation from capsule #2** (20 mg Test product at pH 5.4 at 0 minute)

(b) (4)

**Firm's Observation:**

For 20 mg and 40 strengths of the reference product at the different water pHs (5.4, 5.9 and 6.4), the pellets started to rupture, disintegrate, and were irregular in shape after 30 and 15 minutes of soaking time, respectively. In contrast, for the 20 mg and 40 mg strengths of the test product, the pellets remained intact throughout soaking and maintained their oval to circular shape at the different water pHs (representative scanned pictures below). No clogging, adherence to the walls and no aggregation of pellets were observed for both test and reference products under these conditions.

20 mg Test: **0 min** at pH 5.9

20 mg Test: **15 min** at pH 5.9

(b) (4)

20 mg Test: **30 min** at pH 5.9

20 mg Test: **60 min** at pH 5.9

(b) (4)

20 mg RLD: **0 min** at pH 5.9

20 mg RLD: **15 min** at pH 5.9

(b) (4)

20 mg RLD: **30 min** at pH 5.9 20 mg RLD: **60 min** at pH 5.9

(b) (4)

40 mg RLD: **0 min** at pH 5.9 40 mg RLD: **15 min** at pH 5.9

(b) (4)

40 mg RLD: **30 min** at pH 5.9 40 mg RLD: **60 min** at pH 5.9

(b) (4)

**Reviewer's Comments on particle size distribution study:**

1. Firm's particle size analysis after delivery through syringe and NG tube using microscopy is not accurate and not suitable for particle size distribution (D10, D50 and D90), therefore it is not acceptable. Since the firm did not provide the particle size distribution data of D10, D50 and D90, the reviewer could not perform the statistical analysis of the particle size. In addition, the firm did not conduct particle size distribution in syringe only, which is before delivery through combination of syringe and NG tube.

Per internal meeting minutes dated 4/11/2014 (Attachment 4.2.2), the laser diffraction method for measuring particle size in lieu of microscopy should be recommended.

2. Based on the microscopy data there is a general trend that the particle size of the test product is slightly larger than that of reference products. (b) (4) Given the fact the internal diameter of CH8 or French 8 is only 2.64 mm (8 x 0.33 mm), the test product with larger size of granule has a higher risk of clogging the NG tube compared to the reference product in patients who require the need for alternative route of administration.

   Based on our in-house ANDA data, the size of particle is strongly correlated to pellet performance in NG tube (recovery testing). The test particle size (b) (4) mm) over (b) (4)% larger than the reference may have a risk of causing clogging or blockage of 8-F NG tube.

   To date, (b) (4) ANDAs submitted the particle size distribution data. In ANDA 078279[12] and 078936[13], the particle size of test pellets is comparable to that of the reference product. (b) (4) (b) (4) (b) (4) . Please note that granule size distribution is not required to demonstrate equivalence between test and reference product, if the recovery studies are acceptable.

   Reviewer summaries particle distribution data and the result of recovery testing in the following table:

| Combination of syringe and NG tube 8-F (20 mg and 40 mg) | | | | | |
|---|---|---|---|---|---|
| **ANDA No.** | **Sponsor** | **Particle Size D50 (mm)** | **Particle 90% CI** | **Recovery Testing** | **Comments** |
| ANDA078279 | Dr. Reddy's | (b) (4) | Passed | Passed | Minor deficiency |

[12] DARRTS: REV-BIOEQ-21(Primary Review) for ANDA 078279, final date 12/20/2013.
[13] DARRTS: REV-BIOEQ-21(Primary Review) for ANDA 078936, final date 12/31/2013.
[14] (b) (4)
[15]

| | | | | | |
|---|---|---|---|---|---|
| | | (b) (4) | | | for NG tube study |
| ANDA78936 | Mylan | | Passed | Passed | Minor deficiency |
| (b) (4) | | | | | |
| ANDA 202784 | Hetero | (b) (4) | Possible failed | Passed | Not reviewed |

For current application (ANDA 078003), statistical analysis for particle size distribution study will be performed once the firm's particle size data (D10, D50 and D90) become available.

3. Since the pH for different types of water (e.g. distilled, sterile and tap water) may vary between 5.0 to 8.5, there is a concern that the process of dispersing an esomeprazole product in water, soaking for a certain time, and dispensing through an oral syringe with an NG tube might adversely impact the integrity of the enteric coating. As per the control correspondence #140139[Error! Bookmark not defined.], the current FDA guidance on Esomeprazole Magnesium DR Capsules will be revised to recommend in vitro NG tube studies using water with different pH (e.g., pH 5.5, 6.5, and 7.5) with different soak time (e.g., 0 minute and 15 minutes).

4. In its current amendment the firm voluntarily conducted particle size distribution study using water with pHs of 5.4, 5.9 and 6.4, which were chosen to represent routine hospital water conditions per its claim. Since the firm had conducted particle size study at water pHs of 5.4 and 6.4, which are close to the DB II-recommended water pHs of 5.5 and 6.5, therefore, the firm is requested to determine the comparative particle size of granule dispersion in pH 7.5 water with soak times of 0 min and 15 mins. The particle size study should be conducted using 12 units each of the test and the reference products after delivery to the container through a combination of syringe and the 8F NG tube. The firm is requested to provide all particle size data at D10, D50, and D90 levels. The firm is recommended to determine particle size using the method of laser diffraction or other method that is sufficiently reproducible and sensitive. The firm is also requested to submit validation reports for the particle size distribution study.

**Firm's particle size distribution study is incomplete.**

**Deficiency #2:**

*Please provide validation reports for particle size distribution study.*

**Firm's Response:**
The requirement for method validation was considering for the employment of laser

diffraction method for the PSD study. In this case, particle size distribution determination of pellets is beyond the scope of this technique and was therefore evaluated by microscopy. The microscope is used as a measuring device.

**Reviewer's Comment:**
Firm's particle size analysis by microscopy is not acceptable. The firm is recommended to repeat comparative particle size of granule dispersion using 12 units each of the test and reference products, for both 20 mg and 40 mg strengths, in 50 mL of water at pH 7.5 with soaking time of 0 and 15 minutes as mentioned in reviewer's comment on deficiency #1 above.

The firm should use laser diffraction method for particle size distribution analysis and provide data at D10, D50 and D90 level. The firm should also provide validation reports for particle size distribution study.

**Deficiency #3:**

*Please provide information of the nasogastric tube and syringe (e.g material, brand, size) and type and pH of Water used in in vitro NG tube study (e.g sedimentation, particle size, recovery, acid resistance)*

**Firm's Response:**
Information for the NG tubing, Syringe, purified water and pHs utilized for the NG tube study is provided below.

Nasogastric Tubing: 8.0 French tube of material PVC manufactured by Kendall Argyle.
Syringe: 50 ml syringe, BD syringe 60 ml capacity (BD 50 ml precise syringe) Luer-Lok Tip Latex Free sterile syringe.

The in vitro NG tube study was conducted using Millipore/SG purified water at pHs: 5.4, 5.9 and 6.4 throughout all stages of the in vitro NG tube study as well as the particle size study by microscopy.

**Reviewer's Comment:**

Firm's response to deficiency #3 is satisfactory.

### 3.4.2 Deficiency #4 (Acid Resistance Stability Testing):

*Since your test product is designed in such a way that enteric coating starts dissolving above pH 5.5, and the pH of water may vary between 6.5 to 8.5, there is a concern that the process of dispersing capsule in water, soaking for a certain time, and dispensing through an oral syringe with an NG tube might adversely impact the integrity of the enteric coating. Please demonstrate stability of the dispersed granules in different pH of water with different soak time prior to performing acid resistance testing.*

*Please repeat acid resistance stability testing using 12 units of both strengths of the test and reference products as follows:*

a) *Prepare granule dispersion in 50ml water (soak for 15 min), and collect the contents of granule dispersion at the tube exit. Please measure the initial pH of water and pH of the water after the dispersed granules are delivered through the combination of syringe and NG tube.*
b) *Transfer the contents of granule dispersion into dissolution vessel containing 300ml of 0.1N HCl maintained at 37± 0.5°C*
c) *Flush the Nasogastric tube with additional water and transfer any remaining contents into the dissolution media mentioned above.*
d) *Acid resistance testing should be conducted using USP Apparatus II at 100 rpm. Analyze the amount of Esomeprazole released at 120 minutes.*

*Please repeat the above steps using different pH of water (e.g pH 6, 7 and 8) with different soak times in syringe (e.g. 15 min, 30min and 60 min).*

**Firm's Response:**

Per Agency's recommendation NG tube study was performed using 0, 15, 30 and 60 minute soaking times in a 50 mL syringe at 3 different pHs (5.4, 5.9 and 6.4) as these pHs best represent water conditions in a hospital setting. pH of water was measured before and after the dispersed granules are delivered through the combination of syringe and NG tube. It was observed that the change in the pH of water at the initial and at the end once the granules exited the NG tube was not significant.

The tubing and the syringe were inspected for any aggregation, adherence or clogging of granules. It was observed that no aggregation, adherence or clogging of granules were found for both Test (Cipla) and RLD product.

The contents from the NG tube were transferred to a dissolution vessel containing 300 mL of 0.1M HCl at 37°C(+/-0.5°C) where acid resistance testing was conducted using USP Apparatus II at a speed of 100 rpm. (b) (4) (b) (4) (b) (4)

The table below provides a summary of the NG Tube study, it can be concluded from the table that the Test (Cipla) product (pellets) remains intact throughout the soaking stage at various pHs (5.4, 5.9 and 6.4) up to 60 minutes which is in agreement with the particle size morphology that shows the pellets as unchanged circular shaped pellets. Conversely, the RLD product pellets begin to rupture, deteriorate, disintegrate and lose their shape at pHs 5.4, 5.9 and 6.4 for the soaking intervals up to 30 and 60 minutes which agrees with the low assay values following the 120 minute of acid treatment obtained for the RLD product.

Please refer to **Module 3.2.P.2** product development report for complete NG tube study report and photographs of pellets taken at different stages (syringe with capsule's content,

NG tube with capsule content, pellets in beaker after exiting NG Tube and pellets after two hours of acid treatment.). Representative photographs are provided herein for the 40 mg strength only, which are representative of 20 mg. The photographs and observations from the NG tube study are consistent with the microscopy study findings for both Test (Cipla) and RLD products (20 mg and 40 mg) as referenced under Bioequivalence Query No. 1.

**Test 40 mg pH 6.4 30 min**

(b) (4)

**RLD 40 mg pH 6.4 30 min**

(b) (4)

**20 mg: Acid Resistant Study Summary Results using 8.0 French NG Tube**

| Test Product-Esomeprazole Magnesium Delayed-Release Capsules USP, 20 mg, | | | | | | Reference Product Nexium Capsules 20 mg | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Soaking Time (minutes) | Initial HPLC Assay % | % Assay of pellets after Acid Treatment | | | | Soaking Time (minutes | Initial HPLC Assay % | % Assay of pellets after Acid Treatment | | | |
| | | Mean | Min | Max | %RSD | | | Mean | Min | Max | %RSD |
| **(8.0 French) Millipore Water at pH 5.4** | | | | | | | | | | | |
| 0 | 99.3 | 96.3 | (b) (4) | | 0.78 | 0 | 99.6 | 93.4 | (b) (4) | | 1.33 |
| 15 | 99.3 | 95.8 | | | 0.79 | 15 | 99.6 | 93.1 | | | 1.87 |
| 30 | 99.3 | 95.9 | | | 1.71 | 30 | 99.6 | 73.1 | | | 6.99 |
| 60 | 99.3 | 96.7 | | | 1.92 | 60 | 99.6 | 18.6 | | | 23.79 |
| **(8.0 French) Millipore Water at pH 5.9** | | | | | | | | | | | |
| 0 | 99.3 | 99.3 | (b) (4) | | 1.96 | 0 | 99.6 | 92.7 | (b) (4) | | 2.50 |
| 15 | 99.3 | 100.0 | | | 2.07 | 15 | 99.6 | 90.0 | | | 5.79 |
| 30 | 99.3 | 98.7 | | | 2.28 | 30 | 99.6 | 77.4 | | | 6.03 |
| 60 | 99.3 | 98.6 | | | 1.91 | 60 | 99.6 | 17.7 | | | 20.77 |
| **(8.0 French) Millipore Water at pH 6.4** | | | | | | | | | | | |
| 0 | 99.3 | 98.3 | (b) (4) | | 2.59 | 0 | 99.6 | 94.8 | (b) (4) | | 1.56 |
| 15 | 99.3 | 97.8 | | | 0.72 | 15 | 99.6 | 94.3 | | | 1.30 |
| 30 | 99.3 | 97.9 | | | 1.50 | 30 | 99.6 | 87.4 | | | 4.96 |
| 60 | 99.3 | 97.7 | | | 1.66 | 60 | 99.6 | 17.7 | | | 21.00 |

**40 mg: Acid Resistant Study Summary Results using 8.0 French NG Tube**

| Test Product-Esomeprazole Magnesium Delayed-Release Capsules USP, 20 mg, | | | | | | Reference Product Nexium Capsules 20 mg | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Soaking Time (minutes) | Initial HPLC Assay % | % Assay of pellets after Acid Treatment | | | | Soaking Time (minutes | Initial HPLC Assay % | % Assay of pellets after Acid Treatment | | | |
| | | Mean | Min | Max | %RSD | | | Mean | Min | Max | %RSD |
| **Millipore Water at pH 5.4** | | | | | | | | | | | |
| 0 | 98.2 | 89.4 | (b) (4) | | 3.47 | 0 | 99.5 | 91.6 | (b) (4) | | 6.07 |
| 15 | 98.2 | 89.6 | | | 3.53 | 15 | 99.5 | 12.9 | | | 30.65 |
| 30 | 98.2 | 89.5 | | | 3.50 | 30 | 99.5 | 1.6 | | | 30.79 |
| 60 | 98.2 | 88.1 | | | 5.70 | 60 | 99.5 | 0.5 | | | 54.54 |
| **Millipore Water at pH 5.9** | | | | | | | | | | | |
| 0 | 98.2 | 95.9 | (b) (4) | | 1.77 | 0 | 99.5 | 91.2 | (b) (4) | | 4.97 |
| 15 | 98.2 | 95.3 | | | 0.58 | 15 | 99.5 | 2.4 | | | 42.40 |
| 30 | 98.2 | 95.4 | | | 1.16 | 30 | 99.5 | 1.2 | | | 33.11 |
| 60 | 98.2 | 92.7 | | | 1.79 | 60 | 99.5 | ND | | | ND |
| **Millipore Water at pH 6.4** | | | | | | | | | | | |
| 0 | 98.2 | 97.7 | (b) (4) | | 1.72 | 0 | 99.5 | 97.6 | (b) (4) | | 1.93 |
| 15 | 98.2 | 97.3 | | | 1.36 | 15 | 99.5 | 1.3 | | | 48.79 |
| 30 | 98.2 | 97.9 | | | 1.47 | 30 | 99.5 | 2.2 | | | 19.83 |
| 60 | 98.2 | 97.6 | | | 1.46 | 60 | 99.5 | 0.9 | | | 42.53 |

## Review of the firm's data:

Materials and Instrument:

a) Instrument: High Performance Liquid Chromatography.

b) Column type: (b) (4)

( Make : (b) (4) column, (b) (4) is suitable)

c) <u>Reagent / Chemicals:</u> (b) (4)

(b) (4)

d) 8 French NG feeding tube-material type and manufacturer: 1) 8 French tube of material PVC manufactured by Kendall Argyle

e) Syringe description: 50 ml syringe:- BD syringe 60 ml capacity (BD 50 ml Precise syringe) Luer-Lok Tip Latex Free sterile syringe

**Acid Resistance Testing Procedure:**

Dissolution Conditions:
Dissolution Medium : 300 ml of 0.1 M HCI
Apparatus : USP TYPE II
Speed : 100 RPM
Time : 120 minutes
Temperature : 37°C ± 0.5°C

(b) (4)

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(b) (4)

**Results:**
The results of acid resistance study are summarized in the tables below.

**Table 7. Acid resistance stability data for 20 mg and 40 mg**

| | | |
|---|---|---|
| **Dissolution Conditions** | **Apparatus:** | USP Apparatus II (Paddle) |
| | **Speed of Rotation:** | 100 RPM |
| | **Medium:** | Acid stage: 0.1N HCl |
| | **Volume:** | 300 mL |
| | **Temperature:** | 37 ± 0.5° C |
| **Firm's Proposed Specifications** | Acid stage: Not more than (b) (4)% in 120 min | |

| **pH** | **Soaking Time** | **No. of Dosage Units** | | **Release (%) 20 mg** | | **Release (%) 40 mg** | |
|---|---|---|---|---|---|---|---|
| | | | | **Test (batch #)** | **RLD (batch #)** | **Test (batch #)** | **RLD (batch #)** |
| **5.4** | 0 min | 12 | Mean | **3.0** | **6.2** | **8.8** | **7.9** |
| | | | Range | (b) (4) | | | |
| | | | %CV | 0.78 | 1.33 | 3.47 | 6.07 |
| | 15 min | 12 | Mean | **3.5** | **6.5** | **8.6** | **86.6** |
| | | | Range | (b) (4) | | | |
| | | | %CV | 0.79 | 1.87 | 3.53 | 30.65 |
| | 30 min | 12 | Mean | **3.4** | **26.5** | **8.7** | **97.9** |
| | | | Range | (b) (4) | | | |
| | | | %CV | 1.71 | 6.99 | 3.5 | 30.79 |
| | 60 min | 12 | Mean | **2.6** | **81** | **10.1** | **99** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | Range | (b) (4) | | | |
| | | | %CV | 1.92 | 23.79 | 5.7 | 54.54 |
| 5.9 | 0 min | 12 | Mean | **0** | **6.9** | **2.3** | **8.3** |
| | | | Range | (b) (4) | | | |
| | | | %CV | 1.96 | 2.50 | 1.77 | 4.97 |
| | 15 min | 12 | Mean | **-0.7** | **9.6** | **2.9** | **97.1** |
| | | | Range | (b) (4) | | | |
| | | | %CV | 2.07 | 5.79 | 0.58 | 42.4 |
| | 30 min | 12 | Mean | **0.6** | **22.2** | **2.8** | **98.3** |
| | | | Range | (b) (4) | | | |
| | | | %CV | 2.28 | 6.03 | 1.16 | 33.11 |
| | 60 min | 12 | Mean | **0.7** | **81.9** | **5.5** | ND |
| | | | Range | (b) (4) | | | |
| | | | %CV | 1.91 | 20.77 | 1.79 | ND |
| 6.4 | 0 min | 12 | Mean | **1.0** | **4.8** | **0.5** | **1.9** |
| | | | Range | (b) (4) | | | |
| | | | %CV | 2.59 | 1.56 | 1.72 | 1.93 |
| | 15 min | 12 | Mean | **1.5** | **5.3** | **0.9** | **98.2** |
| | | | Range | (b) (4) | | | |
| | | | %CV | 0.72 | 1.30 | 1.36 | 48.79 |
| | 30 min | 12 | Mean | **1.4** | **12.2** | **0.3** | **97.3** |
| | | | Range | (b) (4) | | | |
| | | | %CV | 1.50 | 4.96 | 1.47 | 19.83 |
| | 60 min | 12 | Mean | **1.6** | **81.9** | **0.6** | **98.6** |
| | | | Range | (b) (4) | | | |
| | | | %CV | 1.66 | 21 | 1.46 | 42.53 |

**Reviewer's Comments on the acid resistance stability test:**

1. Esomeprazole is an acid labile drug substance; therefore, the firm should measure esomeprazole from the beadlets of the capsule and not from the dissolution medium (0.1N HCl) during the acid stage. As per the firm's test produce shown above, the firm follows the above described method in its acid stage testing.

2. In its current amendment dated 3/31/2014, the firm repeated acid resistance testing at 3 different water pHs (5.4, 5.9 and 6.4) with different soaking times (0, 15, 30 and 60 minutes), the water pHs and soaking times are the same as those used in its particle size distribution study. The firm reported that the change in the pH of water at the initial and at the end once the granules exited the NG tube was not significant.

3. The results show that less than 4% of Esomeprazole for 20 mg (CV% < 3) and less than or equal to10.1% of Esomeprazole for 40 mg (CV% <6) DR granules of the test product collected from NG tube releases in the acidic medium at all three water pHs with all soaking times (0, 15, 30 and 60 minutes). Mean of the amount released in acid medium meet the specification of NMT (b) (4) % drug released in acid stage for both strengths of the test products.

   In contrast, under the same conditions, the 20 mg reference drug released greater than (b) (4) % at 30 minutes and up to 81.9% of Esomeprazole at 60 minutes, and the 40 mg reference drug released greater than 85% at 15 minutes and up to 99% of Esomeprazole at 60 minutes. Comparing with the acid resistance data with 0 minute soaking time (immediate delivery), both strengths of the reference product released less than (b) (4) % only. This indicates that the enteric coating of the reference product is damaged by 15 and 30 minutes water pretreatment.

4. The acid resistance data are in agreement with the particle size morphology. The pellets from test product remain intact throughout the soaking stage at various pHs (5.4, 5.9 and 6.4) up to 60 minutes, whereas the pellets from the reference pellets begin to rupture, deteriorate, disintegrate and lose their shape at the pHs from 15 to 60 minutes soaking minutes.

5. Based on our in house data, the % release of the reference drug product in (b) (4) applications was over (b) (4) % after soaking in water from 15 min to 60 min (b) (4) (b) (4) Yet, none of test drug products has release over (b) (4) %. The particle rupture of the reference drug product was also observed in ANDA78003 from the soaking times of 15 min to 60 min with different pH water (pH 5.4, 5.9 and 6.4). The soaking time seems to be more relevant to the rupture of pellet than water pH as long as it is above pH 5.5.

**Summary of Acid Resistance Stability Data in ANDAs**

| | NG tube information (8F) | | % Released in the Acid Stage for 2 hours | | | |
|---|---|---|---|---|---|---|
| | Time | Water pH | 20 mg | | 40 mg | |
| | | | Test | RLD | Test | RLD |
| (b) (4) | | | | | | |
| 078279 | 15 min | No define | 6.1 | 11.8 | 5.6 | 2.3 |
| 078936 | 15 min | No define | 2.6 | 3.2 | 2.7 | 1.0 |
| 202784 | 15 min | No define | 5.5 (94.5%) | 6.2 (93.8%) | 6.7 (93.3%) | 7.7 (92.3%) |
| 78003 | 0 min | 5.4 | 3 | 6.2 | 8.8 | 7.9 |
| | 15 min | | 3.5 | 6.5 | 8.6 | 86.6 |
| | 30 min | | 3.4 | 26.5 | 8.7 | 97.9 |
| | 60 min | | 2.6 | 81 | 10.1 | 99 |
| | 0 min | 5.9 | 0 | 6.9 | 2.3 | 8.3 |
| | 15 min | | -0.7 | 9.6 | 2.9 | 97.1 |
| | 30 min | | 0.6 | 22.2 | 2.8 | 98.3 |
| | 60 min | | 0.7 | 81.9 | 5.5 | ND |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 0 min | | 1.0 | 4.8 | 0.5 | 1.9 |
| | 15 min | **6.4** | 1.5 | 5.3 | 0.9 | 98.2 |
| | 30 min | | 1.4 | 12.2 | 0.3 | 97.3 |
| | 60 min | | 1.6 | 81.9 | 0.6 | 98.6 |
| | | | | | | (b) (4) |

Based on the bio-meeting minute 04/11/2014 (see Attachment 4.2.2), the DB considers that 0 and 15 min soaking times are appropriate for acid resistance testing. To confirm the results of ANDAs, the DB will request the FDA laboratory to conduct acid resistance testing for each strength of reference drug products with different the soaking time in water with different pH (pH 5.5, 6.5, and 7.5). The DB will accept the test product as long as it doesn't release more than the RLD, even if it technically fails the acid resistance test according to the less than (b) (4)% release criteria.

6. For NDA 021153, the innovator evaluated the integrity of the enteric-coated pellets following administration of the esomeprazole pellets through the NG- or G-tubes. The study indicated that an average of 98.8-99.5% of the contents of the 20mg Nexium capsules and 98.7-99.3% of the contents of the 40mg Nexium capsules are retained following passage through the NG tube and subsequent acid exposure. Therefore, the administration of the esomeprazole pellets through the NG tube does not appear to affect the acid resistance of the pellets (i.e., the integrity of the enteric coating) [16]. Please note the dispersed pellets were injected into the NG tube without prior soaking in the water in the syringe (Detailed summaries of the results are provided in Attachment 4.2.5).

   Per CMC review[8], studies submitted in the original NDA (April 3, 2000 amendment (Page 004-001-013)) showed that the pellets maintained their acid resistance for up to 30 minutes in tap water at pH 7.9, as well as in various acidic media (e.g. apple juice). However, the innovator did not adequately address the stability of the suspension of these enteric coated pellets in tap water, i.e. it does not define the maximum time in which it must be delivered after preparation of the suspension, therefore, the current labeling of NG tube administration states: *'The suspension must be used immediately after preparation."* Please see details at 3.3.2. The innovator did not conduct the pellets stability in different pH of water before exposure to acid either.

7. In the Prevacid® SoluTab™ (Lansoprazole) Delayed Release ODT (NDA 021428) submission, to test the feasibility of dispersing LODT in water prior to administration to the patient, the innovator conducted in vitro studies to demonstrate the stability profile of the dispersed tablet as a function of pH, time and temperature. Studies were conducted over a pH range of 6.5-8.5 (the acceptable pH range for tap water per EPA guideline), temperature ranges of 5 to

[16] DARRTS: REV-CLINPHARM-01 (General Review) for NDA 021153 final date 04/16/2003.

37ºC, soak times of 5 to 30 minutes and different volumes of tap water (5 ml, 10 ml and 30 ml) to support administration of LODT through the combination of a syringe and NG tube.

**Table 4.1d Acid Resistance Stability Data for 30 mg LODT Dispersed in Tap Water**

| Lot Number | Exposure Time (Min) | Amount of Water (mL) | Initial pH of Water | pH of Water After Adding Tablet | Temp (°C) | Syringe and NG Tube | Control % Drug Release (Range) | Mean %LC (SD) Control | % Drug Release | Mean %LC (SD) |
|---|---|---|---|---|---|---|---|---|---|---|
| Z5134074 | 5 | 5 | 7.97 | 8.05, 7.91,7.84 | RT | No | (b) (4) | 6.1 (0.4) | (b) (4) | 6.0 (0.7) |
| Z5134074 | 5 | 30 | 6.91 | 6.45, 6.74, 7.02 | RT | No | | 6.1 (0.4) | | 6.0 (0.3) |
| Z5134074 | 10 | 5 | 7.97 | 8.02, 7.94, 8.02 | RT | No | | 6.1 (0.4) | | 5.5 (0.2) |
| Z5134074 | 10 | 30 | 6.91 | 6.98, 7.09, 6.98 | RT | No | | 6.1 (0.4) | | 5.9 (0.2) |
| Z5134074 | 15 | 5 | 7.97 | 7.94, 7.94, 7.82 | RT | No | | 6.1 (0.4) | | 6.0 (0.7) |
| 010019P22 | 15 | 10+10* | 8.51 | 5.96, 5.84, 5.91 | 37.0 | Yes | | 5.7 (0.3) | | 7.9 (0.4) |
| 010019P22 | 15 | 10+10* | 8.51 | 5.90, 5.76, 5.70 | 5 | Yes | | 5.7 (0.3) | | 7.5 (0.6) |
| 010019P22 | 15 | 10+10* | 6.52 | 5.64, 5.47, 5.55 | 37.0 | Yes | | 5.7 (0.3) | | 8.3 (0.3) |
| 010019P22 | 15 | 10+10* | 6.52 | 5.10, 5.04, 5.07 | 5 | Yes | | 5.7 (0.3) | | 6.9 (1.0) |
| Z5134074 | 15 | 30 | 6.91 | 6.51, 6.84, 6.66 | RT | No | | 6.1 (0.4) | | 6.4 (0.2) |
| Z5134074 | 30 | 5 | 7.97 | 7.86, 7.75, 7.83 | RT | No | | 6.1 (0.4) | | 6.2 (0.6) |
| Z5134074 | 60 | 5 | 7.97 | 7.37, 7.77, 6.48 | RT | No | | 6.1 (0.4) | | 8.3 (0.5) |
| Z5134074 | 120 | 5 | 7.97 | 7.35, 6.46, 6.8 | RT | No | | 6.1 (0.4) | | 25.6 (0.8) |

RT = Room Temperature; SD = Standard Deviation; %LC = % Label Claim; * Flush Volume.
Yes = Experiment performed with syringe and NG tube; No = Experiment not performed with Syringe and NG tube.

8. As per the RLD labeling, Nexium ® can be given with water through a nasogastric tube (NG tube). Since the labeling does not specify which type of water should be used, the healthcare person may provide the patients with different types of water, such as tap water, sterile water, distilled water, and drinking bottled water. These different types of water have different pH. The pH of tap water ranges from 6.5 to 8.5 according to USA Environment Protection Agency[17]. The pH of sterile water is 6.0 (5.0-7.0) based on FDA approved sterile water[18], or is pH 7.1± 0.2 after sterilization based on USP acceptance criteria[19]. Distilled water is pH ~5.8. The initial reading for deionized water should be pH 7. Yet, when deionized water comes into contact with atmospheric CO2, it can reduce the water's pH to 5.5.

   Both of test and reference were formulated as enteric-coated pellets to prevent rapid degradation in the acid environment of the stomach. The test product contains (b) (4) and the reference product contains (b) (4)[20]. (b) (4) Esomeprazole DR Capsules is designed in such a way that the enteric starts dissolving above pH 5.5. Low pH water may retain granules gastro-resistant coating, while high pH water may damage the enteric coating of the granules of

[17] Part 143-National Secondary Drinking Water Regulations, November 14, 2013: Secondary Maximum contaminant level for public water system, United States Environmental Protection Agency.
[18] Pharmacy Bulk Packages in B. Braun Glass Containers: Sterile water for injection USP Labeling for 500 mL and 1000 mL sterile water container approved by the FDA.
[19] *USP36–NF31* Page 71: Sterile test
[20] (b) (4)

Esomeprazole delayed-release capsules and cause the earlier release of drug substance and/or swollen of beads which may subsequently clog the NG tubing.

As per discussion with Dr. John Peter (the Division of Clinical Review/OGD), the OGD should use conservative approach and require in vitro testing in a range of pH for water (see Appendix 4.5). Based on pH distribution in drinking water, the review team has decided to recommend in vitro testing in three pH, i.e. pH 5.5, 6.5, and 7.5 because they are good representations over the pH range of water. It should be noted that although the well water, "hard water" could have a pH 8.5, most people will use a filter or ion exchange process to soft the water by removing $Mg^{2+}$ and $Ca^{2+}$ (hardness minerals). As a result, the "softer water" has a lower pH than hard water.

In its current amendment dated 3/31/2014 for this application, the firm conducted acid resistance testing using water with pHs of 5.4, 5.9 and 6.4 instead of pH 6, 7, and 8 which was previously recommended by the DB. The firm stated the pHs they used best represent water conditions in a hospital setting. The DB disagrees the firm's statement. Since the tab water may be used to deliver the medicine in hospital, its pH may vary between 6.5 to 8.5. The DB is in the process of posting a guidance to recommend the firm conducting in vitro NG tube testing in water with pH 5.5, 6.5 and 7.5**Error! Bookmark not defined.**. Since the firm has conducted acid resistance test in PH 5.4 and 6.4 which are closed to DB-recommended water pHs of 5.5 and 6.5, therefore, the firm is requested to repeat the acid resistance testing using water at pH 7.5 with soak times of 0 and 15 minutes.

9. NG tube administration may damage the granules enteric coating and expose Esomeprazole to gastric acid which would inactive the drug substance. Therefore, the firm is requested to repeat acid resistance stability testing using 12 units of both strengths of the test and the reference products as follows:

   Please conduct comparative acid resistance stability testing after recovery through a combination of oral syringe and 8 F NG tube using 12 units of both strengths of the test and the reference products using pH 7.5 water with 0 and 15 minutes soaking time. Please use the following method:

   a) Prepare the granule dispersion in 50 ml water and collect the contents of granule dispersion at the tube exit immediately (0 min).
   b) Transfer the contents of granule dispersion into dissolution vessel containing 300 mL of 0.1 N HCl maintained at 37 ±0.5°C.
   c) Flush the nasogastric tube with additional water and transfer any remaining contents into the dissolution media mentioned above.
   d) Please repeat the testing described above with a fresh set of 12 units and hold for 15 min.

   Please measure the initial pH of water and pH of the water after the dispersed granules are delivered through NG tube. Acid resistance testing should be

conducted using USP Apparatus II at 100 rpm. Analyze the amount of Esomeprazole released from the pellets of the DR capsule [not from the dissolution medium (0.1N HCl)] at 120 minutes.

Firm's acid resistance stability test is **incomplete.**

### 3.5 Waiver Request(s)

| | |
|---|---|
| **Strengths for which waivers are requested** | 20 mg |
| **Proportional to strength tested in vivo?** | Yes |
| **Is dissolution acceptable?** | Yes |
| **Waivers granted?** | **WAIVERS DENIED** |
| **If not then why?** | Pending firm's response to deficiencies identified in NG tube study. |

### 3.6 Deficiency Comments

**<u>In vitro tests for Nasogastric (NG) Tube administration:</u>**

1. The DB II acknowledge that the firm conducted particle size distribution study after delivery through syringe and NG tube using water with different pH (5.4, 5.9 and 6.4) and different soak times (0, 15, 30 and 60 minutes). However, firm's particle size distribution analysis using microscopy may not be suitable for particle size distribution (D10, D50 and D90), therefore it is not acceptable.

   In addition, we disagree with firm's statement that the pH (5.4, 5.9 and 6.4) represent routine hospital water conditions. Since the pH for different types of water (e.g. distilled, sterile and tap water) may vary between 5.0 to 8.5, there is a concern that the process of dispersing an esomeprazole product in water, soaking for a certain time, and dispensing through an oral syringe with an NG tube might adversely impact the integrity of the enteric coating. Therefore, water with different pH (5.5, 6.5, and 7.5) is currently recommended in the in vitro NG studies.

   The firm is requested to determine the comparative particle size of granule dispersion using 12 units each strength of the test and the reference products **in pH 7.5 water with soak times of 0 and 15 minutes**. Please follow the procedure described in the deficiency letter (deficiency #2) issued by the DB II on 9/26/2012.

   The firm is requested to provide the particle size data at the D10, D50, and D90 levels and report flush volume used in these studies. The firm is requested to **determine particle size using laser diffraction method**, and also provide validation reports for particle size distribution study.

2. We acknowledge that the firm has conducted acid resistance stability testing for both 20 mg and 40 mg strengths after recovery through a combination of oral syringe and 8 French NG tube in water with different pH (5.4, 5.9, and 6.4) at 0, 15, 30 and 60 minutes. Significant release and pellets rupture in acid from the reference listed product were observed after the water treatment.

   To ensure that the test product doesn't release more than the reference listed product throughout the soaking stages at currently recommended water pH (5.5, 6.5 and 7.5), the firm is requested to repeat comparative acid resistance stability testing for both strengths using 12 units of the test and the reference products **in pH 7.5 water at 0 minute and 15 minutes.** Please follow the procedure described in the deficiency letter (deficiency #4) issued by the DB II on 9/26/2012.

3. We acknowledge that the firm had conducted comparative recovery testing in its previous amendment dated 04/25/2013, where the pH of water used in the recovery test was not reported. The firm is requested to repeat the comparative recovery studies of the dispersed granules for both 20 mg and 40 mg strengths using the 8 French nasogastric tubes. Please use 12 units of the test and the reference products in 50 ml water **with different pH (5.5, 6.5, and 7.5) at 0 minute and 15 minutes.** Please follow the procedure described in previous deficiency letter (deficiency #3) issued by the DB II on 9/26/2012.

4. The firm is requested to provide the expiration date for the reference listed product (20 mg: batch #J014509; 40 mg: batch# J012025) and testing dates for the particle size distribution study and acid resistance testing submitted in firm's current amendment dated 3/31/2014.

### 3.7 Recommendations

1. The single-dose, *in vivo* **fasting** bioequivalence study (#P1BD05001) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable.**

2. The single-dose, *in vivo* **fed** bioequivalence study (#P1BD05002) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable**.

3. The single-dose, *in vivo* **sprinkled fasting** bioequivalence study (#P1BD05010) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable**.

4. The *in vitro* dissolution testing conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 20 mg (Lot #Y51231) and 40 mg (Lot # Y51232, same as Lot#Y51286 used in the *in vivo* bioequivalence studies, but different package number), comparing to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 20 mg (Lot#P4879) and 40 mg (Lot #N5819), is **acceptable**.

   The dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b)(4)% in 120 minutes<br>Buffer stage: NLT (b)(4)% in 30 minutes |

5. The 20 mg strength is proportionally formulated to the 40 mg strength. The DB can not deem the 20 mg strength of the test product to be bioequivalent to the 20 mg strength of the reference product based on CFR 320.24(b)(6) at this time pending acceptable response to deficiencies related to in vitro NG tube studies.

The application is **incomplete** due to identified deficiencies shown above.

### 3.8 Comments for Other OGD Disciplines

| Discipline | Comment |
|---|---|
| None | N/A |

## 4 APPENDIX

### 4.1 Formulation Data

**Test Product**[21]

| Ingredient | 20 mg (mg/Capsule) | wt/wt (%) 20 mg | 40 mg (mg/Capsule) | wt/wt (%) (40 mg) |
|---|---|---|---|---|

[21] v:\Firmsam\IvaxPharm\ltrs&rev\78003N1105.doc

(b) (4)

**Reference Product**[22]

| Composition of Nexium® Delayed-Release Capsules | | |
|---|---|---|
| **Component** | **EQ. 20.00 mg Base strength (mg)** | **EQ. 40.00 mg Base strength (mg)** |
| Esomeprazole as Magnesium Trihydrate | 22.30 | 44.50 |
| Glyceryl monostearate (b) (4) (b) (4) | (b) (4) | |
| Hydroxypropyl Cellulose | | |
| Magnesium Stearate | | |

[22] Control Document # 03-165; Esomeprazole Magnesium Delayed-Release Capsules.

| | | | |
|---|---|---|---|
| Methacrylic Acid Copolymer Type C | | (b) (4) | |
| Polysorbate 80 | | | |
| Sugar spheres (b) (4) (b) (4) | | | |
| Talc | | | |
| Hard gelatin capsules | | | |

**Formulation Data**

| | RLD | IVAX |
|---|---|---|
| (b) (4) | | |

Diameter of Size of feeding tube (1 French unit=0.33 millimeters):
16 French = 5.28 mm
8 French =2.666 mm

## 4.2 Additional Attachments

### 4.2.1 Particle Size Distribution Data Submitted in Current Amendment dated 3/31/2014

## RESULTS

**Product** : Esomeprazole Magnesium Delayed Release capsules 20mg & 40mg.

**Method** : Particle Size Distribution by Microscopy.

**A.R. No.** : I1VK14C02181, I1VK14C02180,I1VKC02435, I1VKC02344



### Cipla Product 20mg at pH 5.4

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) |
| 1 | (b) (4) | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 29.80 | 43.09 | 42.41 | 78.82 | 38.43 | 82.94 | 58.87 | 91.02 | 58.87 | 91.02 |
| %RSD | 4.3 | 4.7 | 5.9 | 8.6 | 5.0 | 8.6 | 8.1 | 10.0 | 8.1 | 10.0 |

**Observation:**

| | |
|---|---|
| **Initial** | Oval to circular shaped pellets |
| **0 Minute** | Oval to circular shaped pellets (Remained Intact) |
| **15 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **30 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **60 Minutes** | Oval to circular shaped pellets (Remained Intact) |

No clogging, adherence to the walls and no aggregation of pellets is observed in any of the time intervals.

**Prepared By** : (b) (6)

**Date** : 27-03-2014

**Reviewed By** : (b) (6)

**Date** : 27-03-2014

## RESULTS

| | | |
|---|---|---|
| **Product** | : | Esomeprazole Magnesium Delayed Release capsules 20mg & 40mg. |
| **Method** | : | Particle Size Distribution by Microscopy. |
| **A.R. No.** | : | I1VK14C02181, I1VK14C02180,I1VKC02435, I1VKC02344 |



### Reference Product 20mg at pH 5.4

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) |
| 1 | (b) (4) | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 23.75 | 74.93 | 35.57 | 50.50 | 36.50 | 62.33 | 32.22 | 24.18 | 60.46 | 58.72 |
| %RSD | 5.3 | 10.4 | 7.2 | 7.8 | 6.7 | 9.5 | 6.3 | 3.4 | 10.3 | 8.1 |

**Observation:**

| | |
|---|---|
| **Initial** | Oval to circular shaped pellets |
| **0 Minute** | Oval to circular shaped pellets (Remained Intact) |
| **15 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **30 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |
| **60 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |

No clogging, adherence to the walls and no aggregation of pellets is observed in any of the time intervals.

**Prepared By** : (b) (6)

**Date** : 27-03-2014

**Reviewed By** : (b) (6)

**Date** : 27-03-2014

## RESULTS

**Product** : Esomeprazole Magnesium Delayed Release capsules 20mg & 40mg.

**Method** : Particle Size Distribution by Microscopy.

**A.R. No.** : I1VK14C02181, I1VK14C02180,I1VKC02435, I1VKC02344



### Cipla Product 40mg at pH 5.4

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) |
| 1 | (b) (4) | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 39.98 | 95.73 | 49.51 | 50.32 | 50.86 | 108.60 | 53.56 | 67.89 | 48.35 | 56.99 |
| %RSD | 5.7 | 10.7 | 6.9 | 5.6 | 7.2 | 11.9 | 7.7 | 7.2 | 6.7 | 6.4 |

**Observation:**

| | |
|---|---|
| **Initial** | Oval to circular shaped pellets |
| **0 Minute** | Oval to circular shaped pellets (Remained Intact) |
| **15 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **30 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **60 Minutes** | Oval to circular shaped pellets (Remained Intact) |

No clogging, adherence to the walls and no aggregation of pellets is observed in any of the time intervals.

**Prepared By** : (b) (6)

**Date** : 27-03-2014

**Reviewed By** : (b) (6)

**Date** : 27-03-2014

## RESULTS

| | | |
|---|---|---|
| **Product** | : | Esomeprazole Magnesium Delayed Release capsules 20mg & 40mg. |
| **Method** | : | Particle Size Distribution by Microscopy. |
| **A.R. No.** | : | I1VK14C02181, I1VK14C02180,I1VKC02435, I1VKC02344 |



### Reference Product 40mg at pH 5.4

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) |
| 1 | [redacted] | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 22.24 | 77.98 | 30.12 | 51.84 | N/A | N/A | N/A | N/A | N/A | N/A |
| %RSD | 4.9 | 10.8 | 6.1 | 7.8 | N/A | N/A | N/A | N/A | N/A | N/A |

**Observation:**

| | |
|---|---|
| **Initial** | Oval to circular shaped pellets |
| **0 Minute** | Oval to circular shaped pellets (Remained Intact) |
| **15 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |
| **30 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |
| **60 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |

No clogging, adherence to the walls and no aggregation of pellets is observed in any of the time intervals.

**Note : N/A = Not applicable (Particle size could not be determined due to ruptured and complete deformation of pellets).**

| | | | | | |
|---|---|---|---|---|---|
| **Prepared By** | : | (b) (6) [redacted] | **Reviewed By** | : | (b) (6) [redacted] |
| **Date** | : | 27-03-2014 | **Date** | : | 27-03-2014 |

## RESULTS

| | | |
|---|---|---|
| **Product** | : | Esomeprazole Magnesium Delayed Release capsules 20mg & 40mg. |
| **Method** | : | Particle Size Distribution by Microscopy. |
| **A.R. No.** | : | I1VK14C02181, I1VK14C02180,I1VKC02435, I1VKC02344 |



### Cipla Product 20mg at pH 5.9

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) |
| 1 | (b) (4) | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 29.80 | 43.09 | 58.46 | 28.86 | 53.39 | 90.18 | 23.92 | 58.80 | 38.65 | 40.15 |
| %RSD | 4.3 | 4.7 | 7.6 | 2.7 | 6.9 | 9.5 | 3.2 | 6.1 | 5.4 | 4.4 |

**Observation:**

| | |
|---|---|
| **Initial** | Oval to circular shaped pellets |
| **0 Minute** | Oval to circular shaped pellets (Remained Intact) |
| **15 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **30 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **60 Minutes** | Oval to circular shaped pellets (Remained Intact) |

No clogging, adherence to the walls and no aggregation of pellets is observed in any of the time intervals.

**Prepared By** : (b) (6)

**Date** : 27-03-2014

**Reviewed By** : (b) (6)

**Date** : 27-03-2014

## RESULTS

**Product** : Esomeprazole Magnesium Delayed Release capsules 20mg & 40mg.

**Method** : Particle Size Distribution by Microscopy.

**A.R. No.** : I1VK14C02181, I1VK14C02180,I1VKC02435, I1VKC02344



### Reference Product 20mg at pH 5.9

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) |
| 1 | (b) (4) | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 23.75 | 74.93 | 99.23 | 105.42 | 36.40 | 61.57 | 70.35 | 103.19 | 156.94 | 53.53 |
| %RSD | 5.3 | 10.4 | 14.2 | 12.7 | 6.8 | 8.9 | 10.7 | 11.9 | 28.8 | 7.5 |

**Observation:**

| | |
|---|---|
| **Initial** | Oval to circular shaped pellets |
| **0 Minute** | Oval to circular shaped pellets (Remained Intact) |
| **15 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **30 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |
| **60 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |

No clogging, adherence to the walls and no aggregation of pellets is observed in any of the time intervals.

**Prepared By** : (b) (6)

**Date** : 27-03-2014

**Reviewed By** : (b) (6)

**Date** : 27-03-2014

## RESULTS

**Product** : Esomeprazole Magnesium Delayed Release capsules 20mg & 40mg.

**Method** : Particle Size Distribution by Microscopy.

**A.R. No.** : I1VK14C02181, I1VK14C02180,I1VKC02435, I1VKC02344



### Reference Product 40mg at pH 5.9

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximun (µm) |
| 1 | (b) (4) | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 22.24 | 77.98 | 38.09 | 61.56 | N/A | N/A | N/A | N/A | N/A | N/A |
| %RSD | 4.9 | 10.8 | 7.7 | 9.2 | N/A | N/A | N/A | N/A | N/A | N/A |

**Observation:**

| | |
|---|---|
| **Initial** | Oval to circular shaped pellets |
| **0 Minute** | Oval to circular shaped pellets (Remained Intact) |
| **15 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |
| **30 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |
| **60 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |

No clogging, adherence to the walls and no aggregation of pellets is observed in any of the time intervals.

**Note : N/A = Not applicable (Particle size could not be determined due to ruptured and complete deformation of pellets).**

**Prepared By** : (b) (6)

**Date** : 27-03-2014

**Reviewed By** : (b) (6)

**Date** : 27-03-201

## RESULTS

| | | |
|---|---|---|
| **Product** | : | Esomeprazole Magnesium Delayed Release capsules 20mg & 40mg. |
| **Method** | : | Particle Size Distribution by Microscopy. |
| **A.R. No.** | : | I1VK14C02181, I1VK14C02180,I1VKC02435, I1VKC02344 |



### Cipla Product 20mg at pH 6.4

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) |
| 1 | (b) (4) | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 29.80 | 43.09 | 59.60 | 51.31 | 79.71 | 62.04 | 44.43 | 74.66 | 64.03 | 74.89 |
| %RSD | 4.3 | 4.7 | 8.4 | 5.6 | 10.4 | 6.5 | 5.9 | 7.7 | 8.7 | 7.4 |

**Observation:**

| | |
|---|---|
| **Initial** | Oval to circular shaped pellets |
| **0 Minute** | Oval to circular shaped pellets (Remained Intact) |
| **15 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **30 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **60 Minutes** | Oval to circular shaped pellets (Remained Intact) |

No clogging, adherence to the walls and no aggregation of pellets is observed in any of the time intervals.

(b) (6)

**Prepared By** :

**Date** : 27.03.2014

(b) (6)

**Reviewed By** :

**Date** : 27.03.2014

## RESULTS

**Product** : Esomeprazole Magnesium Delayed Release capsules 20mg & 40mg.

**Method** : Particle Size Distribution by Microscopy.

**A.R. No.** : I1VK14C02181, I1VK14C02180,I1VKC02435, I1VKC02344



### Reference Product 20mg at pH 6.4

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) |
| 1 | (b) (4) | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 23.75 | 74.93 | 28.52 | 49.08 | 32.72 | 92.62 | 34.42 | 48.96 | 40.98 | 57.16 |
| %RSD | 5.3 | 10.4 | 5.3 | 6.8 | 6.0 | 13.1 | 6.4 | 6.6 | 7.4 | 8.1 |

**Observation:**

| | |
|---|---|
| **Initial** | Oval to circular shaped pellets |
| **0 Minute** | Oval to circular shaped pellets (Remained Intact) |
| **15 Minutes** | Oval to circular shaped pellets (Remained Intact). |
| **30 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |
| **60 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |

No clogging, adherence to the walls and no aggregation of pellets is observed in any of the time intervals.

**Prepared By** : (b) (6)

**Date** : 27-03-2014

**Reviewed By** : (b) (6)

**Date** : 27-03-2014

## RESULTS

| | | |
|---|---|---|
| **Product** | : | Esomeprazole Magnesium Delayed Release capsules 20mg & 40mg. |
| **Method** | : | Particle Size Distribution by Microscopy. |
| **A.R. No.** | : | I1VK14C02181, I1VK14C02180,I1VKC02435, I1VKC02344 |



### Cipla Product 40mg at pH 6.4

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) |
| 1 | (b) (4) | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 39.98 | 95.73 | 42.26 | 83.53 | 43.12 | 59.71 | 56.67 | 54.04 | 40.22 | 65.44 |
| %RSD | 5.7 | 10.7 | 5.9 | 9.1 | 6.0 | 6.8 | 7.9 | 6.1 | 5.8 | 7.3 |

**Observation:**

| | |
|---|---|
| **Initial** | Oval to circular shaped pellets |
| **0 Minute** | Oval to circular shaped pellets (Remained Intact) |
| **15 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **30 Minutes** | Oval to circular shaped pellets (Remained Intact) |
| **60 Minutes** | Oval to circular shaped pellets (Remained Intact) |

No clogging, adherence to the walls and no aggregation of pellets is observed in any of the time intervals.

(b) (6)

**Prepared By** :

**Date** : 27-03-2014

(b) (6)

**Reviewed By** :

**Date** : 27-03-2014

## RESULTS

| | | |
|---|---|---|
| **Product** | : | Esomeprazole Magnesium Delayed Release capsules 20mg & 40mg. |
| **Method** | : | Particle Size Distribution by Microscopy. |
| **A.R. No.** | : | I1VK14C02181, I1VK14C02180,I1VKC02435, I1VKC02344 |



### Reference Product 40mg at pH 6.4

| Sr. No | Initial | | 0 Minute | | 15 Minutes | | 30 Minutes | | 60 Minutes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) | Minimum (µm) | Maximum (µm) |
| 1 | | | | | | | | | | (b) (4) |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | 22.24 | 77.98 | 33.34 | 31.64 | N/A | N/A | N/A | N/A | N/A | N/A |
| %RSD | 4.9 | 10.8 | 6.6 | 5.1 | N/A | N/A | N/A | N/A | N/A | N/A |

**Observation:**

| | |
|---|---|
| **Initial** | Oval to circular shaped pellets |
| **0 Minute** | Oval to circular shaped pellets (Remained Intact) |
| **15 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |
| **30 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |
| **60 Minutes** | Ruptured, disintegrated and decoated irregular shaped pellets. |
| No clogging, adherence to the walls and no aggregation of pellets is observed in any of the time intervals. | |

**Note : N/A = Not applicable (Particle size could not be determined due to ruptured and complete deformation of pellets)**

| | | | |
|---|---|---|---|
| **Prepared By** | : (b) (6) | **Reviewed By** | : (b) (6) |
| **Date** | : 27-03-2014 | **Date** | : 27-03-2014 |

### 4.2.2 Internal Meeting Minutes (04/11/2014)

**Internal Meeting Minutes**

| | |
|---|---|
| **Topic**: | Esomeprazole Delayed Release Capsules, 20 mg and 40 mg (Control 140139) |
| **Date:** | Friday, April 11th, 2014, 3:30 PM to 4:30 PM |
| **Meeting Location:** | MM2 Third Floor Room 373 |
| **FDA Attendees:** | John Peters, Ethan Stier, Xiaojian Jiang, Minglei Cui, Ping Ren, and Nabeel Babaa (meeting recorder) |

**Background Summary**

This meeting was arranged to discuss issues identified in several applications of the noted drug product and the impact of these findings to the current draft guidance. Control 140139 is intended to revise the current FDA guidance on Esomeprazole Magnesium and request comparative *in vitro* NG tube tests (sedimentation testing, particle size distribution study, recovery testing, and acid resistance stability testing) to compare the performance of the test product to that of the reference product under NG tube administration.

(b) (4) applications in house failed acid resistance test for the reference product. U. The failed acid resistance data from (b) (4) were summarized and referenced. The ultimate goal of the meeting was to finalize the guidance as there are (b) (4) ANDAs pending its completion, to discuss acid resistance testing condition, and to discuss the allowed difference in particle size between test and reference product if the recovery test passed.

**Discussion**

(b) (4)
.

**ANDA 078003:**

**Acid Resistance Test Data for** It was noted that the firm conducted the acid resistance test in water with pHs of 5.4, 5.9, and 6.4 instead of pH 6, 7 and 8 as recommended. The firm justified this by saying that the former pH values best represent water in hospital setting; however, no reference source for this assertion was provided. For the 20 mg strength, approximately 20% and 80% of reference drug were released from enteric coated pellets after soaking in water (pH 5.4, 5.9 and 6.4) for 30 and 60 minutes, respectively whereas less than (b) (4)% of test product was released under the same conditions. For the 40 mg strength, approximately 90% of reference product was released after soaking in the water for 15, 30 or 60 minutes, whereas less than (b) (4)% of the test product was released under the same treatment conditions.

**Particle Size Microscopy**: It was noted that in the case of the 20 mg and 40 strengths of the reference product, the pellets started to rupture, disintegrate, and were irregular in shape after 30 and 15 minutes of soaking time, respectively. In contrast, for the 20 mg and 40 mg strengths of the test product, the pellets remained intact throughout soaking and maintained their oval to circular shape. It was noted that if microscopy data is not accurate, particle size data can be measured using laser diffraction. It should be noted that the particle size of the test product is slightly larger than that of reference products based on Microscopy data (approximately $D_{50}$ 0.8 mm reference vs. 0.6 mm test).

(b) (4)

**Proposals:**

1. Based above ANDAs, we recommend the in vitro NG tube testing to be conducted in water with pH 5.5, 6.5, and 7.5 at soaking time 0 and 15 min (instead of previous 15, 30 and 60 min).

   Proposal #1 was agreed upon. It was noted that the pH of tap water ranges from 6.5 to 8.5, and the mean pH value of sterile water pH is 5.5.

2. Discuss with Division of New Drug on issues regarding failed acid resistance test of the RLD after soaking in water for a period of time, e.g. even for 15 min. (note: labeling does indicate immediate delivery)[23]

   Proposal #2 was dismissed. We do not need to discuss with Division of New Drug on issues regarding failed acid resistance test of the RLD after soaking in water for a period of time, e.g. even for 15 min since the RLD label indicates immediate delivery (the data show acceptable acid resistance at 0 min for the RLD). The in vitro data would be acceptable if the test product shows acid résistance no worse than that of the RLD.

3. How to evaluate acid resistance testing. Should the test be no worse than RLD in all pH, and 0 or 15 min?

   Proposal #3 pertaining to evaluating acid resistance testing was agreed upon.

4. Ask FDA lab to conduct the in vitro NG tube study for the reference product and some problematic test product. In history, generic firm submitted acceptable NG tube studies for its product (particle size different, but acceptable recovery and acid resistance test). However, the FDA's lab data showed failed results.

   Proposal #4 was agreed upon. It was agreed that the new guidance not be posted until after the FDA lab completes their analysis. The FDA lab can forward the data to the new drug division.

5. How to evaluate data if the firm does not conduct the pH we recommended for In vitro NG tube testing (such as 78003)

   a. Ask firm re-conduct the study in our recommended pH

   b. Further discussion on allowed difference on enteric coated particle size between the test and reference product (include Chemistry division) if recover test is passed.

   c. Studies on NG tube with different material?

Proposal #5 was agreed upon. We should ask the firm to re-conduct the study in our recommended pH. In this manner, we will accept the test product as long as it doesn't release more than the RLD, even if it technically fails the acid resistance test according to the less than (b) (4) 0% release criteria.

**Action Items**

1. Deficiency letter can be sent but hold off on posting the new guidance until after the FDA lab conducts its test, per Proposal #4. The new guidance will include our recommended pH values of 5.5, 6.5, and 7.5 for NG tube testing in water, as well as a soaking time of 0

[23] NDA chemistry indicated that the reference product is stable up to 30 min in tape water with pH 7.8.

min and 15 min. Note: the pH of tap water ranges from 6.5 to 8.5 and the mean pH value of sterile water is 5.5.

2. Ask FDA lab to conduct the in vitro NG tube study for the reference product and some test product, per Proposal #4. The DB should coordinate with science team on the testing.

3. The drug specific guidance should recommend the laser method for measuring particle size in lieu of microscopy. The DB can summarize the particle size method in lansoprazole and esomeprazole applications and reference the nasal guidance to determine the appropriate method.

4. For ANDA 78003, firm should conduct the study using our recommended pH. The particle size is acceptable. There is no need to ask the NG tube study with different materials. The criteria will be: if the test product doesn't release more than the RLD it will pass ( even if it technically fails the acid resistance test according to the less than (b) (4)% release criteria).

Draft by: Nabeel Babaa (04/16/2014)

Comments: Minglei Cui (04/18/2014)

Comments: Xiaojian Jiang (04/20/2014)

Comments: Ethan Stier (04/21/2014)

### 4.2.3 Internal Email Regarding the NG tube Study

**From:** Jiang, Xiaojian
**Sent:** Friday, May 09, 2014 9:39 AM
**To:** Lionberger, Robert
**Cc:** Stier, Ethan; Huang, Yih Chain; Peters, John (CDER); Cui, Minglei; Wen, Hong
**Subject:** RE: NG tube guidance for esomeprazole manesium DR capsule

Thanks, Rob
Yes, for the particle size, we do not require to pass the statistical analysis if the recover studies are fine.
Sedimentation volume is a test copied from the FDA lab when they did it for lansoprazole ODT (b) (4). It is measurement of the total mass settling in the syringe.
It seems useful only for lansoprazole ODT but not for beaded capsule because all the beads fall down in the bottom, volume is less than 1 ml.

Since we have detailed instruction how to measure the sedimentation in the guidance, the firm appears not having problem and it is pretty easy to measure.

"Sedimentation testing measures the settling of particle or floccules occur under gravitational force in liquid condition. Sedimentation velocity (v) is directly

proportional to the square of diameter of particle and inversely proportional to viscosity of dispersion medium. "

Will talk to Team leader and Reviewer to see if we can find simple word to explain sedimentation volume in the guidance..

Thanks a lot.
Xiaojian

**From:** Lionberger, Robert
**Sent:** Friday, May 09, 2014 8:39 AM
**To:** Jiang, Xiaojian
**Cc:** Stier, Ethan; Huang, Yih Chain; Peters, John (CDER); Cui, Minglei; Wen, Hong
**Subject:** RE: NG tube guidance for esomeprazole manesium DR capsule

In general, we agree with the proposed tests. I want to confirm that there is not an intention to require equivalence in the granule size distribution, if the recovery studies are acceptable. (This was my interpretation of the guidance)

I am not exactly sure what the sedimentation volume is, so probably need to describe it more in the guidance.

Rob

**From:** Jiang, Xiaojian
**Sent:** Tuesday, May 06, 2014 8:21 PM
**To:** Lionberger, Robert
**Cc:** Stier, Ethan; Huang, Yih Chain; Peters, John (CDER); Cui, Minglei
**Subject:** FW: NG tube guidance for esomeprazole manesium DR capsule

Dear Rob,

We have been working on the control to revise the draft guidance for Esomeprazole. The new guidance will include the NG tube requirements in addition to previous fasting, fed and fasting sprinkle studies. We have discussed the draft guidance with Dr. John Peters and would like you to take a look at the draft guidance before we post it as requested by John (see below email). Please find the attached control and draft guidance and let us know your concurrence if we can post the guidance by Friday, May 9, 2014). Thank you very much for your advice in advance.

The following are some background for NG tube project:
Nasogastric (NG) tubes are sometimes used to administer medication to patients who are unable to safely swallow or tolerate oral intake. One such product that can be administered in this manner is the Proton Pump Inhibitor (PPI), Lansoprazole,

esomeprazole, omeprazole, and lansoprazole delayed-release orally disintegrating tablets. We have TSI issue with Teva's now discontinued ANDA 078730, Lansoprazole Delayed-Release Orally Disintegrating Tablets (LODT).

Since 2011, through several internal meetings with chemistry, it was conclude that In vitro NG testing should be requested if a product is a solid oral dosage form and contains instructions for NG tube administration in the RLD labeling. So far we have sent the NG tube requirements to quite number of ANDAs mostly for PPI drug products (e.g. lansoprazole, esomeprazole, omeprazole, (b) (4) through deficiency letters. However, we believe that posting daft guidance immediately will benefit both FDA and generic companies the most due to the following reasons:

1. The current guidance do not have NG tube study requirement. The firm will only know NG tube requirement through our deficiency letter after their submission. We can refuse to file the applications with the new guidance. With GUDUFA deadline, this may help us to meet the 10 month deadline.

2. If the firm knows that NG tube requirement ahead of time, they will be more careful on particle size design. They will less likely fall in the situation in which fasting, fed and fasting sprinkle studies all passed 90% confidence acceptance criteria but they have to reformulate the test product due to failed recovery NG tube studies as the result of large particle size (which we saw in same cases now).

We also learn during our review of some NG tube studies submitted by the applicants, different pH of water can damage the enteric coating. So we asked the firm to conduct testing in different pH of water if the label indicates that water is the medium. In case where that apple juice is used for NG tube administration (e.g. lansoprazole DR capsule), there is no need to using different type of juice. We also had agreement with CMC division, they will also send out deficiencies asking in vitro study using different tube material etc. Bio will do statistical comparison while, CMC conducts qualitative evaluation for the comparison.

Sincerely,
Xiaojian

**From:** Peters, John (CDER)
**Sent:** Friday, May 02, 2014 10:54 AM
**To:** Jiang, Xiaojian
**Cc:** Cui, Minglei; Stier, Ethan
**Subject:** RE: NG tube guidance

Makes sense. When the draft is complete let's make sure that we have Rob's ok too. He was at the meetings so should be up to date on the content of the draft.

Tx

J

**From:** Jiang, Xiaojian
**Sent:** Thursday, May 01, 2014 10:25 AM
**To:** Peters, John (CDER)
**Cc:** Cui, Minglei; Stier, Ethan
**Subject:** NG tube guidance

Hi, John
At our last meeting (4/11/2014), we decided to postpone posting the draft guidance for Esomeprazole until FDA conduct and finish confirmative NG tube studies for reference and some test products for us. The new guidance will include the NG tube requirements in addition to previous fasting, fed and fasting sprinkle studies.
However after giving some more thought for GDUFA deadlines and the current guidance, we would like to suggest posting the draft guidance now instead of waiting for FDA's label results due to the following reasons:

1. The current guidance do not have NG tube study requirement. The firm will only know NG tube requirement through deficiency letter after their submission. With GUDUFA deadline, this may post a risk for us missing 10 month deadline.

2. If the firm knows that NG tube requirement ahead of time, they will be more careful on particle size design. They will less likely fall in the situation in which fasting, fed and fasting sprinkle studies all passed 90% confidence acceptance criteria but they have to reformulate the test product due to failed recovery NG tube studies as the result of large particle size (which we saw now).

3. The FDA lab studies may take a long time. The draft guidance can be changed anytime if the lab result indicates that change is necessary. However, because the guidance we proposed is using a very conservative method, it is less likely that more studies will be required based on the lab results (most likely reducing the amount of testing)

Based above rationale, we suggest posting guidance now and would like to get your approval on this decision.

Thanks,
Xiaojian

### 4.2.4 DB II Biomanagement Meeting Minutes (05/13/2014)

**DBII Bio Management Meeting Minutes**

**Meeting Date:** May 13, 2014
**Meeting Time:** 11:00 am – 12:00 pm

**Meeting Location:** Conference Room 255

**Attendees:** Ethan Stier, Xiaojian Jiang, Parthapratim Chandaroy, Moheb Makary, Svetlana Cherstniakova, Kuldeep Dhariwal, Chandra Chaurasia, Saied Raofi, Minglei Cui, Om Anand, Nabeel Babaa, Chitra Mahadevan, and Diane Nhu

Team 7 – Minglei Cui – please see Attachment 2 for additional data.

**Summary of key issues, background information discussed and discussion:**

| | |
|---|---|
| **OGD Control No./ANDAs** | 140139/ANDA 202784, (b) (4), 78003 |
| **Drug Product Name** | Esomeprazole Delayed Release Capsules |
| **Strength(s)** | 20 mg and 40 mg |

The Division of Bioequivalence (DB) recommendations for the In Vitro Comparative Nasogastric (NG) Tube Studies:

1. Sedimentation testing
2. Particle size distribution study
3. Recovery testing
4. Comparative acid resistance stability testing

As recommended in the approved RLD labeling for Esomeprazole Magnesium Delayed Release Capsules, the product may be administered by NG tube. Therefore, DBII requested sponsors for ANDA 202784, (b) (4) and 078003 to perform comparative in vitro tests to compare the performance of its test to the reference for both strengths (20 mg and 40 mg) under NG tube administration. The firms responded to the deficiency comments in the recent amendment and submitted the comparative in vitro tests using 12 units of both strengths of the test and the reference to compare the performance of its test product to the reference at 0 min and 15 min. Based on new criteria, the sedimentation testing, particle size distribution study, recovery testing are acceptable (reference product failed acid resistance test in some ANDAs).

Since the enteric coating of test product is dissolved at pH > 5.5 and the pH of the water may vary between 6.5 to 8.5, then there is a concern that the process of dispersing a test product in an oral syringe and/or an oral syringe with an NG tube might adversely impact the integrity of the enteric coating. To ensure consistent stability of the enteric coating in water between the test and reference product, the firm needs to conduct additional in vitro study to demonstrate the stability of the dispersed granules in different pH of water within different soak time prior to performing the acid resistance testing.

Issue: Whether recovery studies are needed in addition to acid resistance testing in water with different pH and soaking time. The reason for requesting additional recovery studies are following:

1) (b) (4) in-house (b) (4) ) showed failed Acid Resistance Test for the RLD under conditions that we previously recommended (different pH and soaking time)

2) DBII requested the firm to re-conduct acid resistance test in the water with different pH and soaking time even if both test and reference passed acid resistance test under certain pH (unknown).

**Question**:
Based on the information provided, the acid resistance may fail in water in different pH and different soaking time. In this case, DBII does not know whether recovery study would also fail in these conditions. Can DBII recommend the firm to re-do recovery studies using different pH of water (e.g. pH 5.5, 6.5 and 7.5) with different soak times in syringe (e.g. 0 and 15 min)?

**Team's proposal and rationale for the proposal:**

Team 7's proposal is to repeat recovery studies using different pH of water (e.g. pH 5.5, 6.5 and 7.5) with different soak times in syringe (e.g. 0 and 15 min) for ANDA 202784, (b) (4) and 78003 due to the following reasons:

1) If the firm measures the drug release in acid resistance test at isosbestic point (for parent drug and degradation) instead of from remaining tablets, we will not know whether the recovery study would fail or not under the same conditions.

2) Since DBII has decided that bioequivalence of particle size is not critical, recovery and acid resistance testing become key studies in NG tube testing.

3) The NG tube studies in updated guidance for Esomeprazole Delayed Release Capsules require the pre-treatment of the test and reference product in water with different pH and soaking time for four studies.

**Management Decision:**

*DBII management concurred with the team's proposal to ask the firm to repeat recovery studies using different pH of water (e.g. pH 5.5, 6.5 and 7.5) with different soak times in syringe (e.g. 0 and 15 min).*

### 4.2.5 Acid Resistance Study in NDA 021153

In the study, the content of pellets (defined as the amount of esomeprazole after exposure to acid for 2 hrs) from 10 individual 20 & 40 mg Nexium capsules passed through the tubes (using the 25 + 25 mL method) was compared with the content of 10 individual 20 & 40 mg Nexium capsules directly exposed to acid.

The results indicate that an average of 98.8-99.5% of the contents of the 20 mg Nexium capsules & 98.7-99.3% of the contents of the 40 mg Nexium capsules are retained following passage through the NG tubes & subsequent acid exposure. Overall, the administration of esomeprazole pellets through the NG tubes does not appear to affect the acid resistance of the pellets (i.e., integrity of the enteric coating).

**The NG- and G-tubes tested are:**

| Trade name | Manufacturer | Ref. no | Length (cm) | French Size |
|---|---|---|---|---|
| Dobbhoff feeding tube (polyurethane with stylet) | Kendell, Division of Tyco International | 8884-710867 | 109 | 8 |
| Argyle Salem Sump | Sherwood Medical | 264945 | 111 | 14 |
| Levin | Medline Industry Inc. | 1A3249 | 118 | 16 |
| Bard Tri-Funnel Gastrostomy Replacement Tube | Bard Interventional Products | 000724 | 21 | 20 |

***Experimental*:**

**The tubes are tested according to the following procedure:**

(b) (4)

**Results:**

Table 1. The content of esomeprazole as per cent of stated amount (20 mg) after pre exposure in acid for 2 hours.

| | Dobbhoff | Salem Sump | Levin | Gastrostomy | Reference |
|---|---|---|---|---|---|
| Replicate | 8884-710867 | 8888-264945 | 1A3249 | 000 742 | |
| 1 | | | | | (b) (4) |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| 6 | | | | | |
| 7 | | | | | |
| 8 | | | | | |
| 9 | | | | | |
| 10 | | | | | |

Analysis no: SMP 0200680

Table 2. The content of esomeprazole as per cent of stated amount (40 mg) after pre exposure in acid for 2 hours.

| | Dobbhoff | Salem Sump | Levin | Gastrostomy | Reference |
|---|---|---|---|---|---|
| Replicate | 8884-710867 | 8888-264945 | 1A3249 | 000 742 | |
| 1 | | | | | (b) (4) |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| 6 | | | | | |
| 7 | | | | | |
| 8 | | | | | |
| 9 | | | | | |
| 10 | | | | | |

Analysis no: SMP 0200681

Table 3. Mean of per cent of stated amount (20 and 40 mg).

| Strength | Sond | Mean | 95% CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| 20 | Dobbhoff | 99.4 | 98.3 | 100.5 |
| | Gastrostomy | 99.2 | 98.1 | 100.3 |
| | Levin | 99.6 | 98.4 | 100.7 |
| | Salem Sump | 98.8 | 97.7 | 99.9 |
| | Referens | 99.5 | 98.3 | 100.6 |
| 40 | Dobbhoff | 99.2 | 98.5 | 99.9 |
| | Gastrostomy | 99.1 | 98.3 | 99.8 |
| | Levin | 98.7 | 98.0 | 99.4 |
| | Salem Sump | 99.3 | 98.6 | 100.1 |
| | Referens | 98.8 | 98.1 | 99.6 |

Table 4. A comparison between per cent of stated amount for reference capsule pellets and capsule pellets administrated through the four different tubes, respectively.

| Strength | | Difference | 95% CI | | Pr > \|t\| |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| 20 | Dobhoff - Ref | -0.1 | -1.7 | 1.5 | > 0.2 |
| | Gastrostomy - Ref | -0.3 | -1.9 | 1.3 | > 0.2 |
| | Levin - Ref | 0.2 | -1.5 | 1.7 | > 0.2 |
| | Salem - Ref | -0.6 | -2.2 | 1.0 | > 0.2 |
| 40 | Dobhoff - Ref | 0.4 | -0.7 | 1.4 | > 0.2 |
| | Gastrostomy - Ref | 0.2 | -0.8 | 1.3 | > 0.2 |
| | Levin - Ref | -0.1 | -1.2 | 0.9 | > 0.2 |
| | Salem - Ref | 0.5 | -0.5 | 1.5 | > 0.2 |

## Discussion

(b) (4)

(b) (4). The difference in content of esomeprazole between the pellets administered through tube and the reference capsule pellets is not significant and the variation between replicates is small.

The results of the present experiment show that the acid resistance is satisfactory when using the tubes. However, under some circumstances the tube may be sub-optimal (as follows):

In order not to get any pellets left in the syringe the instructions regarding syringe position and shaking need to be followed strictly. It is difficult to follow these instructions when using a short tube, such as the Bard Tri-funnel Gastrostomy Replacement tube, due to the limited flexibility of the tube.

When using the Dobbhoff feeding tube, pellets (about 10 pellets for the 20 mg capsules and 20 pellets for the 40 mg capsules, respectively) stick alongside the metallic weight at the very end of the tube. These pellets were removed into the acid with a spatula when making the analysis. However, the number of pellets potentially lost due to this is not likely to reduce the dose delivered to a significant extent.

## Conclusions

The pellets pass readily through the tubes and the administration through the tubes does not affect the acid resistance. However, practical difficulties when using short tubes, such as the Bard Tri-Funnel Replacement Gastrostomy Tube should be considered.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 078003

APPLICANT: IVAX Pharmaceuticals, Inc.,
(subsidiary of Teva Pharmaceuticals USA)

DRUG PRODUCT: Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

The Division of Bioequivalence II (DB II) has completed its review of your submissions acknowledged on the cover sheet. The following deficiencies have been identified:

**Deficiencies related to your In vitro test for Nasogastric (NG) Tube administration:**

1. We acknowledge that you conducted particle size distribution study after delivery through syringe and NG tube using water with different pH (5.4, 5.9 and 6.4) and different soak times (0, 15, 30 and 60 minutes). However, your particle size distribution analysis using microscopy may not be suitable to determine particle size distribution (D10, D50 and D90), therefore it is not acceptable.

   In addition, since a tap water with pH varying between 6.5 to 8.5 may be possibly used to deliver the medicine to hospitably patients, please determine the comparative particle size of granule dispersion using 12 units each strength of the test and the reference products **in pH 7.5 water with soak times of 0 and 15 minutes**. Please follow the procedure described in the deficiency letter (deficiency #2) issued by the DB II on 9/26/2012.

   Please provide the particle size data at the **D10, D50**, and **D90** levels **using laser diffraction method**. Please also provide validation reports for particle size distribution study.

2. We acknowledge that you have conducted acid resistance stability testing for both 20 mg and 40 mg strengths after recovery through a combination of oral syringe and 8 French NG tube in water with different pH (5.4, 5.9, and 6.4) at 0, 15, 30 and 60 minutes. For the same reason mentioned above in deficiency 1, please repeat comparative acid resistance stability testing for both

strengths using 12 units of the test and the reference products **in pH 7.5 water at 0 minute and 15 minutes.** Please follow the procedure described in the deficiency letter (deficiency #4) issued by the DB II on 9/26/2012.

3. We acknowledge that you had conducted comparative recovery testing in your previous amendment dated 04/25/2013, where the pH of water used in the recovery test was not defined. To ensure that the test product has the same recovery as that of the RLD using different pH of water (5.5, 6.5 and 7.5), please repeat the comparative recovery studies of the dispersed granules for both 20 mg and 40 mg strengths using the 8 French nasogastric tubes in 50 ml water **with different pH (5.5, 6.5, and 7.5) at 0 minute and 15 minutes.** Please use 12 units of the test and the reference products and follow the procedure described in previous deficiency letter (deficiency #3) issued by the DB II on 9/26/2012.

4. Please provide the expiration date for the reference listed product (20 mg: batch #J014509; 40 mg: batch# J012025) and testing dates for your particle size distribution study and acid resistance testing submitted in your current amendment dated 3/31/2014.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

## 5 *Completed Assignment for 078003 ID: 22778*

**Reviewer:** Xia, Li

**Date Completed:**

**Verifier:** ,

**Date Verified:**

**Division:** Division of Bioequivalence

**Description:** Esomeprazole Magnesium Delayed-Release Capsules, Eq. 20 mg and 40 mg base - In Vitro NG tube study

---

*Productivity:*

| *ID* | *Letter Date* | *Productivity Category* | *Sub Category* | *Productivity* | *Subtotal* |
|---|---|---|---|---|---|
| 22778 | 3/31/2014 | Other (REGULAR) | Study Amendment - Acid resistance 20 mg | 1 | 1 |
| 22778 | 3/31/2014 | Other (REGULAR) | Study Amendment - Acid resistance 40 mg | 1 | 1 |
| | | | | Total: | 2 |

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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.**

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/s/

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LI XIA
06/13/2014

MINGLEI CUI
06/13/2014

ETHAN M STIER
06/15/2014

# DIVISION OF BIOEQUIVALENCE REVIEW

| | | | |
|---|---|---|---|
| **ANDA No.** | 078003 | | |
| **Drug Product Name** | Esomeprazole Magnesium Delayed-Release Capsules, USP | | |
| **Strength(s)** | Eq. 20 mg and 40 mg base | | |
| **Applicant Name** | IVAX Pharmaceuticals, Inc.,<br>(An indirect and wholly owned subsidiary of Teva Pharmaceuticals USA) | | |
| **Address** | 400 Chestnut Ridge Road<br>Woodcliff Lake, NJ, 07677 | | |
| **Applicant's Point of Contact** | Patricia Jaworski, Vice President, Regulatory Affairs | | |
| **Contact's Telephone Number** | 201-930-2230 | | |
| **Contact's Fax Number** | 201-489-1403 | | |
| **Submission Dates of Original Application and Previous Amendment** | November 23, 2005<br>November 13, 2006 (study amendment) | | |
| **Submission Date of Amendment Under Review** | **04/25/2013 (In vitro NG tube study)** | | |
| **Reviewer** | Li Xia, Ph.D. | | |
| | | | |
| **Study Number (s)** | P1BD05001 | P1BD05002 | P1BD05010 |
| **Study Type (s)** | Fasting | Fed | Sprinkled Fasting |
| **Strength (s)** | eq. to 40 mg base | eq. to 40 mg base | eq. to 40 mg base |
| **Clinical Site** | Allied Research International Inc. | | |
| **Clinical Site Address** | 4520 Dixie Road, Mississauga, Ontario, Canada L4W 1N2 | | |
| **Analytical Site** | (b) (4) | | |
| **Analytical Site Address** | | | |
| | | | |
| **OVERALL REVIEW RESULT** | **Inadequate pending firm's response to deficiencies related to in vitro NG tube study** | | |
| **OSI REPORT RESULT** | **Adequate** | | |
| **BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #** | **STUDY/TEST TYPE** | **STRENGTH** | **REVIEW RESULT** |
| **1** | **Dissolution** | **20 mg and 40 mg** | **Adequate** |
| **1** | **Fasting study** | **40 mg** | **Adequate** |
| **1** | **Fed study** | **40 mg** | **Adequate** |
| **1** | **Sprinkled Fasting Study** | **40 mg** | **Adequate** |
| **1** | **Biowaiver Request** | **20 mg** | **Inadequate** |
| **1** | **NG Tube Test** | **20 mg and 40 mg** | **Inadequate** |

**Review of a Study Amendment**

# 1 EXECUTIVE SUMMARY

This is a review of a study amendment.

IVAX Pharmaceuticals, Inc. previously submitted an application (11/23/2005) consisting of three bioequivalence (BE) studies comparing its test product, Esomeprazole Magnesium Delayed-Release (DR) Capsules, 40 mg, to the corresponding reference product, AstraZeneca's NEXIUM® (Esomeprazole Magnesium) DR Capsules, 40 mg, under fasting, fed, and fasting "sprinkled" conditions. Firm's fed and fasting sprinkled BE studies were found acceptable; the dissolution testing conducted using the FDA-recommended method was also acceptable. However, the fasting BE study was incomplete pending firm's response to the bioanalytical deficiencies[1]. In its current amendment dated 04/25/2013, the firm provided acceptable response to deficiencies for the fasting BE study. Thus, the fasting BE study on its Esomeprazole DR Capsules, 40 mg is now acceptable.

Since Esomeprazole Magnesium DR Capsules include an alternate administration method through a nasogastric (NG) tube per the approved labeling of the reference product, the DB II requested the firm perform the comparative *in vitro* tests (sedimentation testing, particle size distribution study, recovery testing, and acid resistance stability testing) to compare the performance of its test product to that of the reference product for both strengths, 20 mg and 40 mg, under NG tube administration conditions[2].

In response to the DB II deficiency letter dated 09/26/2012, the firm submitted the results of in vitro NG tube study in its current amendment. The firm conducted the comparative in vitro tests (sedimentation testing, particle size distribution study, recovery testing, and acid resistance stability testing) using 12 units of both strengths of the test and the reference products to compare the performance of its test product to that of the reference product at 0 min and 15 min. The results for sedimentation testing and recovery testing are acceptable, which demonstrate similar performance profiles between the test and the reference products.

However, due to its improper sample preparation for particle size analysis by laser diffraction method, the firm did not determine the particle size distribution on test and reference products before delivery (in syringe) and after delivery through the combination of syringe and NG tube. The firm's testing procedure states that "*take out 10ml of the dispersion and proceed for particle size test at 0 minutes/15 minutes as mentioned in section D for particle size test.*" Due to rapid sedimentation, there was absence of particles remaining in solution per firm's observation. Instead of taking out 10 ml of sample from the dispersion, the firm should collect the pellets in the container in order to determine the particle size distribution of the pellets. The firm is also requested

[1] DARRTS: REV-BIOEQ-01(General Review) for ANDA 078003, final date 01/04/2007.
[2] DARRTS: REV-BIOEQ-01(General Review) for ANDA 078003, final date 09/26/2012.

to provide validation reports for particle size distribution study, and provide information of the NG tube and syringe (e.g. material, brand, size, etc.) and the type of water used in the in vitro NG tube study.

Since the enteric coating of test product starts dissolving above pH 5.5 and the pH of the water may vary between 6.5 to 8.5, there is a concern that the process of dispersing a test product in an oral syringe and/or an oral syringe with an NG tube might adversely impact the integrity of the enteric coating. Therefore, the firm is requested to demonstrate the stability of the dispersed granules in different pH of water (e.g. 6, 7 and 8) with different soak times (e.g. 15, 30 and 60 min) prior to performing the acid resistance testing. Firm's acid resistance stability testing is incomplete (see details at 3.4.4).

The 20 mg strength is proportionally formulated to the 40 mg strength. Yet, the DB can not deem the 20 mg strength to be bioequivalent to the 20 mg strength of the reference product based on CFR 320.24(b)(6) at this time due to deficiencies identified in the in vitro NG tube study.

No Office of Scientific Investigations (OSI) inspection is pending or necessary.

The application is **incomplete** pending firm's response to deficiencies related to the in vitro NG tube study.

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# 3 SUBMISSION SUMMARY

## 3.1 Drug Product Information

| | |
|---|---|
| **Test Product** | Esomeprazole Magnesium Delayed-Release capsules, 20 mg and 40 mg |
| **Reference Product** | NEXIUM® (Esomeprazole magnesium)<br>Delayed-Release capsules, 20 mg and 40 mg |
| **RLD Manufacturer** | AstraZeneca |
| **NDA No.** | 021153 |
| **RLD Approval Date** | Feb 20, 2001 |
| **Indication** | Treatment of Gastroesophageal Reflux Disease (GERD), Maintenance of Healing of Erosive Esophagitis, Symptomatic Gastroesophageal Reflux Disease, Risk Reduction of NSAID-Associated Gastric Ulcer, H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence, Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome. |

## 3.2 Contents of Current Submission

| Study Types | Yes/No? | How many? |
|---|---|---|
| **Single-dose fasting** | No | 0 |
| **Single-dose fed** | No | 0 |
| **Single-dose sprinkled fasting** | No | 0 |
| **In vitro NG tube study** | Yes | 4 tests for 20 mg<br>4 tests for 40 mg |
| **In vitro dissolution** | No | 0 |
| **Waiver requests** | No | 0 |
| **BCS Waivers** | No | N/A |
| **Clinical Endpoints** | No | N/A |
| **Amendments** | Yes | 04/25/2013 amendment for in vitro NG tube studies |

## 3.3 Study for Nasogastric Tube Administration

### 3.3.1 Labeling of NEXIUM (Esomeprazole Magnesium) Delayed-Release Capsules[3]

**Dosage and administration**

NEXIUM Delayed-Release Capsules should be swallowed whole.

For patients who have a nasogastric tube in place, NEXIUM Delayed-Release Capsules can be opened and the intact granules emptied into a 60 mL catheter tipped syringe and mixed with 50 mL of water. It is important to only use a catheter tipped syringe when administering NEXIUM through a nasogastric tube. Replace the plunger and shake the syringe vigorously for 15 seconds. Hold the syringe with the tip up and check for granules remaining in the tip. Attach the syringe to a nasogastric tube and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the granules, the nasogastric tube should be flushed with additional water. Do not administer the granules if they have dissolved or disintegrated.

### 3.3.2 Background

Enteral feeding tubes are sometimes used to administer medication to patients who cannot safely swallow or unable to tolerate oral intake. Esomeprazole is indicated for treatment of GERD, risk reduction of NSAID-associated gastric ulcer, H. pylori eradication to reduce the risk of duodenal ulcer recurrence, and treatment of pathological hypersecretory conditions Including Zollinger-Ellison syndrome. According to the labeling, Esomeprazole Magnesium DR capsules include an alternate administration method through a combination of syringe and a nasogastric (NG) tube. Esomeprazole is a substituted benzimidazole, and inhibits gastric acid secretion by specific inhibition of the enzyme, H+K+-ATPase at the surface of the gastric parietal cells. Esomeprazole has the similar chemical structure and the same bio-function as Lansoprazole.

Several current FDA adverse event report indicates that Teva's Lansoprazole DR Orally Disintegrating Tablets when dosing the product using an oral syringe or feeding tube has clogged and blocked oral syringes and feeding tubes including both gastric and jejunostomy types. The tablets may not fully disintegrate when water is added to them and/or they may disintegrate but later form clumps. These clumps can adhere to the inside walls of oral syringes and feeding tubes. In some cases, patients have had to seek emergency medical assistance and their feeding tubes have had to be unclogged or removed and replaced. In addition, the laboratory results conducted by the Division of

[3] Labeling of Nexium at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f4853677-1622-4037-688b-fdf533a11d96#nlm34068-7

Pharmaceutical Analysis (DPA) dated 11 March 2011 demonstrated that there is a risk of clogging the NG tube when using the RLD and Teva's product for 15 min or longer[4].

The results from the previous studies demonstrated that administration of esomeprazole magnesium enteric-coated pellets dispersed in tap water through size 14 French NG tube in vitro delivered over 99% of capsule contents[5]. In NDA 021153, the sponsor conducted an in vitro study to evaluate the delivery of the contents of an Esomeprazole Magnesium Capsule (40 mg) through NG tubes of various sizes (8F and 14F). The study revealed that the average recovery of pellets was >98% following the dispersion of pellets in 50 mL of tap water in a syringe[6]. Both previous studies and NDA 021153 in vitro study have shown excellent delivery of Esomeprazole enteric-coated pellets using water as a medium for NG tube delivery.

### 3.3.3 DB Recommendation

The Office of Generic Drugs (OGD) is concerned about this issue and the potential for harm to patients and is seeking prompt correction of the problem. The successful delivery of test drug product through a combination of syringe and NG tube requires that all of the capsule's contents be able to safely pass through the feeding tube and not cause tube occlusions. Therefore, we request the firm to demonstrate that the generic product has a similar performance profile to the reference product during NG tube administration.

Based on the OGD review team meeting dated 3/14/2011, DPA study reports, and information from the OGD CMC Division of Chemistry II, the DB recommends the following comparative *in vitro* test:

1. Sedimentation testing: Determine comparative sedimentation volume of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, in 50 ml of water at 0 and 15 min.

2. Particle size distribution study: Determine the comparative particle size of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, before and after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 and 15 min. Provide all particle size data at D10, D50, and D90 level.

3. Recovery testing: Conduct the comparative recovery studies of the granule dispersion from a combination of oral syringe and 8 French nasogastric tube using at least 12 units of both strengths of the test and the reference products in 50 ml water. Determine the percentage of esomeprazole recovered at the tube exit relative to the initial dose for both the test and the reference products at 0 and 15 min. The T/R

[4] Interim report from the Division of Pharmaceutical Analysis 03/11/2011: Interim report on Evaluation of Lansoprazole Orally Disintegrating tablets: Dosing with Oral Syringe, Phase 1 Part A and Part B.
[5] Sachin A Shan etc al: Delivery of Esomeprazole magnesium through nasogastric and gastrostomy tubes using an oral liquid vehicle as a suspending agent in vitro. Am J Health-Syst Pharm-vol 63 Oct1, 2006.
[6] DARRTS: REV-CLINPHARM-01(General Review) for NDA 021153 Final date 04/16/2003.

recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated.

4. Comparative acid resistance stability testing: Measure acid resistance on the granule dispersion in water after recovery through a combination of oral syringe and 8F NG tube. Evaluate the stability on 12 units of both strengths of the test and the reference products using acid resistance as stability indicator.

Note: In pediatric practice, the sizes of 8F to 16 F NG tubes are generally used for medication administration. Since the indication of Esomeprazole Magnesium DR Capsules is also for Pediatric GERD from age of 1 month to 17 year old, 8F NG tube size is required for the NG tube study of Esomeprazole Magnesium DR Capsules.

### 3.3.4 CMC Deficiency

CMC issued a deficiency regarding in vitro NG tube testing to the firm in deficiency letter dated 03/07/2012.

CMC deficiency #12:

(b) (4)

As of 07/30/2013, the firm has not responded to this deficiency yet.

## 3.4 Review of Submission

For the current application (ANDA 078003), the CMC[7] and the DB II[2] issued separate deficiency letters regarding in vitro NG tube testing to the firm on 03/07/2012 and 09/26/2012, respectively. In response to DB II's deficiency letter dated 09/26/2012, the firm submitted the results of in vitro NG tube study in its current amendment dated 04/25/2013.

[7] DARRTS: REV-QUALITY-03(General Review) for ANDA 078003, final date 03/07/2012.

### 3.4.1 Deficiency I: Sedimentation Study and Particle Size Distribution in Syringe

***<u>In vitro test for Nasogastric (NG) Tube administration:</u>***

*The approved labeling for the reference product states that the product may be administered by a nasogastric tube. Therefore, we request that you perform the following comparative in vitro tests to compare the performance of your test product to that of the reference product.*

1. *Please determine comparative sedimentation volume and particle size of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, in 50 ml of water as follows:*

    a) *Prepare the catheter tipped syringe (60 ml), remove the syringe plunger, open the capsule and empty the contents of one capsule into the syringe. Insert the syringe plunger, draw up 50 mL of water and shake the syringe vigorously for 15 seconds.*

    b) *Place the syringe perpendicular to the bench with the tip up and record sedimentation volume at 0 min. Please remove the syringe plunger and determine the particle size of the granules in the syringe.*

    c) *Using a new set of 12 units please repeat the process described in step (a) to prepare the granule dispersion, then incubate for 15 min and record the sedimentation volume and determine the particle size of granules.*

    *Please provide all particle size data at the D10, D50, and D90 levels. You may use the markings on the syringe to note the sedimentation volume. Please provide a qualitative description, e.g., particle aggregation and particles adhering to the syringe walls. Please take photos of the contents of the syringe at various intervals throughout the testing process.*

**Firm's Response:**
Teva has completed the testing requested above. A sedimentation volume of approximately 2mL was observed for both the test product and the reference product, for both strengths and at both time points. After an initial 15 seconds of shaking, the test samples displayed a floating and aggregation of the pellets within the syringe. This also occurred for shaken product held 15 minutes after shaking. These pellets were found to sink immediately with a gentle tapping of the syringe. For the reference product, no floating, aggregation or adhering of the pellets to the wall was observed.

Particle size analysis could not be performed due to rapid sedimentation (absence of particles remaining in solution), as can be seen in the photographs provided in **Module 3.2.P.2**. The comparative sedimentation study protocol, methods and report are provided in **Module 3.2.P.2**.

**Review of the firm's data:**

- **Test and reference product information:**

  All testing was performed on unexpired test and referenced batches.

| Strength | Test Material (Lot No.) | Expiry | Reference Product (Lot No.) | Expiry |
|---|---|---|---|---|
| 20 mg | Y21936 | May/ 2014 | H010166 | Apr/ 2015 |
| 40 mg | Y21935 | May/ 2014 | H005206 | Nov/ 2014 |

  **Note:** The test batches for NG tube study are different from the exhibit batches used in the BE studies and dissolution testing in the original application (Test: 20 mg: # Y51282; 40 mg: # Y51286; RLD: 20 mg: #/ P4879; 40 mg: # N5819) because those exhibition batches were expired.

- **Materials:**

  The firm did not provide information of syringe, NG tube and type of water used in the testing; the firm is requested to provide information of the NG tube and syringe (e.g. material, brand, size, length, etc.) and type of water used in the in vitro NG tube study (e.g. sentimentation, particle size, recovery and acid resistance).

**<u>Test Procedure:</u>**

***A. Sedimentation volume test:***

1. Select randomly not less than 12 capsules.
2. (b) (4)
3.
4.

***B. Particle size distribution test from catheter tipped syringe***

*For 0 minutes:*

Carry out the test on 12 capsules.

(b) (4)

(b) (4)

*For 15 minutes:*
Carry out the test on 12 capsules.

(b) (4)

***C. Particle size distribution test method***
Method: By Laser Diffraction
Determine using laser diffraction particle size analyzer.

(b) (4)

(b) (4)

Reporting: Report as a value in µm at **D10, D50, D90 for 0 minutes and 15 minutes**.
**Sedimentation Testing Results:**

**Table 1. Sedimentation by volume (mL) for 20 mg and 40 mg test and reference products at 0 and 15 min:**

| Testing Date | Time | Dosage Strength & Form | No. of Dosage Units | | Sedimentation Volume (mL) | |
|---|---|---|---|---|---|---|
| | | | | | Test | RLD |
| 06/03/2013 | 0 min | 20 mg Capsule | 12 | Mean | 2 | 2 |
| | | | | Range | (b) (4) | |
| | | | | %RSD | 0 | 0 |
| 06/03/2013 | 15 min | 20 mg Capsule | 12 | Mean | 2 | 2 |
| | | | | Range | (b) (4) | |
| | | | | %RSD | 0 | 0 |
| 06/03/2013 | 0 min | 40 mg Capsule | 12 | Mean | 2 | 2 |
| | | | | Range | (b) (4) | |
| | | | | %RSD | 0 | 0 |
| 06/03/2013 | 15 min | 40 mg Capsule | 12 | Mean | 2 | 2 |
| | | | | Range | (b) (4) | |
| | | | | %RSD | 0 | 0 |

The Representative photos for sedimentation testing and particle size distribution study in **Syringe only**

**Reference-20 mg-0 min** **Reference-20 mg-15 min**

(b) (4)

**Reference-40mg-0min** **Reference-40mg-15min**

(b) (4)

**Test-20mg-0min** **Test-20mg-15min**

(b) (4)

**Test-40mg-0min** **Test-40mg-15min**

(b) (4)

**Firm's observation**: Floating and aggregation of the pellets was observed which were sunken down immediately by gentle tapping for Cipla samples. No floating, no aggregation or no adhering of the pellets to the wall was observed for RLD samples.

**Reviewer's comments on sedimentation study in syringe:**
The firm measured the sedimentation volume of approximately 2 ml for both strengths of the test and reference products at 0 and 15 min in syringe. According to firm's observation, no floating, aggregation or adhering of the pellets to the wall was observed for the reference product. However, after an initial 15 seconds of shaking, floating and aggregation of the pellets was observed for the test product, these pellets were sunken down immediately by gentle tapping. In reviewer's opinion, firm's sedimentation test is acceptable for the following reasons:

1. There is no difference in sedimentation volume (2 ml) between the test and reference products at time 0 and 15 min in syringe.

2. No significant floating, aggregation and adherence of pellets were observed for both strengths of the test product at 0 min and 15 min, only few granules floating and aggregation inside the syringe is unlikely to impact the result statistically.

3. There is no aggregation, adherence, or clogging observed during test product delivery through the syringe and tubing combination. Clogging of the NG tube, as small as 8F, was not observed (see firm's response in section 3.4.2).

4. The 90% CIs for the least squares geometric means of the recovery of Esomeprazole at 0 min and 15 min meet the acceptable criteria for the recovery testing. The result of recovery study indicates that there is no substantial loss of the drug occurs during administration via a combination of syringe and NG tube.

5. The sedimentation testing itself is not sensitive enough to determine any significant change between the test and reference, which was also observed in other ANDAs 201921 and 202176.

**Reviewer's comments on particle size distribution in syringe:**
Due to its improper sample preparation for particle size analysis by laser diffraction, the firm did not determine particle size distribution (D10, D50, D90, and D-span) on test and reference products in 50 ml of water using syringe at 0 min and 15 min. According to firm's test procedure, the firm prepared the granule dispersion and (b) (4) (b) (4) then "*take out 10ml of the dispersion and proceed for particle size test at 0 minutes/15 minutes as mentioned in section D for particle size test.*" But due to rapid sedimentation there were absence of particles in the 10 ml of collected sample per firm's observation, therefore, the particle size analysis was not conducted by the firm. Instead of taking out 10 ml of sample from the dispersion, the firm should collect the pellets inside the syringe in order to determine the particle size distribution of the pellets.

The firm is requested to determine the comparative particle size of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, in 50 ml of water in syringe (before delivery) at 0 and 15 min. **Please collect the pellets** in the container to determine the particle size distribution of the pellets.

The firm should provide all particle size data at the D10, D50, and D90 levels. The firm should also provide a validation report for particle size distribution test method.

### 3.4.2 Deficiency II: Particle Size Distribution with the Combination of NG Tube and Syringe

2. *Please determine the comparative particle size of the granule dispersion using 12 units each of the test and reference products, 20 mg and 40 mg strengths, after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 and 15 min as follows:*

    a) *Prepare the feeding tube according to the manufacturer's directions. Repeat the process described in 1(a) to prepare the granule dispersion.*

    b) *Attach the syringe to the feeding tube, using the syringe plunger push the granule dispersion through the syringe and the feeding tube into a collection container.*

    c) *Remove the syringe from the feeding tube, draw up additional water and flush the system by pushing the fluid through the feeding tube into the container. Perform particle size analysis of the collected fluid.*

    d) *Please repeat the testing described above with a fresh set of 12 units. However, after suspending the capsule content in step a, wait 15 minutes prior to injecting the contents into the feeding tube.*

    *Please visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and please report all the observations and supporting photographs. Please provide the particle size data at the D10, D50 and D90 levels and report flush volume used in these studies.*

**Firm's Response:**
Teva has completed the testing requested above. Photographs taken during this testing are provided in **Module 3.2.P.2**. No aggregation, adherence, or clogging was observed during product delivery through the syringe–tubing combination. A 10 mL flush volume was required, in addition to the original 50 mL dilution volume, to flush any remaining pellets out of the nasogastric tube, for both products, strengths, and syringe hold times (T=0 and T=15 minutes). Please refer to **Module 3.2.P.2.** for the complete syringe-tubing study report, methods, protocol information and photographs taken.

Particle size analysis could not be performed due to rapid sedimentation (absence of

particles remaining in solution), as can be seen in the photographs provided in **Module 3.2.P.2**.

**Review of the firm's data:**

Test procedure:
*Particle size test through syringe in combination with NG tube*
*For 0 minutes:*
Carry out the test on 12 capsules.

(b) (4)

*For 15 minutes:*
Carry out the test on 12 capsules.

(b) (4)

The representative photo for particle size distribution study with the **combination of syringe and NG tube**

**Test-20 mg 0 min**

(b) (4)

Eight similar photos were provided by the firm to show the delivering of the contents into a beaker through combination of syringe and NG tube on both strengths of test and reference products at 0 min and 15 min.

Physical observation: There is no aggregation of pellets or lumps formation, No adherence of pellets to wall of syringe and NG tube is observed.

**Reviewer's comments on particle size distribution with the combination of syringe and NG tube:**
Firm's test procedure of particle size distribution after delivery through a combination of syringe and NG tube is the same as that before delivery (in syringe only). Due to the improper sample preparation, the firm did not measure the particle size. Per firm's observation, "*Minimum obscuration for the particles was not achieved indicating no presence of particles in the solution.*" Due to rapid sedimentation, there is absence of particles remaining in solution per firm's observation, so the particle size distribution was not measured. Instead of taking out 10 ml of sample from the dispersion solution, the firm should collect the pellets in order to determine the particle size distribution of the pellets after delivery through the combination of syringe and NG tube.

The firm is requested to determine the comparative particle size of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 and 15 min. **Please collect the pellets** in the container to determine the particle size distribution of the pellets.

The firm is requested to provide the particle size data at the D10, D50 and D90 levels. The firm is requested to visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all the observations and supporting photographs. The firm is requested to take photos at different stages (syringe with capsule's content, attach syringe to the NG tube, inject water with pellets into the NG tube, flush NG tube etc.).

### 3.4.3 Deficiency III: Recovery Testing

3. *Please conduct comparative recovery studies to determine what percentage of the initial dose suspended in water passes through the 8 French nasogastric tubes. Please use 12 units of both strengths of the test and the reference products in 50 ml water and follow the process outlined in #2 (above). Please determine the percentage of esomeprazole recovered at the tube exit relative to the initial dose using a validated assay method for both the test and the reference products at 0 and 15 min using a validated assay method. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. The DB II will set an interim specification based upon the review of the submitted data. If high variability is observed, you may increase the numbers of units used for this test.*

**Firm's Response:**
Teva has completed the testing requested above. The mean percent of Esomeprazole recovered through the syringe and tubing is all greater than 96% for each product, strength, and time interval studied. In addition, the mean T/R recovery ratios are all close to 1.00 (100%), with the upper and lower 90% confidence intervals of the mean T/R recovery ratios summarized in the table below. Please refer to **Module 3.2.P.2.** for the complete comparative recovery study report, methods, and protocol information.

| **Product Comparative Recovery Through Syringe Plus 8 French Nasogastric Tube** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **20 mg (0 minutes)** % Labeled Claim Recovered | | | **20 mg (15 minutes) %** Labeled Claim Recovered | | | **40 mg (0 minutes) %** Labeled Claim Recovered | | | **40 mg (15 minutes)** % Labeled Claim Recovered | | |
| | **Test** | **Ref** | **T/R Ratio** | **Test** | **Ref** | **T/R Ratio** | **Test** | **Ref** | **T/R Ratio** | **Test** | **Ref** | **T/R Ratio** |
| **Mean** | 99.0 | 98.8 | **1.0017** | 100.2 | 100.8 | **0.9949** | 96.7 | 100.9 | **0.9582** | 99.8 | 100.1 | **0.997** |
| **% RSD** | 1.5 | 2.4 | 3.2 | 1.8 | 3.4 | 4.5 | 2.2 | 3.0 | 3.4 | 1.8 | 1.7 | 2.0 |
| **90% CI (upper)** | 101.567 | | | 101.411 | | | 97.6115 | | | 100.937 | | |
| **90% CI (lower)** | 98.7878 | | | 97.6089 | | | 94.0691 | | | 98.4780 | | |

**Review of the firm's data:**

**A. Testing Procedure:**

(b) (4)

[redacted]

Following this page, 2 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

**B. Analytical Procedure:**

The Analytical method for Assay and Uniformity Of Dosage Units by HPLC of Esomeprazole Magnesium Delayed Release Capsules (20mg /40mg) is validated (see Appendix 4.6 for the validation report). It is found to give specific, linear, accurate, precise and reproducible results in the range of [redacted] (b) (4) mg/l. The method can be used for routine quality control and stability analysis of Esomeprazole Magnesium Delayed Release Capsules (20 mg /40 mg) for Assay and Uniformity of dosage units. Please see details of analytical assay for Esomeprazole Magnesium DR Capsules at Appendix 4.6.

**Results:**
The results of recovery study are summarized in the tables below.

**Table 3: Comparative Recovery Study Using Syringe and NG Tube (Arithmetic mean)**

| Formulation | Strength | No. of Dosage Units | | % Labeled Claim Recovered | |
|---|---|---|---|---|---|
| | | | | 0 min | 15 min |
| Esomeprazole DR Capsules, 20 mg, lot # Y21936 Expiry Date: 05/2014 Test Date: 06/03/2013 | 20 mg Capsule | 12 | Mean | 99.0 | 100.2 |
| | | | Range | (b) (4) | |
| | | | %CV | 1.5 | 1.8 |
| Nexium ® DR Capsules, 20 mg, lot # H010166 Expiry Date: 04/2015 Test Date: 06/03/2013 | 20 mg Capsule | 12 | Mean | 98.8 | 100.8 |
| | | | Range | (b) (4) | |
| | | | %CV | 2.4 | 3.4 |
| Esomeprazole DR Capsules, 40 mg, batch # Y21935 Expiry Date: 05/2014 Test Date: 06/03/2013 | 40 mg Capsule | 12 | Mean | 96.7 | 99.8 |
| | | | Range | (b) (4) | |
| | | | %CV | 2.2 | 1.8 |
| Nexium ® DR Capsules, 40 mg, batch # H005206 Expiry Date: 11/2014 Test Date: 06/03/2013 | 40 mg Capsule | 12 | Mean | 100.9 | 100.1 |
| | | | Range | (b) (4) | |
| | | | %CV | 3.0 | 1.7 |

**Table 4. Geometric Means and 90% Confidence Intervals - Firm Calculated**

| Esomeprazole DR Capsules<br>20 mg and 40 mg<br>Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals | | | | | |
|---|---|---|---|---|---|
| Comparative Recovery Testing | | | | | |
| Strength | Time | Test | Reference | Ratio | 90% C.I. |
| 20 mg | 0 min | 99.0 | 98.8 | 1.00 | 98.79-101.57 |
| | 15 min | 100.2 | 100.8 | 1.00 | 97.61-101.41 |
| 40 mg | 0 min | 96.7 | 100.9 | 0.96 | 94.07-97.61 |
| | 15 min | 99.8 | 100.1 | 1.00 | 98.48-100.94 |

**Table 5. Geometric Means and 90% Confidence Intervals - Reviewer Calculated**

| Esomeprazole DR Capsules<br>20 mg and 40 mg<br>Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals | | | | | |
|---|---|---|---|---|---|
| Comparative Recovery Testing | | | | | |
| Strength | Time | Test | Reference | Ratio | 90% C.I. |
| 20 mg | 0 min | 99.0 | 98.8 | 1.00 | 98.79-101.57 |
| | 15 min | 100.2 | 100.7 | 1.00 | 97.62-101.42 |
| 40 mg | 0 min | 96.7 | 100.9 | 0.96 | 94.07-97.61 |
| | 15 min | 99.8 | 100.1 | 1.00 | 98.48-100.94 |

The firm did not provide photos for recovery test.

**Reviewer's comments on the recovery study:**
The 90% CIs for the least squares geometric means of the recovery of Esomeprazole at 0 min and 15 min calculated by the reviewer agree with the firm's calculations and meet the 90% CI criteria for the recovery testing. The result of recovery study indicates that there is no substantial loss of the drug occurs during administration via a combination of syringe and NG tube.

The recovery testing for the strengths of 20 mg and 40 mg test product at 0 min and 15 min is acceptable.

### 3.4.4 Deficiency IV: Comparative Acid Resistance Stability Testing

4. *Please conduct comparative acid resistance stability testing using 12 units of both strengths of the test and the reference products. Please use the following method:*

   a) *Prepare the granule dispersion in 50 ml water (hold for 15 min), and collect the contents of granule dispersion at the tube exit.*

   b) *Transfer the contents of granule dispersion into dissolution vessel containing 300 mL of 0.1 N HCl maintained at 37 ±0.5°C.*

   c) *Flush the nasogastric tube with additional water and transfer any remaining contents into the dissolution media mentioned above.*

   d) *Acid resistance testing should be conducted using USP Apparatus II at 100 rpm. Analyze the amount of esomeprazole released at 120 minutes.*

**Firm's Response:**
Teva has completed the testing requested above. Plots of the percent release of Esomeprazole in acid for the test and reference products are provided in **Module 3.2.P.2**. The table below summarizes the acid resistance comparable results obtained for the test and reference product for both the 20 mg and 40 mg strengths. The percent of Esomeprazole released for the 20 mg test product is 6.0% versus 2.0% for the reference product; and the percent of Esomeprazole released for the 40 mg strength is 3.7 % for the test product versus 4.4 % for the reference product.

| Percent of Esomeprazole Released in the Acid Stage | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 20 mg | | | | 40 mg | | | |
| | *Test* | | *Reference* | | *Test* | | *Reference* | |
| | %LC | % Release | %LC | % Release | %LC | % Release | %LC | % Release |
| Mean (before Acid) | 99.1 | N/A | 99.6 | N/A | 98.4 | N/A | 101.1 | N/A |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Mean (after Acid) | 93.1 | **6.0** | 97.7 | **2.0** | 94.7 | **3.7** | 96.7 | **4.4** |
| Min | (b) (4) | | | | | | | |
| Max | | | | | | | | |
| SD | 3.8 | 3.7 | 1.9 | 1.9 | 3.1 | 3.1 | 1.8 | 1.8 |
| % RSD | 4.1 | 61.9 | 2.0 | 94.6 | 3.3 | 84.0 | 1.9 | 41.0 |

Please refer to **Module 3.2.P.2.** for the complete comparative acid resistance study report, methods, and protocol information.

The firm performed an additional study for the 20 mg Cipla product by taking greater care to ensure no pellet loss occurred during transfer. This was performed to examine the effect on test variability. The results are presented below.

| | **Percent of Esomeprazole Released in the Acid Stage** | |
|---|---|---|
| | **20 mg Test** | |
| | %LC | % Release |
| Mean (before Acid) | 99.1 | N/A |
| Mean (after Acid) | 98.8 | 0.3 |
| Min | (b) (4) | |
| Max | | |
| SD | 1.3 | 1.1 |
| % RSD | 1.3 | 182 |

**Review of the firm's data:**

**Acid resistance testing procedure:**
Dissolution Conditions:
Dissolution Medium : 300 ml of 0.1M HCI
Apparatus : USP TYPE II
Speed : 100 RPM
Time : 120 Minutes
Temperature : 37°C ± 5°C

Note: Buffer, Mobile Phase preparation, Chromatographic conditions, Standard preparation, Procedure, Sequence of Injections, System suitability requirement and Calculations is same as in Recovery Study through Catheter Tipped Syringe in combination with Nasogastric Feeding tube.

**Sample preparation (For 20mg & 40mg):**
(b) (4)

(b) (4)

The firm provided analytical method validation protocol and analytical method validation summary for dissolution in acid stage of Esomeprazole Delayed Release Capsules 20 mg/40 mg by HPLC.

**Dissolution Method Validation (acid stage)**

The firm provided validation of analytical method used for dissolution in acid stage for Esomeprazole in Esomeprazole Magnesium Delayed Release Capsules 20 mg/40 mg by using HPLC technique. The validation of the method was assessed by establishing validation criteria's such as specificity and system suitability study, precision study and reproducibility study (see details at Appendix 4.5).

**Results:**

**Table 7. Acid resistance stability data for 20 mg and 40 mg**

| **Dissolution Conditions** | | | **Apparatus:** | USP Apparatus II (Paddle) | | | |
|---|---|---|---|---|---|---|---|
| | | | **Speed of Rotation:** | 100 RPM | | | |
| | | | **Medium:** | Acid stage: 0.1N HCl | | | |
| | | | **Volume:** | 300 mL | | | |
| | | | **Temperature:** | 37 ± 0.5° C | | | |
| **Firm's Proposed Specifications** | | | Acid stage: Not more than (b) (4)% in (b) (4) min | | | | |
| **Study Ref No.** | **Time** | **No. of Dosage Units** | | **Release (%) 20 mg** | | **Release (%) 40 mg** | |
| | | | | **Test (batch # Y21936)** | **RLD (batch # H010166)** | **Test (batch # Y21935)** | **RLD (batch # H005206)** |
| | (b) (4) | 12 | Mean | **6.0** | **2.0** | **3.7** | **4.4** |
| | | | Range | (b) (4) | | | |
| | | | %CV | 61.9 | 94.6 | 84.0 | 41.0 |

**Reviewer's Comments on the acid resistance stability test:**

1. The results in the acid resistance testing show that 6% of Esomeprazole for 20 mg and 3.7% of Esomeprazole for 40 mg DR granules of the test product collected from NG tube releases in the acidic medium. Mean of the amount released in acid medium meet the specification of NMT (b) (4)% drug released in acid stage for both strengths of the test products.

2. However, for 20 mg test product, out of total 12 units two capsules released (b) (4)% in acid stage through the combination of syringe and NG tube (#1: (b) (4)%; #5: (b) (4)%), the dissolution data met the acid stage specification of NMT (b) (4)% in 120 min at A2 level. Whereas all twelve units of 40 mg test product and all strengths of reference drug released (b) (4)% in acid stage. Comparing with the original dissolution data at the acid stage without dispersing in water (capsules were placed directly into the dissolution bath)[8], both strengths of the test product and reference product only released 2% - 3% and 1% at acid stage, respectively (see Appendix 4.4).

3. Esomeprazole is acid labile drug substance, therefore both of test and reference were formulated as enteric-coated pellets to prevent rapid degradation in the acid environment of the stomach. The test product contains (b) (4)[9]

[8] DARRTS: REV-BIOEQ-01(General Review) for ANDA 078003, final date 01/04/2007.

[9] (b) (4)

(b) (4) and the reference product contains (b) (4) Esomeprazole DR Capsules is designed in such a way that the enteric (b) (4) starts dissolving above pH 5.5. In the in vitro NG tube testing, it is dispersed in water and administered through syringe or combination of syringe and feeding tubes. Since the quality of the water can vary depending on the source of the water, the pH value of the water is not as strictly controlled as in case of buffer solution, and the pH value can vary from day to day and can also change during the run, therefore, it is very important to measure pH of water for the acid resistance testing.

The firm did not provide details about the type of water used in the in vitro testing, it did not report the initial pH of the water and pH of water after pellets delivered through syringe and NG tube either. Two units of 20 mg test product dissolved (b) (4)% in acid medium, it may be due to the some degree of dissolving of the enteric coating in water where pH is greater than 5.5. There is concern that the process of dispersing a test product in an oral syringe and/or an oral syringe with an NG tube might adversely impact the integrity of the enteric coating when water pH > 5.5. This may indicate potentially differences in bioavailability / bioequivalence since, if the test product is administered via NG tube to Gastric site, more test product may be degraded, thus less drug is likely to be available for absorption after administration of the test product.

4. In the Prevacid® SoluTab™ (Lansoprazole) Delayed Release ODT (NDA 021428) submission, to test the feasibility of dispersing LODT in water prior to administration to the patient, the innovator conducted in vitro studies to demonstrate the stability profile of the dispersed tablet as a function of pH, time and temperature. Studies were conducted over a pH range of 6.5-8.5 (the acceptable pH range for tap water per EPA guideline), temperature ranges of 5 to 37°C, soak times of 5 to 30 minutes and different volumes of tap water (5 ml, 10 ml and 30 ml) to support administration of LODT through the combination of a syringe and NG tube.

**Table 4.1d Acid Resistance Stability Data for 30 mg LODT Dispersed in Tap Water**

| Lot Number | Exposure Time (Min) | Amount of Water (mL) | Initial pH of Water | pH of Water After Adding Tablet | Temp (°C) | Syringe and NG Tube | Control % Drug Release (Range) | Mean %LC (SD) Control | % Drug Release | Mean %LC (SD) |
|---|---|---|---|---|---|---|---|---|---|---|
| Z5134074 | 5 | 5 | 7.97 | 8.05, 7.91,7.84 | RT | No | (b) (4) | 6.1 (0.4) | (b) (4) | 6.0 (0.7) |
| Z5134074 | 5 | 30 | 6.91 | 6.45, 6.74, 7.02 | RT | No | | 6.1 (0.4) | | 6.0 (0.3) |
| Z5134074 | 10 | 5 | 7.97 | 8.02, 7.94, 8.02 | RT | No | | 6.1 (0.4) | | 5.5 (0.2) |
| Z5134074 | 10 | 30 | 6.91 | 6.98, 7.09, 6.98 | RT | No | | 6.1 (0.4) | | 5.9 (0.2) |
| Z5134074 | 15 | 5 | 7.97 | 7.94, 7.94, 7.82 | RT | No | | 6.1 (0.4) | | 6.0 (0.7) |
| 010019P22 | 15 | 10+10* | 8.51 | 5.96, 5.84, 5.91 | 37.0 | Yes | | 5.7 (0.3) | | 7.9 (0.4) |
| 010019P22 | 15 | 10+10* | 8.51 | 5.90, 5.76, 5.70 | 5 | Yes | | 5.7 (0.3) | | 7.5 (0.6) |
| 010019P22 | 15 | 10+10* | 6.52 | 5.64, 5.47, 5.55 | 37.0 | Yes | | 5.7 (0.3) | | 8.3 (0.3) |
| 010019P22 | 15 | 10+10* | 6.52 | 5.10, 5.04, 5.07 | 5 | Yes | | 5.7 (0.3) | | 6.9 (1.0) |
| Z5134074 | 15 | 30 | 6.91 | 6.51, 6.84, 6.66 | RT | No | | 6.1 (0.4) | | 6.4 (0.2) |
| Z5134074 | 30 | 5 | 7.97 | 7.86, 7.75, 7.83 | RT | No | | 6.1 (0.4) | | 6.2 (0.6) |
| Z5134074 | 60 | 5 | 7.97 | 7.37, 7.77, 6.48 | RT | No | | 6.1 (0.4) | | 8.3 (0.5) |
| Z5134074 | 120 | 5 | 7.97 | 7.35, 6.46, 6.8 | RT | No | | 6.1 (0.4) | | 25.6 (0.8) |

RT = Room Temperature; SD = Standard Deviation; %LC = % Label Claim; * Flush Volume.
Yes = Experiment performed with syringe and NG tube; No = Experiment not performed with Syringe and NG tube.

5. Since the enteric coating is dissolved at pH greater than 5.5 and the pH of the water may vary between 6.5 to 8.5, to ensure that the consistent stability of the enteric coating in water between the test product and the reference product, the firm needs to conduct additional in vitro study to demonstrate the stability of the dispersed granules in different pH of water within different soak time prior to performing the acid resistance testing.

   The firm is requested to repeat acid resistance stability testing using 12 units of both strengths of the test and the reference products as follows:

   a) Prepare the granule dispersion in 50 ml water (soak for 15 min), and collect the contents of granule dispersion at the tube exit. **Please measure initial pH of water and pH of the water after the dispersed granules are delivered through the combination of syringe and NG tube.**

   b) Transfer the contents of granule dispersion into dissolution vessel containing 300 mL of 0.1 N HCl maintained at 37 ±0.5°C.

   c) Flush the nasogastric tube with additional water and transfer any remaining contents into the dissolution media mentioned above.

   d) Acid resistance testing should be conducted using USP Apparatus II at 100 rpm. Analyze the amount of esomeprazole released at 120 minutes.

   Please repeat the above steps using different pH of water (e.g. pH 6, 7 and 8) within different soak time in syringe (e.g. 30 and 60 minutes).

   Firm's acid resistance stability test is **incomplete**.

### 3.4.5 Deficiency V:

5. *Please submit standard operating procedures for sedimentation, particle size, acid resistance and recovery testing. Please submit individual data, mean values, standard deviations, coefficient of variation (CV%), and plots of percent release of esomeprazole in acid resistance test. The photographs should be submitted to support your observations and results. Please also provide the pre-study and within-study assay validation report.*

   *Please conduct all the above testing on unexpired test and reference batches.*

**Firm's response:**
The standard operating procedures, photographs, observations, individual data, mean values, standard deviations, coefficients of variation (CV%), and plots, for the sedimentation, particle size, recovery, and acid resistance tests are provided in **Module 3.2.P.2**. Validation reports for the Assay and Dissolution test methods are also provided in **Module 3.2.P.2**. As noted above, due to rapid sedimentation, particle size testing could not be performed; therefore, a validation report for the Particle Size Distribution test method is not included.

All testing was performed on unexpired test and referenced batches. The lot and expiry information is provided in the table below.

| Strength | Test Material (Lot No.) | Expiry | Reference Product (Lot No.) | Expiry |
|---|---|---|---|---|
| 20 mg | Y21936 | May/ 2014 | H010166 | Apr/ 2015 |
| 40 mg | Y21935 | May/ 2014 | H005206 | Nov/ 2014 |

**Reviewer's comment:**
Firm's response is acceptable.

### 3.4.6 Deficiency VI, VII and VIII:

***Please note that the following deficiencies were provided to you in the DB II deficiency letter dated 01/10/2007 after our review of your original application and is provided to you again since we has not yet received your responses.***

*6. For the fasting study (#P1BD05001), although you have provided explanation for the 12 Discretionary Rejection" reassays, you did not provide any supporting data along with the response. Please provide supporting data, such as chromatograms of the original 12 samples showing the abnormal internal standard responses and 12 original assay values. In the response, you have also stated that visually observed discrepancy in remaining sample volumes in the injection vials subjected to "Discretionary Rejection" were noted. Please provide evidence in support of that statement.*

**Firm's response:**

The chromatograms and assay value results for the 12 "Discretionary Rejection" reassays (abnormal internal standard response) are provided in **Module 5.3.1**. As can be seen from this data, the 12 samples selected for "Discretionary Rejection" reassay displayed either an absence of internal standard (IS) response or double the IS response as compared to the rest of the run.

On the same day of analysis, the LC-MS/MS operator documented in the Batch Approval Log that vial volumes for the samples subjected to "Discretionary Rejection" were either significantly lower than the rest of the batch (for samples with no response), or significantly higher than the rest of the batch samples (for samples with double the IS response). This operator record is provided in **Module 5.3.1**.

**Reviewer's comment:**
In the current amendment the firm responded the deficiencies issued by the DB on 01/10/2007.

The firm submitted supporting documentation (chromatograms) to show that the 12 samples selected for "Discretionary Rejection" reassay displayed either an absence of internal standard (IS) response or double the IS response as compared to the rest of the run. The data were not reliable due to possible transfer/processing error. Some samples (29-1-4.0, 29-1-4.5, 29-1-5.0, 29-1-6.0, 29-1-8.0 and 29-1-10.0) received no IS / analyte during processing. This was based on the fact there was no response in the anyalyte / IS channel. The drug and IS from these samples were instead added to samples (29-2-4.0, 29-2-4.5, 29-2-5.0, 29-2-6.0, 29-2-8.0 and 29-2-10.0), where there was a noticeable higher (2x) IS response. Also, the volumes of the samples with no IS response was significantly lower than the rest of the batch while the samples with 2x IS response had volumes in the vials that were significantly higher than the rest of the batch.

Firm's response to deficiency #6 is acceptable.

*7. For the fasting study (#P1BD05001), you have conducted sample reanalysis based on "Discretionary Rejection", but there is no mention of "Discretionary Rejection" in any of the submitted Standard Operating Procedures (SOPs). Since all reasons for reanalysis should be included in the SOPs a priori, please explain the absence of "Discretionary Rejection", as a cause for reanalysis, in the SOPs.*

**Firm's response:**
The fasting study (#P1BD05001) study was conducted in 2005 and the bioanalytical laboratory analyzing these samples was closed in 2008. As such, it is unknown at this time why the SOPs did not describe "Discretionary Rejection." The data identified in #P1BD05001 as "discretionary rejection" displayed unexpected results, such as a lack of internal standard (IS) peak or double the IS response as compared to the rest of the batch. The term "discretionary rejection" may have been used due to the absence of another term available to identify samples for repeat analysis due to IS variability. The bioanalytical laboratory updated their SOP #7320 on November 11, 2005 to incorporate a

consistency check of the IS response throughout batch analysis. The revised SOP along with additional details is provided in **Module 5.3.1**.

**Reviewer's comment:**
The firm provided SOP #7320, in which "*Inspect unknowns for internal standard response variability, if out of specification, code as UIS*". It described a consistent check of the IS response throughout batch analysis. The rejection criteria due to IS variability in SOP #7320 is shown below:

*"9. Variability of Internal Standard Response*
*9.1 Unknown samples are unacceptable if the IS response is more than 1.7 times, or less than 0.5 times, the average IS response of the nearest two acceptable extracted samples.*

*NB: 1: IS response of calibration and quality control standards is used as input to this rule but only unknown samples are rejected.*

*NB: 2: When there is a two-way tie for the second closest injection, it is preferred to pick one IS value on each side of the unknown under test unless the instrument stopped."*

Firm's response to deficiency #7 is acceptable.

*8. The DB II agrees that the dissolution testing should be conducted using the following FDA-recommended method:*

| | |
|---|---|
| ***Medium*** | *Acid stage: 0.1N HCl*<br>*Buffer stage: Sodium Phosphate Buffer, pH 6.8* |
| ***Volume*** | *Acid stage: 300 mL*<br>*Buffer stage: 1000 mL* |
| ***Temperature*** | *37 °C* |
| ***Apparatus*** | *II (Paddle)* |
| ***Rotational Speed*** | *100 rpm* |
| ***Specifications*** | *Acid stage: NMT* (b)(4)*% in 120 minutes*<br>*Buffer stage: NLT* (b)(4)*% in 30 minutes* |

**Firm's response:**
Teva acknowledges the above Agency recommended dissolution test method and specifications. These parameters were employed in the enclosed comparative acid resistance study. In addition, Teva has amended the drug product specifications and test methods for Esomeprazole Magnesium Delayed Release Capsules USP, 20 mg and 40 mg to incorporate the above listed dissolution test method and acceptance criteria. These documents are provided in **Module 3.2.P.5** and will be submitted under separate cover in our response to the March 3, 2012 quality (minor) deficiency letter.

**Reviewer's comment:**

In this amendment, firm updated the dissolution method for both acid and buffer stage. (b) (4)

(b) (4)

Please note USP method is available for Esomeprazole DR Capsules. Firm's dissolution testing procedure in buffer stage is different from that described in USP method. As per USP method, threat the samples in 300 ml of 0.1 N HCl for 2 hours firstly, then add 700 mL of pH 6.8 Phosphate buffer (adjust with 2 N HCl or 2 N NaOH if necessary) using Apparatus 2 at 100 rpm. (b) (4) There is no acid resistant testing listed in USP method. Since previous FDA-recommended two stage dissolution method is better than the current USP method, there is no need to change the dissolution method.

Firm's response is acceptable.

### 3.5 Waiver Request(s)

| | |
|---|---|
| **Strengths for which waivers are requested** | 20 mg |
| **Proportional to strength tested in vivo?** | Yes |
| **Is dissolution acceptable?** | Yes |
| **Waivers granted?** | **WAIVERS DENIED** |
| **If not then why?** | Pending firm's response to deficiencies identified in NG tube study. |

### 3.6 Deficiency Comments

**<u>In vitro tests for Nasogastric (NG) Tube administration:</u>**

1. Firm's sample preparation for particle size analysis by laser diffraction method is incorrect. According to its test procedure, "*take out 10ml of the dispersion and proceed for particle size test at 0 minutes/15 minutes as mentioned in section D for particle size test.*" However, due to rapid sedimentation there was absence of particles remaining in solution per firm's observation. Instead of taking out 10 ml of sample from the dispersion, the firm should collect the pellets in the container in order to determine the particle size distribution of the pellets.

   The firm should determine the comparative particle size of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, before (in syringe) and after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 and 15 min. **The firm should collect the pellets** in the container to determine the particle size distribution of the pellets.

   The firm should provide all particle size data at the D10, D50, and D90 levels. The firm should provide validation reports for particle size distribution study.

2. The firm should provide details of the nasogastric tube and syringe (e.g. material, brand, size, length etc.) and type of water used in the in vitro NG tube study (e.g. sentimentation, particle size, recovery and acid resistance).

3. Since the test product is designed in such a way that the enteric coating starts dissolving above pH 5.5, and the pH of the water may vary between 6.5 to 8.5, to ensure that the consistent stability of the enteric coating in water between the test product and the reference product, the firm needs to demonstrate the stability of the dispersed capsule in different pH of water within different soak time prior to performing the acid resistance testing.

   The firm is requested to repeat acid resistance stability testing using 12 units of both strengths of the test and the reference products as follows:

   a) Prepare the granule dispersion in 50 ml water (soak for 15 min), and collect the contents of granule dispersion at the tube exit. **Please measure initial pH of water and pH of the water after the dispersed contents are delivered through the combination of syringe and NG tube.**

   b) Transfer the contents of granule dispersion into dissolution vessel containing 300 mL of 0.1 N HCl maintained at 37 ±0.5°C.

   c) Flush the nasogastric tube with additional water and transfer any remaining contents into the dissolution media mentioned above.

   d) Acid resistance testing should be conducted using USP Apparatus II at 100 rpm. Analyze the amount of esomeprazole released at 120 minutes.

**Please repeat the above steps using different pH of water (e.g. pH 6, 7 and 8) within different soak time in syringe (e.g. 30 min and 60 min).**

### 3.7 Recommendations

1. The single-dose, *in vivo* **fasting** bioequivalence study (#P1BD05001) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable.**

2. The single-dose, *in vivo* **fed** bioequivalence study (#P1BD05002) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable**.

3. The single-dose, *in vivo* **sprinkled fasting** bioequivalence study (#P1BD05010) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable**.

4. The *in vitro* dissolution testing conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 20 mg (Lot #Y51231) and 40 mg (Lot # Y51232, same as Lot#Y51286 used in the *in vivo* bioequivalence studies, but different package number), comparing to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 20 mg (Lot#P4879) and 40 mg (Lot #N5819), is **acceptable**.

   The dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b)(4)% in 120 minutes<br>Buffer stage: NLT (b)(4)% in 30 minutes |

5. The 20 mg strength is proportionally formulated to the 40 mg strength. The DB can not deem the 20 mg strength of the test product to be bioequivalent to the 20 mg strength of the reference product based on CFR 320.24(b)(6) at this time pending acceptable response to deficiencies related to in vitro NG tube studies.

The application is **incomplete** due to identified deficiencies shown above.

### 3.8 Comments for Other OGD Disciplines

| Discipline | Comment |
|---|---|
| None | N/A |

## 4 APPENDIX

### 4.1 Formulation Data

**Test Product**[10]

| Ingredient | 20 mg (mg/Capsule) | wt/wt (%) 20 mg | 40 mg (mg/Capsule) | wt/wt (%) (40 mg) |
|---|---|---|---|---|
| | | | | (b) (4) |

[10] v:\Firmsam\IvaxPharm\ltrs&rev\78003N1105.doc

(b) (4)

**Reference Product**[11]

| Composition of Nexium® Delayed-Release Capsules | | |
|---|---|---|
| **Component** | **EQ. 20.00 mg Base strength (mg)** | **EQ. 40.00 mg Base strength (mg)** |
| Esomeprazole as Magnesium Trihydrate | 22.30 | 44.50 |
| Glyceryl monostearate (b) (4) (b) (4) | (b) (4) | |
| Hydroxypropyl Cellulose | | |
| Magnesium Stearate | | |
| Methacrylic Acid Copolymer Type C | | |
| Polysorbate 80 | | |
| Sugar spheres (b) (4) (b) (4) | | |
| Talc | | |
| Hard gelatin capsules | | |

**Formulation Data**

| | RLD | IVAX |
|---|---|---|
| | | (b) (4) |

Diameter of Size of feeding tube (1 french unit=0.33 millimeters):
16 French = 5.28 mm
8 French =2.666 mm

[11] Control Document # 03-165; Esomeprazole Magnesium Delayed-Release Capsules.

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## 4.4 % release in acid stage (acid resistance stability)

### 4.4.1 % release in acid stage through catheter tipped syringe in combination with 8.0 French NG tube (raw data) submitted in current amendment

| CIPLA (8.0 FRENCH) | | | | | | |
|---|---|---|---|---|---|---|
| Sr. No. | For 20mg | | | For 40mg | | |
| | Assay mean (%LC) | Content of Esomeprazole after acid stage | % Release in Acid | Assay mean (%LC) | Content of Esomeprazole after acid stage | % Release in Acid |
| 1 | 99.1 | (b) (4) | | 98.4 | (b) (4) | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | | 93.1 | 6.0 | | 94.7 | 3.7 |
| Minimum | | (b) (4) | | | (b) (4) | |
| Maximum | | | | | | |
| SD | | 3.8 | 3.7 | | 3.1 | 3.1 |
| % RSD | | 4.1 | 61.9 | | 3.3 | 84.0 |

Prepared By : (b) (6) Reviewed By : (b) (6)

Date : 06·03·2013 Date : 06·03·2013

| REFERENCE PRODUCT (8.0 FRENCH) | | | | | | |
|---|---|---|---|---|---|---|
| Sr. No. | For 20mg | | | For 40mg | | |
| | Assay mean (%LC) | Content of Esomeprazole after acid stage | % Release in Acid | Assay mean (%LC) | Content of Esomeprazole after acid stage | % Release in Acid |
| 1 | 99.6 | (b) (4) | | 101.1 | (b) (4) | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| 11 | | | | | | |
| 12 | | | | | | |
| Mean | | 97.7 | 2.0 | | 96.7 | 4.4 |
| Minimum | | (b) (4) | | | (b) (4) | |
| Maximum | | | | | | |
| SD | | 1.9 | 1.9 | | 1.8 | 1.8 |
| % RSD | | 2.0 | 94.6 | | 1.9 | 41.0 |

Prepared By : (b) (6) Reviewed By : (b) (6)

Date : 06·03·2013 Date : 06·03·2013

### 4.4.2 Original dissolution data in acid stage without dispersion into the water

**20 mg Capsules**:

| Study Ref. No. | Product ID/Batch No. | Dosage Form | Dissolution Conditions | No. of Dosage Units | Collection Times Mean % Dissolved (Range) | Study Report Location |
|---|---|---|---|---|---|---|
| | | | | | 2 hr. | |
| KR621025 | Esomeprazole Magnesium Delayed Release Capsules 20 mg / Y51282 | 20 mg/ cap | **Apparatus:** Type II (Paddle)<br>**Medium:** 0.1 M Hydrochloric acid<br>**Volume:** 300 ml<br>**Temperature of Medium:** 37° ± 0.5° C<br>**Speed:** 100 rpm<br>**Time:** 2 hours<br>**Limit:** Not more than (b)(4)% (Q) equivalent to (b)(4)% of Esomeprazole is released in 2 hours.<br>**Method:** FPS E1171<br>**Revision No.** 03 | 12 | 2 (b) (4) | (b) (4) |
| KR621070 | NEXIUM® (esomeprazole magnesium) Delayed Release Capsules 20 mg / F4793 | 20 mg/ cap | | 12 | 1 (b) (4) | |

**40 mg Capsules**:

| Study Ref. No. | Product ID/Batch No. | Dosage Form | Dissolution Conditions | No. of Dosage Units | Collection Times Mean % Dissolved (Range) | Study Report Location |
|---|---|---|---|---|---|---|
| | | | | | 2 hr. | |
| KR621026 | Esomeprazole Magnesium Delayed Release Capsules 40 mg / Y51286 | 40 mg/ cap | **Apparatus:** Type II (Paddle)<br>**Medium:** 0.1 M Hydrochloric acid<br>**Volume:** 300 ml<br>**Temperature of Medium:** 37° ± 0.5° C<br>**Speed:** 100 rpm<br>**Time:** 2 hours<br>**Limit:** Not more than (b)(4)% (Q) equivalent to (b)(4)% of Esomeprazole is released in 2 hours.<br>**Method:** FPS E1172<br>**Revision No.** 03 | 12 | 3 (b) (4) | (b) (4) |
| KR621069 | NEXIUM® (esomeprazole magnesium) Delayed Release Capsules 40 mg / F1802 | 40 mg/ cap | | 12 | 1 (b) (4) | |

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 078003

APPLICANT: IVAX Pharmaceuticals, Inc.,
(subsidiary of Teva Pharmaceuticals USA)

DRUG PRODUCT: Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

The Division of Bioequivalence II (DB II) has completed its review of your submissions acknowledged on the cover sheet. The following deficiencies have been identified:

**Deficiencies related to your In vitro test for Nasogastric (NG) Tube administration:**

1. Your sample preparation for particle size analysis by laser diffraction method is incorrect. Your test procedure states that, *"take out 10 ml of the dispersion and proceed for particle size test at 0 minutes/15 minutes as mentioned in section D for particle size test."* However, due to rapid sedimentation, there is absence of particles remaining in solution per your observation. Instead of taking out 10 mL of sample from the dispersion, you should collect the pellets in the container in order to determine the particle size distribution of the pellets.

   Please determine the comparative particle size of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, before (in syringe) and after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 and 15 min. **Please collect the pellets** in the container to determine the particle size distribution of the pellets.

   Please provide all particle size data at the D10, D50, and D90 levels. Please visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all the observations and supporting photographs. Please take photos at different stages (syringe with capsule's content, attaching syringe to the NG tube, injecting water with pellets into the NG tube, flushing NG tube etc.).

2. Please provide validation reports for your particle size distribution study.

3. Please provide information of the nasogastric tube and syringe (e.g. material, brand, size, etc.) and type and pH of the water used in your in vitro NG tube study (e.g. sedimentation, particle size, recovery and acid resistance).

4. Since your test product is designed in such a way that enteric coating starts dissolving above pH 5.5, and the pH of the water may vary between 6.5 to 8.5, there is a concern that the process of dispersing capsule in water, soaking for a certain time, and dispensing through an oral syringe with an NG tube might adversely impact the integrity of the enteric coating. Please demonstrate the stability of the dispersed granules in different pH of water with different soak time prior to performing the acid resistance testing.

   Please repeat acid resistance stability testing using 12 units of both strengths of the test and the reference products as follows:

   a) Prepare the granule dispersion in 50 mL water (soak for 15 min), and collect the contents of granule dispersion at the tube exit. **Please measure the initial pH of water and pH of the water after the dispersed granules are delivered through the combination of syringe and NG tube.**

   b) Transfer the contents of granule dispersion into dissolution vessel containing 300 mL of 0.1 N HCl maintained at 37 ±0.5°C.

   c) Flush the nasogastric tube with additional water and transfer any remaining contents into the dissolution media mentioned above.

   d) Acid resistance testing should be conducted using USP Apparatus II at 100 rpm. Analyze the amount of esomeprazole released at 120 minutes.

**Please repeat the above steps using different pH of water (e.g. pH 6, 7 and 8) with different soak times in syringe (e.g. 15 min, 30 min and 60 min).**

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

## 5 *COMPLETED ASSIGNMENT FOR 078003 ID: 20209*

**Reviewer:** Xia, Li

**Date Completed:**

**Verifier:**

**Date Verified:**

**Division:** Division of Bioequivalence

**Description:** Esomeprazole Magnesium Delayed-Release Capsules, Eq. 20 mg and 40 mg base - In Vitro NG tube study

---

*Productivity:*

| *ID* | *Letter Date* | *Productivity Category* | *Sub Category* | *Productivity* | *Subtotal* |
|---|---|---|---|---|---|
| 20209 | 4/25/2013 | Other (REGULAR) | Study Amendment - sedimentation testing 20 mg | 1 | 1 |
| 20209 | 4/25/2013 | Other (REGULAR) | Study Amendment - sedimentation testing 40 mg | 1 | 1 |
| 20209 | 4/25/2013 | Other (REGULAR) | Study Amendment- Particle size study 20 mg | 1 | 1 |
| 20209 | 4/25/2013 | Other (REGULAR) | Study Amendment - Particle size study 40 mg | 1 | 1 |
| 20209 | 4/25/2013 | Other (REGULAR) | Study Amendment - Recovery testing 20 mg | 1 | 1 |
| 20209 | 4/25/2013 | Other (REGULAR) | Study Amendment- Recovery testing 40 mg | 1 | 1 |
| 20209 | 4/25/2013 | Other (REGULAR) | Study Amendment - Acid resistance 20 mg | 1 | 1 |
| 20209 | 4/25/2013 | Other (REGULAR) | Study Amendment - Acid resistance 40 mg | 1 | 1 |
| | | | | Total: | 8 |

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

**Typical BE Study Applications**

| **Sedimentation Test** | |
|---|---|
| Strength 20 mg | 1 |
| Strength 40 mg | 1 |
| **Particle Size Study** | |

| | |
|---|---|
| Strength 20 mg | 1 |
| Strength 40 mg | 1 |
| **Recovery Testing** | |
| Strength 20 mg | 1 |
| Strength 40 mg | 1 |
| **Acid Resistance Test** | |
| Strength 20 mg | 1 |
| Strength 40 mg | 1 |
| *Study Summary Total* | *8* |

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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.**

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/s/

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LI XIA
09/09/2013

XIAOJIAN JIANG
09/09/2013

ETHAN M STIER
09/19/2013

# DIVISION OF BIOEQUIVALENCE REVIEW

| | | | |
|---|---|---|---|
| **ANDA No.** | 078003 | | |
| **Drug Product Name** | Esomeprazole Magnesium Delayed-Release Capsules | | |
| **Strength(s)** | Eq. 20 mg and 40 mg base | | |
| **Applicant Name** | IVAX Pharmaceuticals, Inc.,<br>An indirect and wholly owned subsidiary of Teva Pharmaceuticals USA | | |
| **Address** | 400 Chestnut Ridge Road<br>Woodcliff Lake, NJ, 07677 | | |
| **Applicant's Point of Contact** | Robert S. Vincent, Director, Regulatory Affairs | | |
| **Contact's Telephone Number** | 201-930-3610 | | |
| **Contact's Fax Number** | 201-489-1403 | | |
| **Original Submission Date** | November 23, 2005 | | |
| **Submission Date of Previous Amendment** | November 13, 2006 (study amendment) | | |
| **Reviewer** | Li Xia, Ph.D. | | |
| | | | |
| **Study Number (s)** | P1BD05001 | P1BD05002 | P1BD05010 |
| **Study Type (s)** | Fasting | Fed | Sprinkled Fasting |
| **Strength (s)** | eq. to 40 mg base | eq. to 40 mg base | eq. to 40 mg base |
| **Clinical Site** | Allied Research International Inc. | | |
| **Clinical Site Address** | 4520 Dixie Road, Mississauga, Ontario, Canada L4W 1N2 | | |
| **Analytical Site** | (b) (4) | | |
| **Analytical Site Address** | | | |
| | | | |
| **OVERALL REVIEW RESULT** | **INADEQUATE pending NG tube study and satisfactory response to the deficiencies for fasting study** | | |
| **OSI REPORT RESULT** | **ADEQUATE** | | |
| **BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #** | **STUDY/TEST TYPE** | **STRENGTH** | **REVIEW RESULT** |
| **2** | **Dissolution** | **20 and 40 MG** | **ADEQUATE** |
| **1** | **Fasting study** | **40 MG** | **INADEQUATE** |
| **1** | **Fed study** | **40 MG** | **ADEQUATE** |
| **1** | **Sprinkled Fasting Study** | **40 MG** | **ADEQUATE** |
| **1** | **Biowaiver Request** | **20 mg** | **INADEQUATE** |
| **1** | **NG Tube Test** | **20 mg and 40 mg** | **INADEQUATE** |



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## ADDENDUM TO REVIEW OF ANDA 078003

# 1 EXECUTIVE SUMMARY

IVAX Pharmaceuticals, Inc. previously submitted an application (11/23/2005) consisting of three, bioequivalence (BE) studies comparing its test product, Esomeprazole Magnesium Delayed-Release (DR) Capsules, 40 mg, to the corresponding reference product, AstraZeneca's NEXIUM® (Esomeprazole Magnesium) DR Capsules, 40 mg, under fasting, fed, and fasting "sprinkled" conditions. Firm's fed and fasting sprinkled BE studies were found acceptable, the dissolution testing conducted using the FDA-recommended method was also acceptable. However, the fasting BE study is **incomplete** pending acceptable response to the bioanalytical deficiencies[1]. As of 09/05/2012, the firm has not responded the deficiency comments communicated to it in DB's deficiency letter dated 1/10/2007.

The objective of this addendum is to request the firm to perform the comparative *in vitro* tests on both the strengths of the test and reference products using nasogastric (NG) tube for Esomeprazole Magnesium DR Capsules.

Since Esomeprazole Magnesium DR Capsules include an alternate administration method through a NG tube per the approved labeling for the reference product, we request that the firm performs the comparative *in vitro* tests (Sedimentation, Particle size distribution, Recovery, and Acid resistance stability testing) to compare the performance of its test product to that of the reference product for both strengths, 20 mg and 40 mg, under NG tube administration.

The 20 mg strength is proportionally formulated to the 40 mg strength. Yet, the DB can not deem the 20 mg strength to be bioequivalent to the 20 mg strength of the reference product based on CFR 320.24(b)(6) at this time pending NG tube study and acceptable fasting study.

No Office of Scientific Investigations (OSI) inspection is pending or necessary (see section 3.5 for details).

The application is **incomplete** pending NG tube studies and acceptable response to the bioanalytical deficiencies for fasting study.

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[1] DARRTS: REV-BIOEQ-01(General Review) for ANDA 078003, final date 01/04/2007.



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# 3 SUBMISSION SUMMARY

## 3.1 Drug Product Information

| | |
|---|---|
| **Test Product** | Esomeprazole Magnesium Delayed-Release capsules, 20 mg and 40 mg |
| **Reference Product** | NEXIUM® (Esomeprazole magnesium)<br>Delayed-Release capsules, 20 mg and 40 mg |
| **RLD Manufacturer** | AstraZeneca |
| **NDA No.** | 021153 |
| **RLD Approval Date** | Feb 20, 2001 |
| **Indication** | Treatment of Gastroesophageal Reflux Disease (GERD), Maintenance of Healing of Erosive Esophagitis, Symptomatic Gastroesophageal Reflux Disease, Risk Reduction of NSAID-Associated Gastric Ulcer, H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence, Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome. |

## 3.2 Study for Nasogastric Tube Administration

**Labeling of NEXIUM (Esomeprazole Magnesium) Delayed-Release Capsules**[2]

**Dosage and administration**
NEXIUM Delayed-Release Capsules should be swallowed whole.

For patients who have a nasogastric tube in place, NEXIUM Delayed-Release Capsules can be opened and the intact granules emptied into a 60 mL catheter tipped syringe and mixed with 50 mL of water. It is important to only use a catheter tipped syringe when administering NEXIUM through a nasogastric tube. Replace the plunger and shake the syringe vigorously for 15 seconds. Hold the syringe with the tip up and check for granules remaining in the tip. Attach the syringe to a nasogastric tube and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the granules, the nasogastric tube should be flushed with additional water. Do not administer the granules if they have dissolved or disintegrated.

The mixture must be used immediately after preparation.

[2] Labeling of Nexium at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f4853677-1622-4037-688b-fdf533a11d96#nlm34068-7



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Table 1: Recommended Dosage Schedule of NEXIUM

| Indication | Dose | Frequency |
|---|---|---|
| **Gastroesophageal Reflux Disease (GERD)** | | |
| Healing of Erosive Esophagitis | 20 mg or 40 mg | Once Daily for 4 to 8 Weeks |
| Maintenance of Healing of Erosive Esophagitis | 20 mg | Once Daily |
| Symptomatic Gastroesophageal Reflux Disease | 20 mg | Once Daily for 4 Weeks |
| | | |
| **Pediatric GERD** | | |
| **12 to 17 Year Olds** | | |
| Short-term Treatment of GERD | 20 mg or 40 mg | Once Daily for up to 8 Weeks |
| **1 to 11 Year Olds** | | |
| Short-term Treatment of Symptomatic GERD | 10 mg | Once Daily for up to 8 Weeks |
| Healing of Erosive Esophagitis | | |
| weight < 20 kg | 10 mg | Once Daily for 8 Weeks |
| weight ≥ 20 kg | 10 mg or 20 mg | Once Daily for 8 Weeks |
| **1 month to < 1 year old** | | |
| Erosive esophagitis due to acid-mediated GERD | | |
| weight 3 kg to 5 kg | 2.5 mg | Once Daily for up to 6 Weeks |
| weight > 5 kg to 7.5 kg | 5 mg | Once Daily for up to 6 Weeks |
| weight >7.5 kg to 12 kg | 10 mg | Once Daily for up to 6 Weeks |

**Background**

Enteral feeding tubes are sometimes used to administer medication to patients who cannot safely swallow or unable to tolerate oral intake. Esomeprazole is indicated for treatment of GERD, risk reduction of NSAID-associated gastric ulcer, H. pylori eradication to reduce the risk of duodenal ulcer recurrence, and treatment of pathological hypersecretory conditions Including Zollinger-Ellison syndrome. According to the labeling, Esomeprazole Magnesium DR capsules include an alternate administration method through a combination of syringe and a nasogastric (NG) tube. Esomeprazole is a substituted benzimidazole, and inhibits gastric acid secretion by specific inhibition of the enzyme, H+K+-ATPase at the surface of the gastric parietal cells. Esomeprazole has the similar chemical structure and the same bio-function as Lansoprazole.

Several current FDA adverse event report indicates that Teva's Lansoprazole DR Orally Disintegrating Tablets when dosing the product using an oral syringe or feeding tube has clogged and blocked oral syringes and feeding tubes including both gastric and jejunostomy types (Section 4.1 Attachment I). The tablets may not fully disintegrate when water is added to them and/or they may disintegrate but later form clumps. These clumps can adhere to the inside walls of oral syringes and feeding tubes. In some cases, patients have had to seek emergency medical assistance and their feeding tubes have had to be unclogged or removed and replaced. In addition, the laboratory results conducted by the Division of Pharmaceutical Analysis (DPA)



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dated 11 March 2011 demonstrated that there is a risk of clogging the NG tube when using the RLD and Teva's product for 15 min or longer[3].

The results from the previous studies demonstrated that administration of esomeprazole magnesium enteric-coated pellets dispersed in tap water through size 14 French NG tube in vitro delivered over 99% of capsule contents[4]. In NDA 21153, the sponsor conducted an in vitro study to evaluate the delivery of the contents of an Esomeprazole Magnesium Capsule (40 mg) through NG tubes of various sizes (8F and 14F). The study revealed that the average recovery of pellets was >98% following the dispersion of pellets in 50 mL of tap water in a syringe[5]. Both previous studies and NDA 21153 in vitro study have shown excellent delivery of Esomeprazole enteric-coated pellets using water as a medium for NG tube delivery.

**DB Recommendation**

The Office of Generic Drugs (OGD) is concerned about this issue and the potential for harm to patients and is seeking prompt correction of the problem. The successful delivery of test drug product through a combination of syringe and NG tube requires that all of the capsule's contents be able to safely pass through the feeding tube and not cause tube occlusions. Therefore, we request the firm to demonstrate that the generic product has a similar performance profile to the reference product during NG tube administration.

In history, the NG tube study deficiency for ANDA (b) (4) was requested by the OGD Division of Chemistry II (Section 4.2 Attachment II). As per the discussed among review teams consisting of Division of Bioequivalence II and Division of Chemistry II, we will ask this NJ tube study for any product that has labeled feeding tube administration.

Based on the OGD review team meeting dated 3/14/2011 (Section 4.1 Attachment I), DPA study reports, and information from the OGD CMC Division of Chemistry II, the DB recommends the following comparative *in vitro* test:

1. Sedimentation testing: Determine comparative sedimentation volume of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, in 50 ml of water at 0 and 15 min.

2. Particle size distribution study: Determine the comparative particle size of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, before and after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 and 15 min. Provide all particle size data at D10, D50, and D90 level.

3. Recovery testing: Conduct the comparative recovery studies of the granule dispersion from a combination of oral syringe and 8 French nasogastric tube using at least 12 units of both

[3] Interim report from the Division of Pharmaceutical Analysis 03/11/2011: Interim report on Evaluation of Lansoprazole Orally Disintegrating tablets: Dosing with Oral Syringe, Phase 1 Part A and Part B.
[4] Sachin A Shan etc al: Delivery of Esomeprazole magnesium through nasogastric and gastrostomy tubes using an oral liquid vehicle as a suspending agent in vitro. Am J Health-Syst Pharm-vol 63 Oct1, 2006.
[5] DARRTS: REV-CLINPHARM-01(General Review) for NDA 21153 Final date 04/16/2003.



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strengths of the test and the reference products in 50 ml water. Determine the percentage of esomeprazole recovered at the tube exit relative to the initial dose for both the test and the reference products at 0 and 15 min. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated.

4. Comparative acid resistance stability testing: Measure acid resistance on the granule dispersion in water after recovery through a combination of oral syringe and 8F NG tube. Evaluate the stability on 12 units of both strengths of the test and the reference products using acid resistance as stability indicator.

Note: In pediatric practice, the sizes of 8F to 16 F NG tubes are generally used for medication administration. Since the indication of Esomeprazole Magnesium DR Capsules is also for Pediatric GERD from age of 1 month to 17 year old, 8F NG tube size is required for the NG tube study of Esomeprazole Magnesium DR Capsules.

Based on a meeting with CMC team leaders on 11/29/2011, they agreed DB's recommended *in vitro* studies for NG tube study. The CMC will ask NG tube test separately in its deficiency letter (Section 4.3 Attachment III). The details of the in vitro studies will be sent to the firm with deficiency letter (detail please see deficiency comments).

### 3.3 CMC Deficiency

CMC issued a deficiency regarding in vitro NG tube testing to the firm in deficiency letter dated 03/07/2012[6].

**CMC deficiency #12:**

(b) (4)

**As of 09/05/2012, the firm has not responded this deficiency yet.**

### 3.4 Waiver Request(s)

| **Strengths for which waivers are requested** | 20 mg |
|---|---|

[6] DARRTS: REV-QUALITY-03(General Review) for ANDA 078003, final date 03/07/2012.



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| | |
|---|---|
| **Proportional to strength tested in vivo?** | Yes |
| **Is dissolution acceptable?** | Yes |
| **Waivers granted?** | **WAIVERS DENIED** |
| **If not then why?** | Pending NG tube study and acceptable response to the bioanalytical deficiencies for fasting study. |

### 3.5 OSI Inspection History:

A Routine inspection of the clinical site, Allied Clinical Research, 4520 Dixie Rd, Mississauga, Ontario (Canada) was requested for NDA 21210 on 5/22/2003 and was completed on 9/22/2003 with an outcome of VAI. A For Cause inspection of this clinical site was requested for NDA 21210 on 3/30/2004 and was completed on 6/17/2004 with an outcome of NAI. The most recent routine inspection of this clinical site was requested for ANDA 078982 on 10/29/2007 and was completed on 7/16/2008 with an outcome of NAI. Since the three BE studies for the current ANDA were conducted in August-October 2005, thus, the clinical site is acceptable.

A Routine inspection of the Analytical site, (b) (4) was requested for ANDA (b) (4) on (b) (4) and was completed on (b) (4) with an outcome of (b) (4). The OSI inspection report of analytical site was received by the DB and the analytical site was found acceptable[7]. Since the three BE studies for the current ANDA (August-October 2005) and the studies for ANDA (b) (4) are conducted in a similar time period, the inspection for the analytical site for ANDA (b) (4) should be able to cover the current ANDA as well (see project management email in Attachment IV).

### 3.6 Deficiency Comments

**<u>In vitro tests for Nasogastric (NG) Tube administration:</u>**

The approved labeling for the reference product states that the product may be administered by a nasogastric tube with water. Therefore, we request the firm to perform the following comparative *in vitro* tests to compare the performance of the test product to that of the reference product during administration.

1. The firm should determine comparative sedimentation volume and particle size of the granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, in 50 ml of water as follows:

    a) Prepare the catheter tipped syringe (60 mL), remove the syringe plunger, open the capsule and empty the contents of one capsule into the syringe. Insert the syringe plunger, draw up 50 mL of water and shake the syringe vigorously for 15 seconds.

[7] DARRTS: REV-BIOEQ-03(Acceptable DSI Inspection Report Review) for ANDA (b) (4), final date (b) (4)



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b) Place the syringe perpendicular to the bench with the tip up and record sedimentation volume at 0 min. Please remove the syringe plunger and determine the particle size of the granules in the syringe.

c) Using a new set of 12 units please repeat the process described in step (a) to prepare the granule dispersion, then incubate for 15 min and record the sedimentation volume and determine the particle size of the granules.

The firm should provide all particle size data at the D10, D50, and D90 levels. The firm may use the markings on the syringe to note the sedimentation volume. The firm should provide a qualitative description, e.g., particle aggregation and particles adhering to the syringe walls. The firm should take photos of the contents of the syringe at various intervals throughout the testing process.

2. The firm should determine the comparative particle size of the granule dispersion using 12 units each of the test and reference products, 20 mg and 40 mg strengths, after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 and 15 min as follows:

   a) Prepare the feeding tube according to the manufacturer's directions. Repeat the process described in 1(a) to prepare the granule dispersion.

   b) Attach the syringe to the feeding tube, using the syringe plunger push the granule dispersion through the syringe and the feeding tube into a collection container.

   c) Remove the syringe from the feeding tube, draw up additional water, and flush the system by pushing the fluid through the feeding tube into the container. Perform particle size analysis of the collected fluid.

   d) Please repeat the testing described above with a fresh set of 12 units. However, after suspending the capsule content in step a, wait 15 minutes prior to injecting the contents into the feeding tube.

   The firm should visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all the observations and supporting photographs. The firm should provide the particle size data at the D10, D50 and D90 levels and report flush volume used in these studies.

3. The firm should conduct comparative recovery studies to determine what percentage of the initial dose suspended in water passes through the 8 French nasogastric tubes. The firm should use 12 units of both strengths of the test and the reference products in 50 ml water and follow the process outlined in comments# 2. The firm should determine the percentage of esomeprazole recovered at the tube exit relative to the initial dose for both the test and the reference products at 0 and 15 min. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. The DBII will set an



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interim specification based upon the review of the submitted data. If high variability is observed, the firm may increase the numbers of units used for this test.

4. The firm should conduct comparative acid resistance stability testing using 12 units of both strengths of the test and the reference products. The firm should use the following method:

    a) Prepare the granule dispersion in 50 mL water (hold for 15 min) and collect the contents of granule dispersion at the tube exit.

    b) Transfer the contents of granule dispersion into dissolution vessel containing 300 mL of 0.1 N HCl maintained at 37 ±0.5°C.

    c) Flush the nasogastric tube with additional water and transfer any remaining contents into the dissolution media mentioned above.

    d) Acid resistance testing should be conducted using USP Apparatus II at 100 rpm. Analyze the amount of esomeprazole released at 120 minutes.

5. The firm should submit standard operating procedures for sedimentation, particle size, acid resistance and recovery testing. The firm should submit individual data, mean values, standard deviations, and coefficient of variation (CV%) and plots of percent release of Esomeprazole in acid resistance test. The photographs should be submitted to support the firm's observations and results. The firm should also provide the pre-study and within-study assay validation report.

    Please conduct all the above testing on unexpired test and reference batches.

***Please note that the following deficiencies were provided to the firm in the DB II deficiency letter dated 01/10/2007 after our review of the original application and is provided to the firm again since we has not yet received its responses.***

6. For the fasting study (#P1BD05001), although you have provided explanation for the 12 "Discretionary Rejection" reassays, you did not provide any supporting data along with the response. Please provide supporting data, such as chromatograms of the original 12 samples showing the abnormal internal standard responses and 12 original assay values. In the response, you have also stated that visually observed discrepancy in remaining sample volumes in the injection vials subjected to "Discretionary Rejection" were noted. Please provide evidence in support of that statement.

7. For the fasting study (#P1BD05001), you have conducted sample reanalysis based on "Discretionary Rejection", but there is no mention of "Discretionary Rejection" in any of the submitted Standard Operating Procedures (SOPs). Since all reasons for reanalysis should be included in the SOPs *a priori*, please explain the absence of "Discretionary Rejection", as a cause for reanalysis, in the SOPs.



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The DBE agrees that the dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b)(4)% in 120 minutes<br>Buffer stage: NLT (b)(4)% in 30 minutes |

### 3.7 Recommendations

1. The single-dose, *in vivo* **fasting** bioequivalence study (#P1BD05001) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **incomplete** pending adequate explanation of the deficiency comments.

2. The single-dose, *in vivo* **fed** bioequivalence study (#P1BD05002) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable**.

3. The single-dose, *in vivo* **sprinkled fasting** bioequivalence study (#P1BD05010) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable**.

4. The *in vitro* dissolution testing conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 20 mg (Lot #Y51231) and 40 mg (Lot # Y51232, same as Lot#Y51286 used in the *in vivo* bioequivalence studies, but different package number), comparing to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 20 mg (Lot#P4879) and 40 mg (Lot #N5819), is **acceptable**.

   The dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL |



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| | |
|---|---|
| | Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b) (4) % in 120 minutes<br>Buffer stage: NLT (b) (4) % in 30 minutes |

5. The 20 mg strength is proportionally formulated to the 40 mg strength. The DB can not deem the 20 mg strength of the test product to be bioequivalent to the 20 mg strength of the reference product based on CFR 320.24(b)(6) at this time pending NG tube studies and acceptable response to the bioanalytical deficiencies for fasting study.

The application is **incomplete due to deficiencies.**

### 3.8 Comments for Other OGD Disciplines

| Discipline | Comment |
|---|---|
| None | N/A |

## 4 APPENDIX

### 4.1 Attachment I

**LASOPRAZOLE MEETING MINUTES**
**DRAFT**

**Meeting Date:** 14 March 2011 **Time:** 3:00-4:15 PM
**Location:** MPN4, C/R A
**Topic:** Lansoprazole
**Meeting Type:** Internal
**Meeting Chair:** Lawrence Yu

**FDA attendee list:**

Debra Catterson, Nancy Chang, Dale Conner, Barbara Davit, Florence Fang, Rita Hassall, Dena Hixon, Frank Holcombe, Wenlei Jiang[1], Laurie Muldowney, Kiet Nguyen[8], James Osterhout, Radhika Rajagopalan, William Rickman, Vilayat Sayeed, Paul Schwartz, Glen Smith, Keith Webber, and Lawrence Yu

I. Meeting purpose

[8] Prepared meeting minutes.



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In response to reports of Teva's generic Lansoprazole delayed-release orally disintegrating tablets (LODT)[9] clogging enteral feeding tubes (Jejunal (J) and Gastrostomy (G) tubes), OGD held an internal meeting on 14 March 2011. This meeting was to discuss the review policy relating to LODT and lansoprazole delayed-release capsules, as both are indicated for optional administration through feeding tubes.

## II. Discussion Points:

Lansoprazole delayed-release orally disintegrating tablets (LODT)

The LODT product is labeled for use with Nasogastric (NG) tube ≥8F (outer diameter of the tube)[10]. Teva submitted *in-use test* data comparing the reference listed drug (RLD) to its product in order to support the product use with an 8F NG feeding tube. Because the J and G tubes were not on the label, OGD did not ask Teva to submit the in-use tests with those tubes.

Discussion was directed toward the laboratory results conducted by the Division of Pharmaceutical Analysis (DPA) dated 11 March 2001 (Appendix 1). OGD had asked DPA to conduct comparative *in vitro* studies between RLD and Teva generic with a combination of oral syringes and feeding tubes (NG, J, and G), (please see Appendix 4 for additional information on the feeding tubes). Below is the observation summary:

**Syringe**

- The Prevacid® (RLD) 15 mg tablet product disintegrates in 30 seconds in 4 mL DI water in syringe whereas the Teva's 15 mg tablet product disintegrates in 2 minutes. (These results are inconsistent with previous Teva data submitted in their ANDA 78-730).
- For both RLD and Teva's products, there are beads remaining in the syringe after delivery of the 4 mL tablet/water mixture for all types of tubes tested. The following 5mL flush removed most of any remaining beads for Prevacid; however, the flush did not dislodge most of the beads for the TEVA product.

NG tube

The RLD and Teva's products did not clog the NG tube when administered immediately but there is a risk of clogging when the mixtures are allowed to stand for 15 min or longer. The beads of Teva's product stick to the inner wall of the tube, suggesting incomplete delivery. Subsequent flush did not remove the beads. (Teva did not report any product sticking problem in their ANDA 78-730.)

**G tube**

The RLD and Teva's products clogged the 12F G tubes. The RLD beads did not stick to the G tube wall while Teva's product beads did.

**J tube**

[9] It is the first LODT generic product, approved on 15 October 2010.
[10] The feeding tube sizes (outer diameter of the tube) are reported in French Units (F).



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The RLD did not clog the 12F J tube. Teva's product clogged the 12F J tube and subsequent flush did not remove the beads. The RLD beads did not stick to the J tube wall while Teva's product beads did.

The DPA report was forwarded to OND by Nancy Chang. Please note that there were no in-use data with J tube and G tubes in the NDA submission.

It was discussed that:

- The DPA tests should be repeated to confirm above observations. It is ideal to establish a standard method for future testing of products administered via enteral tubes.
- Since the RLD API microgranule size (median (D50) of (b) (4) differ in size from Teva's size (median (D50) of (b) (4) the point was considered that particle size will play a role in the observed feeding tube clog.
- OGD should consider the impact of the increased mass compared to the RLD. Teva's product contains (b) (4) than the RLD, including the (b) (4).
- Teva's product beads stick to the inner wall of tubes independent of the tube material (polyurethane or silicone). Coating material differences on the granules should also be considered. (b) (4)
- The *in vitro in-use* tests should be predictive of microgranule clumping behavior in aqueous solution. This should include, but not be limited to, dispersibility, drug recovery tests, physical observation, analysis of sedimentation and flocculation.

<u>Lansoprazole Capsule</u>

OGD approved 4 (n=4) generic lansoprazole capsule ANDAs without *in vitro* data to support the suitability of product performance with the indicated label use with NG tubes (≥16F).[11] No reports of complaints associated with feeding tube clogging have been received.

The RLD lansoprazole capsule product contains granules with an average size of (b) (4). The 4 approved ANDAs particle size were within the same range or smaller than the RLD granule size. An AERS/DQRS report of adverse events generated no complaints of feeding tube clogging for lansoprazole capsules and feeding tube clogging, but a published literature search indicated that using the lansoprazole capsules in small-bore size (<12 F) feeding tube can lead to tube blockage (Appendix 2). The discussion included the following:

- Since sufficient literature indicates potential for feeding tube blockage, most likely, patients and practitioners avoid use of lansoprazole capsules in the small-bore size feeding tubes, thus fewer clogging issues are reported.
- The granule sizes of the ANDAs do not pose a risk in relation to the RLD product; therefore, the granule size may be an important criterion to predict the tendency of the generic product to clog feeding tubes.

[11] The RLD new labeling for giving lansoprazole delayed-release capsules USP through a nasogastric tube (NG tube ≥ 16 French), was changed from "Nasogastric tube" (prior to 2010) to "Nasogastric tube (≥16 French)" [in NDA 20-406/S-071, 9/03/2010].



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- The *in vitro in-use* tests should be required of the firms in order to establish the use of lansoprazole DR capsule in the labeled NG feeding tube.

Enteral Feeding Tubes

Feeding tubes assist patients who have difficulty in swallowing to deliver food nutrients and medications. They are classified according to the site of insertion (i.e. nasogastric, jejunal, and gastrostomy). The NG tubes are mentioned in the labels of both the LODT and lansoprazole capsule. Alternative administration via J and G tubes are not specifically indicated on the label. However, OGD was advised by the Office of New Drugs (OND) recently that the use of J and G feeding tubes is within the intent of the label. These feeding tubes exhibit a diversity of sizes (inner and outer diameter), lengths, materials (i.e. polyurethane and silicone), and luminal configurations (e.g. taper, partial occlusion of lumen by balloon channel). The feeding tube sizes are associated with the outer diameter of the tube and are reported in French Units; however, the inner diameter can vary and it is not standardized (Appendix 3).

A discussion centered on what feeding tubes should be included in the tests to predict clogging.

- An *in vitro in-use* test comparing the RLD to the generic should be included for the indicated label feeding tube use. For example, an 8F NG tube for LODT and 16F NG tube for the lansoprazole capsule product must accompany the ANDA submission.
- A firm should provide tests to support the compatibility of the product with a variety of feeding tube materials commonly used (polyurethane and silicone). It is suggested that compatibility tests could be done with the tubing material, not necessarily with the actual tubes.
- NDA submission does not contain test data with additional tubes other than the one in the label. Testing of generic products with additional J and G tubes which are not listed on the label may depend on product design and characterization.
- Firms should provide the actual tubes used in the *in vitro in-use* tests so that OGD can confirm the results.

## III. Tentative Proposed Considerations for Generic Product Review:

As the feeding tubes exhibit diversity of sizes (inner and outer diameter), lengths, construction type, and materials (i.e. polyurethane and silicone), it is very difficult to just conduct *in vitro in-use* testing with a limited number of feeding tubes to support drug use and performance when the product is administered via other feeding tube types/sizes. It is agreed that generic applicants need use a QbD approach to design and develop test products that would have a similar product performance profile to the reference product including similar performance during tube administration. Listed below are the proposed considerations (not a complete list). During the ANDA review process, reviewers need pay attention to these aspects and other critical attributes (such as raw material attributes, critical process parameters, etc.) which may impact tube administration of drug products.

### Product design



Reference ID: 3192682

1. Compare formulation and process design of generic and RLD to analyze potential risk. As part of the design features, the ANDA should rationalize the granule particle size, coating material, coating layers, tablet weight, and insoluble excipients in relation to the product performance. If any of the product design poses a potential concern, additional justification should be provided and evaluated.

For example, for a generic product having higher amount of insoluble excipients than the RLD, a reviewer should carefully examine whether the extra amount of insoluble excipients is present inside or outside the DR granules. If the generic has the granule sizes less or equal to that of RLD, and contains the extra amount of insoluble excipients inside the granule, then the extra amount of insoluble excipient in the generic product may not pose additional risk of clogging feeding tubes compared to RLD. As DR granules are designed not to dissolve quickly in acidic media and water, the insoluble excipients inside the DR granules may not get exposed to external media within the administration time, thus not affecting tube administration. However, if a significantly higher amount of insoluble excipients is present outside the generic product DR granules, the reviewer should question whether the added amounts pose a concern for the performance of the generic in the feeding tube.

**Product characterization**

2. Surface properties of the granule particles. This may influence interaction between granules with the inside surface of the enteral tube and oral syringe or among the granules as aggregation.

3. Granule dispersion properties after drug product dispersion in water (e.g., comparable or smaller granule particle size of generic, dispersion viscosity, sedimentation). If necessary, the average particle size and particle size distribution of generic and RLD may be compared using population bioequivalence criteria.

**Product *in vitro in-use* tests**

4. Perform *in vitro in-use* tests (e.g., dispersibility, recovery, physical observation, analysis of sedimentation and flocculation) of drug products with tubes to support labeled routes of administration.

One challenge with the *in vitro in-use* tests is how to advise generic applicants to perform the study since the label does not list all tube types, materials, and sizes that the physicians may potentially use for patients. In general, when the generic and RLD have similar product characteristics, a well designed, robust *in vitro in-use* tests with the labeled feeding tubes (e.g., NG tubes of different material) should reasonably predict the product performance via tube administration. If however the product characterization suggests higher risk of generic product clogging, the *in vitro in-use* test with additional tube types should be performed. When compared via these in-vitro in-use tests, the generic should not differ significantly from the RLD. A quantitative comparison of the test results can be conducted if necessary.



Reference ID: 3192682

5. Demonstrate the *in vitro in-use* test robustness (e.g., test different type of water and holding positions).

DPA and Teva obtained inconsistent performance test results when evaluating *in vitro* performance of Teva's LODT in various types of tubing. OGD will ask generic applicants to submit tubes and product samples for confirmatory testing.

## Appendix 1

**From:** Buhse, Lucinda
**Sent:** Friday, March 11, 2011 5:04 PM
**To:** Rajagopalan, Radhika
**Cc:** Fang, Florence S; Sayeed, Vilayat A; Yu, Lawrence; Lionberger, Robert; Webber, Keith; Chang, Nancy; Buhse, Lucinda; Wokovich, Anna; Jiang, Wenlei; Westenberger, Benjamin J
**Subject:** Two lansoprazole reports

**Attachments:** 11-35 Lansoprazole Interim Report Phase 1 Part A 10MAR2011 Revised .pdf; 11-45 Lansoprazole Interim Report Phase 1 Part B .pdf

Attached are the updated/final reports for Part A and Part B of Phase 1. I hope we put all the changes you wanted in Part A? Please replace the previous report if it was put in DARRTS.

Thanks!

Cindy

11-35
prazole Interim F

11-45
prazole Interim F

## Appendix 2

**From:** Nguyen, Kiet
**Sent:** Monday, February 28, 2011 12:42 PM
**To:** Yu, Lawrence
**Cc:** Lionberger, Robert; Jiang, Wenlei
**Subject:** Lansoprazole Capsule

**Attachments:** lansoprazole capsule AE report (2).doc; Lansoprazole Capsule.doc

Hi Lawrence,

I have received the AE report (AERS/DQRS) for the Lansoprazole capsule that I asked Laurie Muldowney (Medical Officer) to help conduct. The report indicated no cases relating to the use of lansoprazole capsule clogging enteral feeding tubes when dosing as an optional administration, contrary to the literature references. The updated summary of the lansoprazole capsule and her AE report are attached.

Thank you and let me know if you have any questions.



Reference ID: 3192682

lansoprazole apsule AE report.doc (73 K.

Lansoprazole apsule.doc (73 K.

Kiet

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**From:** Fang, Florence S
**Sent:** Friday, February 11, 2011 4:46 PM
**To:** Yu, Lawrence
**Cc:** Smith, Glen J; Rosencrance, Susan M
**Subject:** FW: Lansoprazole Administration by NG Tube....your advice needed Sun's ANDA 91509 for Lansoprazole

Lawrence:

Another Lansoprazole product (capsule) for tube administration.

Please refer to Susan's original email below.

Actually there are already four approved capsule products (Teva 77255, Sandoz 90331, Matrix 90763, and Dr. Reddy's 91269). I don't think this feeding tube issue was addressed prior to approval.

Also I am inviting Susan to the March meeting on this topic.

Florence

---

**From:** Hixon, Dena R
**Sent:** Friday, February 11, 2011 11:33 AM
**To:** Chang, Nancy; Rosencrance, Susan M; Davit, Barbara M
**Cc:** Fang, Florence S; Smith, Glen J; Read, Shanaz; Park, Linda; Sayeed, Vilayat A; Holcombe Jr, Frank O; Osterhout, James; Catterson, Debra M; Muldowney, Laurie; Hixon, Dena R
**Subject:** RE: Lansoprazole Administration by NG Tube....your advice needed

I agree with Nancy, although I think that it is less likely that juices would be used in administration via tubes, since they are bypassing the taste buds. However, if the product is being given by oral syringe, it may be dissolved in juices or even milk. I think that bead size and viscosity and adherence of the "dissolved" product to the materials most likely to be used in the tubes are probably the most important factors.

Dena

---

**From:** Chang, Nancy
**Sent:** Friday, February 11, 2011 11:16 AM
**To:** Rosencrance, Susan M; Davit, Barbara M
**Cc:** Fang, Florence S; Smith, Glen J; Read, Shanaz; Park, Linda; Sayeed, Vilayat A; Holcombe Jr, Frank O; Hixon, Dena R; Osterhout, James; Catterson, Debra M; Muldowney, Laurie



Reference ID: 3192682

**Subject:** RE: Lansoprazole Administration by NG Tube….your advice needed

Hi Susan,

As you are probably aware, the OND review division has stated that for the lansoprazole ODT, even though the labeling only specifies nasogastric tubes, use by other feeding tubes of the same or greater caliber, e.g. gastrostomy tubes (G-tubes) and jejunostomy tubes (J-tubes), are an implied and intended use. This of course then widens the universe of materials and construction available. Ideally, at some point in time, we should get together with OND and CDRH so that we can achieve clearer labeling and also have a little more specificity when it comes to what the range of feeding tube types, construction types, materials, internal diameters, etc might be expected so that we can give sponsors a little more specific guidance on what needs to be tested. For now, the best we can do is probably to advise them to test the available range of NG, G-, and J- tubes, as well as a variety of syringes.

I'm not sure what sorts of variations on apple juice are out there, but it seems that there are apple juices of differing viscosities, concentrations and probably different acidities; if mixed at home from concentrate, then there would also be variations in water hardness etc – ideally, testing would also take those variables, and maybe also other factors such as temperature and agitation, into account.

Finally, this may not be realistic in the current regulatory climate, but one can certainly anticipate that the labeled instructions for use are not going to be followed exactly. In the ideal world, they would also be looking at factors like what if they use water or tomato juice instead, what if they use less than or more than 40 cc, etc. Again, it is a little iffy whether or not we have the authority to ask this – perhaps when we get a little more data from the labs that would be the basis for a clear concern....

I've also copied some of the members of the safety team who have looked at this in case they have additional thoughts.

Thanks,
Nancy

---

**From:** Rosencrance, Susan M
**Sent:** Friday, February 11, 2011 10:21 AM
**To:** Davit, Barbara M; Chang, Nancy
**Cc:** Fang, Florence S; Smith, Glen J; Read, Shanaz; Park, Linda
**Subject:** Lansoprazole Administration by NG Tube….your advice needed

Hi Barbara and Nancy,

We are presently looking at Sun Pharma's ANDA 91509 for Lansoprazole Delayed-release Capsules (encapsulated delayed-release coated pellets). Given the concerns associated with Teva's Lansoprazole delayed-release ODT, we want to address any potential problems with this application early. In addition to a number of CMC deficiencies, we plan to issue the following deficiency to the firm:



Reference ID: 3192682

*"Your labeling states that the drug product may be administered by nasogastric tube. Therefore, we request a use-test to compare the performance of your product to the RLD. Please evaluate and compare the particle size of the beads in the capsule, dispersability in apple juice, sedimentation rate, and perform comparative recovery studies. The recovery should be measured from 1) the injection device; and 2) a combination of the injection device with the nasogastric tube (16 Fr). Since only the size of tubing is defined in the labeling, all materials of construction available on the market (e.g., Tygon, silicone, polyurethane) should be tested to evaluate adsorption."*

We are also requesting samples of Sun's product and the RLD for our own evaluation in the office. If necessary, we plan to ask St. Louis to do confirmatory testing.

Do you feel the above is sufficient for this application, or would you advise additional studies, e.g. other types of feeding tubes? We greatly appreciate your expertise and assistance with this issue.

Thank you,

Susan

## Appendix 3

**From:** Yu, Lawrence
**Sent:** Friday, February 11, 2011 8:40 AM
**To:** Hixon, Dena R; Chang, Nancy; Catterson, Debra M; Muldowney, Laurie; Osterhout, James; Sayeed, Vilayat A; Holcombe Jr, Frank O; Davit, Barbara M; Nguyen, Kiet; Jiang, Wenlei; Lionberger, Robert; Rajagopalan, Radhika; Fang, Florence S; Bui, Hoang; Schwartz, Paul; Iser, Robert; Conner, Dale P
**Subject:** Lansoprazole: Listen leared and paths forward

**Attachments:** Lansoprazole AEs memo v2.doc

Nancy, Dena, and Laurie,

Thanks for your comments.

Hoang,

Please schedule an one hour meeting to discuss review policies related to the drug products administered through enteral feeding tubes.

Thanks,

Lawrence

Lansoprazole
s memo v2.doc (

---

**From:** Hixon, Dena R
**Sent:** Thursday, February 10, 2011 5:05 PM



Reference ID: 3192682

**To:** Nguyen, Kiet; Jiang, Wenlei; Lionberger, Robert; Yu, Lawrence
**Subject:** FW: Please see the attached from the Science Team re: lansoprazole

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**From:** Muldowney, Laurie
**Sent:** Thursday, February 10, 2011 4:18 PM
**To:** Chang, Nancy; Catterson, Debra M; Hixon, Dena R; Osterhout, James; Sayeed, Vilayat A; Holcombe Jr, Frank O; Davit, Barbara M
**Subject:** RE: Please see the attached from the Science Team re: lansoprazole

Nancy,

According to CDRH, applications for feeding tubes need to include both the internal and external diameter (in French units), but it is very difficult to find the internal diameters. It is not, to the best of my knowledge, included on the packaging of feeding tubes, so it would impossible for a HCP to use an ID recommendation in a label, even IF he or she read the label. I am not sure about the "stringency" of requirements to be classified as a J vs G - I think there are a lot of factors (length of tube, flexibility, diameter, and I imagine differing tips, etc for insertion/placement). I agree, that labeling would not be an effective strategy to mitigate the risks, if we do believe the Teva product is behaving differently.

Not sure if I answered your question…

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**From:** Hixon, Dena R
**Sent:** Thursday, February 10, 2011 4:05 PM
**To:** Chang, Nancy; Catterson, Debra M; Muldowney, Laurie; Osterhout, James; Sayeed, Vilayat A; Holcombe Jr, Frank O; Davit, Barbara M; Yu, Lawrence; Nguyen, Kiet; Jiang, Wenlei; Lionberger, Robert
**Cc:** Hixon, Dena R
**Subject:** RE: Please see the attached from the Science Team re: lansoprazole

I agree with Nancy,
Health care providers will use the tubes that they are familiar with, and they will not look at labels to determine exactly what size and materials are compatible with a given product. Furthermore, the use of the RLD with tubes did not result in any significant reports related to this problem, so we cannot conclude that the TEVA product is therapeutically equivalent. We certainly should not attempt to label generic products for use with tube sizes differently than the RLD is labeled. Health care providers and patients rarely see the generic labels!
Dena

---

**From:** Chang, Nancy
**Sent:** Thursday, February 10, 2011 3:41 PM
**To:** Catterson, Debra M; Hixon, Dena R; Muldowney, Laurie; Osterhout, James; Sayeed, Vilayat A; Holcombe Jr, Frank O; Davit, Barbara M
**Subject:** RE: Please see the attached from the Science Team re: lansoprazole

An admirable and ambitions recommendation, but the reality is that we can label materials and inner lumens all we want – that is simply not going to be information readily available to patients and to practitioners, and if I am understanding correctly, CDRH is not being very stringent about what is required to be called a G-tube or J-tube of a certain Fr when it comes to materials or inner diameters – is that correct, Laurie?

---

**From:** Catterson, Debra M
**Sent:** Thursday, February 10, 2011 3:32 PM
**To:** Hixon, Dena R; Chang, Nancy; Muldowney, Laurie; Osterhout, James; Sayeed, Vilayat A; Holcombe Jr, Frank O; Davit, Barbara M
**Subject:** Please see the attached from the Science Team re: lansoprazole

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**From:** Yu, Lawrence
**Sent:** Tuesday, February 08, 2011 12:19 PM
**To:** Catterson, Debra M



Reference ID: 3192682

**Cc:** Nguyen, Kiet; Jiang, Wenlei; Lionberger, Robert
**Subject:** FW: Updated Memo

Debbie,

Please forward to the group.

Thanks,

Lawrence

---

**From:** Nguyen, Kiet
**Sent:** Tuesday, February 08, 2011 11:58 AM
**To:** Yu, Lawrence
**Cc:** Lionberger, Robert; Jiang, Wenlei
**Subject:** Updated Memo

Hi Lawrence,

Please find attached an updated AE memo.

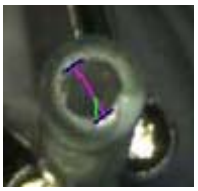
Thanks,

Kiet << File: Lansoprazole AEs memo v2.doc >>

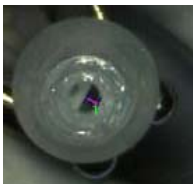
## Appendix 4

Feeding tubes tested by DPA.

Conventional Feeding Tubes:



Nasogastric (NG): polyurethane
8F, 36 inches long, outer diameter (2.8 mm), inner diameter (1.3 mm), distal tip and 3 feeding exit ports.



Gastrostomy (G): silicone
12F, 210 mm long, outer diameter (3.8 mm), inner diameter not circular, inflatable silicone internal retention balloon, distal tip, no additional feeding exit ports

Jejunal (J): Silicone
12F, 26.5 inches long, outer diameter (3.7 mm), inner diameter not circular, inflatable silicone internal retention balloon, distal tip, no additional feeding exit ports



Reference ID: 3192682

Tube details:

| | NG tube | G tube | J tube |
|---|---|---|---|
| Brand | Kendall Kangaroo non-weighted feeding tube # 8884711568 | Kimberly-Clark MIC Gastrostomy Feeding Tube # 0100-12LV | Kimberly-Clark MIC Jejunal Feeding Tube # 0200-12LV |
| French | 8 French | 12 French | 12 French |
| Material | polyurethane | medical grade silicone | medical grade silicone |
| Tubing length | 36 inches | approximately 8 ¼ inches | approximately 26 ½ inches |
| Feeding openings | distal tip and three feeding exit ports: (1) oblong 2 mm opening 52 mm from the distal tip; (2) oblong 2 mm opening 31 mm from the distal tip; and (3) oblong 2 mm opening 6 mm from the distal tip. | tapered distal tip | distal tip |
| Balloon present | No | Yes | Yes |
| Inner tubing for feeding delivery circular | Yes<br>See Attachment A. | No, part of the G tube inner tubing is taken for the balloon filling line.<br>See Attachment B. | No, part of the J tube inner tubing is taken for the balloon filling line.<br>See Attachment C. |

## 4.2 Attachment II

(b) (4)



Reference ID: 3192682

Following this page, 2 Pages Withheld in Full as (b)(4)

(b) (4)_lanso
ole.doc (25 K

**From:** Davit, Barbara M
**Sent:** Thursday, September 01, 2011 10:15 AM
**To:** Jiang, Xiaojian
**Cc:** Smith, Glen J; Rajagopalan, Radhika; Rosencrance, Susan M; Stier, Ethan
**Subject:** in vitro tests to compare test and reference modified-release proton pump inhibitor performance

Xiaojian:

Please work with Radhika and / Susan (not sure which is the lead) in developing an appropriate battery of in vitro tests to compare test and reference performance via alternative routes of administration (as per labeling). You can take the lead from some of the issues that Susan raised (e.g., sedimentation rate, vehicle, etc.) at Tuesday's meeting. I think that some of the tests can be used for both quality and in vitro BE, and the chemists can determine which is which.

We should communicate these as soon as possible for pending applications.

Thanks,

*Barbara*

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
CDER/FDA
240-276-8819

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## 4.4 Attachment IV

**From:** Mahadevan, Chitra
**Sent:** Thursday, July 26, 2012 12:21 PM
**To:** Xia, Li
**Cc:** Jiang, Xiaojian
**Subject:** RE: Help for OSI status for ANDA 78003

Hi Li,

Yes, I do think that you should put a statement or two in your review about OSI. Here is the history that I see in our database:

**OSI Inspection History:**

A Routine inspection of the Clinical site, Allied Clinical Research, 4520 Dixie Rd, Mississauga, Ontario (Canada) was requested for NDA 21210 on 5/22/2003 and was completed on 9/22/2003 with an outcome of VAI. A For Cause inspection of the Clinical site, Allied Clinical Research, 4520 Dixie Rd, Mississauga, Ontario (Canada) was requested for NDA 21210 on 3/30/2004 and was completed on 6/17/2004 with an outcome of NAI.

A Routine inspection of the Analytical site, (b) (4) (b) (4) requested for ANDA (b) (4) on (b) (4) and was completed on (b) (4) with an outcome of (b) (4)

There is nothing prior for the analytical site. It appears that the studies for your ANDA were conducted in August-October 2005. The studies in ANDA (b) (4) were conducted in (b) (4) I think that this inspection should be fine and cover the Esomeprazole ANDA as well.

I also agree that you should resend the outstanding deficiencies to the sponsor along with the request for the NG tube studies.

Let me know if any of the above is unclear.

Thanks,
Chitra

---

**From:** Xia, Li
**Sent:** Thursday, July 26, 2012 11:59 AM
**To:** Mahadevan, Chitra
**Cc:** Jiang, Xiaojian
**Subject:** Help for OSI status for ANDA 78003

Dear Chitra,

I am writing the NG tube addendum for ANDA 078003, I need your help to instruct me how to proceed the OSI status for this ANDA. Since it is an old application, the original review in 2006 did not address the OSI status for the clinical and analytical site, I guess at that time it is not applicable for the review. I am just wondering if I need to address the OSI report in this addendum? If so, I need your help to find out if the OSI status was acceptable or not during the study period.

According to the original review, the application is incomplete pending acceptable response to analytical deficiency for fasting study. However, the firm has not responded to the DB's deficiency letter sent out on 1/10/2007 yet. In this addendum, I think I need to resend the previous deficiencies besides the NG tube testing.

Best wishes,

Li

| | |
|---|---|
| **ANDA No.** | 078003 |
| **Drug Product Name** | Esomeprazole Magnesium Delayed-Release Capsules |
| **Strength(s)** | Eq. 20 mg and 40 mg base |
| **Applicant Name** | IVAX Pharmaceuticals, Inc.,<br>An indirect and wholly owned subsidiary of Teva Pharmaceuticals USA |
| **Address** | 400 Chestnut Ridge Road<br>Woodcliff Lake, NJ, 07677 |
| **Applicant's Point of Contact** | Robert S. Vincent, Director, Regulatory Affairs |



Reference ID: 3192682

| | | | |
|---|---|---|---|
| **Contact's Telephone Number** | 201-930-3610 | | |
| **Contact's Fax Number** | 201-489-1403 | | |
| **Original Submission Date(s)** | November 23, 2005 | | |
| **Submission Date(s) of Previous Amendment(s)** | November 13, 2006 (study amendment) | | |
| **Reviewer** | Li Xia, Ph.D. | | |
| | | | |
| **Study Number (s)** | P1BD05001 | P1BD05002 | P1BD05010 |
| **Study Type (s)** | Fasting | Fed | Sprinkled Fasting |
| **Strength (s)** | eq. to 40 mg base | eq. to 40 mg base | eq. to 40 mg base |
| **Clinical Site** | Allied Research International Inc. | | |
| **Clinical Site Address** | 4520 Dixie Road, Mississauga, Ontario, Canada L4W 1N2 | | |
| **Analytical Site** | (b) (4) | | |
| **Analytical Site Address** | | | |
| | | | |
| **OVERALL REVIEW RESULT** | **INADEQUATE pending response to deficiency for fasting study and NG tube study** | | |
| **OSI REPORT RESULT** | **?** | | |
| **BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #** | **STUDY/TEST TYPE** | **STRENGTH** | **REVIEW RESULT** |
| **2** | **Dissolution** | **20 and 40 MG** | **ADEQUATE** |
| **1** | **Fasting study** | **40 MG** | **ADEQUATE** |
| **1** | **Fed study** | **40 MG** | **ADEQUATE** |
| **1** | **Sprinkled Fasting Study** | **40 MG** | **ADEQUATE** |
| **1** | **Biowaiver Request** | **20 mg** | **INADEQUATE** |
| **1** | **NG Tube Test** | **20 mg and 40 mg** | **INADEQUATE** |



Reference ID: 3192682

BIOEQUIVALENCE DEFICIENCIES

ANDA: 078003

APPLICANT: IVAX Pharmaceuticals, Inc.,
An indirect and wholly owned subsidiary of
Teva Pharmaceuticals USA

DRUG PRODUCT: Esomeprazole Magnesium Delayed-Release
Capsules, 20 mg and 40 mg

The Division of Bioequivalence II (DB II) has completed its review of your submissions acknowledged on the cover sheet. The following deficiencies have been identified:

**In vitro test for Nasogastric (NG) Tube administration:**

The approved labeling for the reference product states that the product may be administered by a nasogastric tube. Therefore, we request that you perform the following comparative *in vitro* tests to compare the performance of your test product to that of the reference product.

1. Please determine comparative sedimentation volume and particle size of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, in 50 ml of water as follows:

   a) Prepare the catheter tipped syringe (60 ml), remove the syringe plunger, open the capsule and empty the contents of one capsule into the syringe. Insert the syringe plunger, draw up 50 mL of water and shake the syringe vigorously for 15 seconds.

   b) Place the syringe perpendicular to the bench with the tip up and record sedimentation volume at 0 min. Please remove the syringe plunger and determine the particle size of the granules in the syringe.

   c) Using a new set of 12 units please repeat the process described in step (a) to prepare the granule dispersion, then incubate for 15 min and record the sedimentation volume and determine the particle size of granules.



Reference ID: 3192682

Please provide all particle size data at the D10, D50, and D90 levels. You may use the markings on the syringe to note the sedimentation volume. Please provide a qualitative description, e.g., particle aggregation and particles adhering to the syringe walls. Please take photos of the contents of the syringe at various intervals throughout the testing process.

2. Please determine the comparative particle size of the granule dispersion using 12 units each of the test and reference products, 20 mg and 40 mg strengths, after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 and 15 min as follows:

   a) Prepare the feeding tube according to the manufacturer's directions. Repeat the process described in 1(a) to prepare the granule dispersion.

   b) Attach the syringe to the feeding tube, using the syringe plunger push the granule dispersion through the syringe and the feeding tube into a collection container.

   c) Remove the syringe from the feeding tube, draw up additional water and flush the system by pushing the fluid through the feeding tube into the container. Perform particle size analysis of the collected fluid.

   d) Please repeat the testing described above with a fresh set of 12 units. However, after suspending the capsule content in step a, wait 15 minutes prior to injecting the contents into the feeding tube.

   Please visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and please report all the observations and supporting photographs. Please provide the particle size data at the D10, D50 and D90 levels and report flush volume used in these studies.



Reference ID: 3192682

3. Please conduct comparative recovery studies to determine what percentage of the initial dose suspended in water passes through the 8 French nasogastric tubes. Please use 12 units of both strengths of the test and the reference products in 50 ml water and follow the process outlined in #2 (above). Please determine the percentage of esomeprazole recovered at the tube exit relative to the initial dose using a validated assay method for both the test and the reference products at 0 and 15 min using a validated assay method. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. The DB II will set an interim specification based upon the review of the submitted data. If high variability is observed, you may increase the numbers of units used for this test.

4. Please conduct comparative acid resistance stability testing using 12 units of both strengths of the test and the reference products. Please use the following method:

   a) Prepare the granule dispersion in 50 ml water (hold for 15 min), and collect the contents of granule dispersion at the tube exit.

   b) Transfer the contents of granule dispersion into dissolution vessel containing 300 mL of 0.1 N HCl maintained at 37 ±0.5°C.

   c) Flush the nasogastric tube with additional water and transfer any remaining contents into the dissolution media mentioned above.

   d) Acid resistance testing should be conducted using USP Apparatus II at 100 rpm. Analyze the amount of esomeprazole released at 120 minutes.



Reference ID: 3192682

5. Please submit standard operating procedures for sedimentation, particle size, acid resistance and recovery testing. Please submit individual data, mean values, standard deviations, coefficient of variation (CV%), and plots of percent release of esomeprazole in acid resistance test. The photographs should be submitted to support your observations and results. Please also provide the pre-study and within-study assay validation report.

   Please conduct all the above testing on unexpired test and reference batches.

***Please note that the following deficiencies were provided to you in the DB II deficiency letter dated 01/10/2007 after our review of your original application and is provided to you again since we has not yet received your responses.***

6. For the fasting study (#P1BD05001), although you have provided explanation for the 12 "Discretionary Rejection" reassays, you did not provide any supporting data along with the response. Please provide supporting data, such as chromatograms of the original 12 samples showing the abnormal internal standard responses and 12 original assay values. In the response, you have also stated that visually observed discrepancy in remaining sample volumes in the injection vials subjected to "Discretionary Rejection" were noted. Please provide evidence in support of that statement.

7. For the fasting study (#P1BD05001), you have conducted sample reanalysis based on "Discretionary Rejection", but there is no mention of "Discretionary Rejection" in any of the submitted Standard Operating Procedures (SOPs). Since all reasons for reanalysis should be included in the SOPs *a priori*, please explain the absence of "Discretionary Rejection", as a cause for reanalysis, in the SOPs.



Reference ID: 3192682

The DB II agrees that the dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b)(4)% in 120 minutes<br>Buffer stage: NLT (b)(4)% in 30 minutes |

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research



Reference ID: 3192682

## 5 *COMPLETED ASSIGNMENT FOR 078003 ID: 17542*

**Reviewer:** Xia, Li

**Date Completed:**

**Verifier:**

**Date Verified:**

**Division:** Division of Bioequivalence

**Description:** Esomeprazole Magnesium Delayed-Release Capsules, Eq. 20 mg and 40 mg base

---

*Productivity:*

| *ID* | *Letter Date* | *Productivity Category* | *Sub Category* | *Productivity* | *Subtotal* |
|---|---|---|---|---|---|
| 17542 | 11/23/2005 | Other (REGULAR) | Study Amendment | 1 | 1 |
| | | | | Total: | 1 |

**DB II complexity points**

**Enter Review Productivity and Generate Report**

| **Amendment study** | |
|---|---|
| Amendment study | 1 |
| *Study Summary Total* | *1* |



Reference ID: 3192682

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/s/

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LI XIA
09/21/2012

MINGLEI CUI on behalf of XIAOJIAN JIANG
09/21/2012

ETHAN M STIER on behalf of BARBARA M DAVIT
09/26/2012

# DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 78-003 |
| **Drug Product Name** | Esomeprazole Magnesium Delayed-Release Capsules |
| **Strength** | 20 mg and 40 mg |
| **Applicant Name** | IVAX Pharmaceuticals, Inc. |
| **Address** | 125 Wells Avenue, Congers, NY 10920 |
| **Contact Information** | Patricia Jaworski, Director Regulatory Affairs,<br>Phone: (845) 267-2444 ext. 201 or 200<br>Fax: (845) 268-0117 |
| **Submission Date(s)** | **November 13, 2006** |
| **Amendment Date(s)** | N/A |
| **Reviewer** | Parthapratim Chandaroy, Ph.D. |
| **First Generic** | No |

## Review of an Amendment

## I. Executive Summary

The firm previously submitted, on November 23, 2005, fasting, fed, and sprinkled fasting bioequivalence (BE) studies comparing its test product, Esomeprazole Magnesium Delayed-Release Capsules, 40 mg to the reference listed drug (RLD), AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg. All the three BE studies were **incomplete** due to bio-analytical method deficiencies. The firm also submitted comparative *in vitro* dissolution data for the 20 mg and 40 mg strengths of the test and reference products, and requested waiver of *in vivo* BE study requirements for the 20 mg strength. The dissolution testing was **incomplete**. The firm was asked to repeat acid stage dissolution testing using the FDA method and indicate if it accepts the FDA-recommended specification for the buffer stage. The application was **incomplete.**

In the current submission, the firm replied to the BE deficiency comments corresponded to the firm on May 5, 2006[1] and October 3, 2006[2]. The firm's response to the DBE deficiency comment regarding reassay of 12 samples due to "Discretionary Rejection" was not acceptable. All other responses were acceptable. The dissolution testing is **acceptable**. The fed and sprinkled fasting BE studies are **acceptable**. The fasting BE study is **incomplete** pending acceptable response to the deficiency comments. The application is **incomplete**.

[1] DBE dissolution review of ANDA #78-003 (\\cdsnas\ogds11\firmsam\ivaxpharm\ltrs&rev\78003d1105.doc)
[2] DBE review of ANDA #78-003 (\\cdsnas\ogds11\firmsam\ivaxpharm\ltrs&rev\78003n1105.doc)

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## III. Review of Submission

**DBE comment #1** (correspondence date: **May 5, 2006**):

*Your dissolution testing at the acid stage using a non FDA-recommended method is not acceptable. The dissolution testing should be conducted using the following FDA-recommended method for acid stage**:

*Medium:* *0.1N HCl at 37°C*
*Volume:* *300 mL*
*Apparatus:* *USP Apparatus II (Paddle) at 100 rpm*

*The test products should meet the following specification:*

*Not more than (b)(4)% of the labeled amount of the drug in the dosage form is dissolved in 120 minutes.*

**Esomeprazole is an acid labile drug substance. Therefore, at the acid stage, esomeprazole should be measured from the beadlets of the esomeprazole delayed release capsules but not from the dissolution medium of 0.1N HCl.*

*Please repeat dissolution testing with the above FDA-recommended method and acknowledge your acceptance of the FDA-recommended method for the acid stage.*

**Firm's Response**:

The firm conducted acid stage dissolution testing according to the above FDA-recommended method. The firm also acknowledged acceptance of the FDA-recommended specification of "Not more than (b)(4)% of the labeled amount of the drug in the dosage form is dissolved in 120 minutes". The acid stage data are provided below:

**20 mg Capsules**:

| Study Ref. No. | Product ID/Batch No. | Dosage Form | Dissolution Conditions | No. of Dosage Units | Collection Times Mean % Dissolved (Range) | Study Report Location |
|---|---|---|---|---|---|---|
| | | | | | 2 hr. | |
| KR621025 | Esomeprazole Magnesium Delayed Release Capsules 20 mg / Y51282 | 20 mg/ cap | **Apparatus:** Type II (Paddle)<br>**Medium:** 0.1 M Hydrochloric acid<br>**Volume:** 300 ml<br>**Temperature of Medium:** 37° ± 0.5° C<br>**Speed:** 100 rpm<br>**Time:** 2 hours<br>**Limit:** Not more than (b) (4)% (Q) equivalent to (b) (4)% of Esomeprazole is released in 2 hours.<br>**Method:** FPS E1171<br>**Revision No.** 03 | 12 | 2<br>(b) (4) | (b) (4) |
| KR621070 | NEXIUM® (esomeprazole magnesium) Delayed Release Capsules 20 mg / F4793 | 20 mg/ cap | | 12 | 1<br>(b) (4) | |

**40 mg Capsules**:

| Study Ref. No. | Product ID/Batch No. | Dosage Form | Dissolution Conditions | No. of Dosage Units | Collection Times Mean % Dissolved (Range) | Study Report Location |
|---|---|---|---|---|---|---|
| | | | | | 2 hr. | |
| KR621026 | Esomeprazole Magnesium Delayed Release Capsules 40 mg / Y51286 | 40 mg/ cap | **Apparatus:** Type II (Paddle)<br>**Medium:** 0.1 M Hydrochloric acid<br>**Volume:** 300 ml<br>**Temperature of Medium:** 37° ± 0.5° C<br>**Speed:** 100 rpm<br>**Time:** 2 hours<br>**Limit:** Not more than (b) (4)% (Q) equivalent to (b) (4) % of Esomeprazole is released in 2 hours.<br>**Method:** FPS E1172<br>**Revision No.** 03 | 12 | 3<br>(b) (4) | (b) (4) |
| KR621069 | NEXIUM® (esomeprazole magnesium) Delayed Release Capsules 40 mg / F1802 | 40 mg/ cap | | 12 | 1<br>(b) (4) | |

**Reviewer's Comment**:

The firm's response is acceptable.

**DBE comment #2** (correspondence date: May 5, 2006):

*Your dissolution testing data at the buffer stage with the FDA-recommended method are acceptable. However, your proposed specification of NLT (b)(4)% (Q) in (b)(4) minutes for the buffer stage is not acceptable. The dissolution testing should be conducted using the following FDA-recommended method for buffer stage*:

| | |
|---|---|
| *Medium:* | *Sodium Phosphate Buffer (pH 6.8) at 37°C* |
| *Volume:* | *1000 mL* |
| *Apparatus:* | *USP Apparatus II (Paddle) at 100 rpm* |

*The test products should meet the following specification:*

> *Not less than (b)(4)% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.*

*Please acknowledge your acceptance of the above FDA-recommended specification for the buffer stage.*

**Firm's Response**:

The firm acknowledged acceptance of the FDA-recommended specification of "Not less than (b)(4)% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes".

**Reviewer's Comment**:

The firm's response is acceptable.

**DBE comment #1** (correspondence date: **October 3, 2006**):

*You did not submit any Standard Operating Procedure for sample repeat analysis. Please submit all relevant Standard Operating Procedures and their effective dates.*

**Firm's Response**:

The firm submitted four Standard Operating Procedures (SOPs) in response:

- SOP#7622 – Quantitation of Omeprazole/Esomeprazole in Human Plasma (effective June 10, 2005);
- SOP#7320 – Chromatography Acceptance (effective December 22, 2004);
- SOP#7325 – Calibration Standard Curves and QC Selection (effective May 27, 2005);
- SOP#7340 – Quantitation of Clinical Study Samples (effective April 16, 2002);

**Reviewer's Comment**:

Two of the SOPs ("Chromatography Acceptance" and "Quantitation of Clinical Study Samples") include description of identification and reporting of repeat analysis. All SOPs were in effect at the time the clinical samples were analyzed. The firm's response is acceptable.

**DBE comment #2** (correspondence date: October 3, 2006):

*Twelve samples in the fasting study (#P1BD05001) were reassayed due to Discretionary Rejection. Please explain the meaning of Discretionary Rejection in this context.*

**Firm's Response**:

The firm's explanation regarding "Discretionary Rejection" is as follows: The twelve samples were reassayed based on "Discretionary Rejection" since it was professional judgment of the data reviewer that the data for those samples were not reliable. Upon investigation, the error in the twelve original samples was attributed to possible transferring error in a transfer step, where 100 µl of processed sample, including internal standard, is added to an injection vial containing 400 µL of dilution solvent. This was speculated since some of the twelve samples had no internal standard response and negligible drug response, while the adjoining samples had substantially elevated (1.5-1.6 times the expected value) internal standard response.

In regard to the 12 reassays, the firm also stated that "sample volume remaining in the injection vials was visually inspected; the volumes of the sample vials with negligible internal standard response was substantially lower than the rest of the batch, while the sample vials with elevated internal standard response had volumes in the vials that were substantially higher than the rest of the batch." The SOP on data acceptance has since been modified to incorporate a consistency check of internal standard response throughout the batch, which will automatically flag such errors in future.

**Reviewer's Comment**:

The firm's explanation of some samples having no internal standard response and adjoining samples having 1.5-1.6 times the expected internal standard response is consistent with the procedure of the sample preparation transfer step mentioned by the firm. However, the firm did not provide any supporting data in addition to the above response. The firm may provide supporting data, such as chromatograms of the original 12 samples showing the above-mentioned internal standard responses and 12 original assay values. In the response, the firm stated visually observed discrepancy in remaining sample volumes in the injection vials subjected to "Discretionary Rejection". The firm may also provide evidence in support of that statement.

Moreover, the firm conducted sample reanalysis based on "Discretionary Rejection", but there is no mention of "Discretionary Rejection" in any of the SOPs submitted by the firm in the current amendment. Since all reasons for reanalysis should be included in the SOPs a priori, the firm should explain the absence of "Discretionary Rejection", as a cause for reanalysis, in their SOPs. The firm's response is **not acceptable**.

**DBE comment #3** (correspondence date: October 3, 2006):

*Sprinkle study (1BD05010): You state that Subject (b) (6) was withdrawn by the investigator due to noncompliance after the completion of the study. Plasma samples of this subject were analyzed. Please explain why this subject was withdrawn after completing the study.*

**Firm's Response**:

The firm's explanation is as follows: When samples were shipped to the Analytical facility, subject (b) (6) was one of the subjects to be analyzed. At the end of the study, it was noted that subject (b) (6) was randomized in error, as the subject was tested positive for cocaine during pre-study screening. By the time this was discovered, the subject's samples were already analyzed but data was not yet sent for statistical analysis. The investigator made the decision, on October 26, 2005, to exclude subject (b) (6) data from the statistical analysis due to non-compliance with protocol requirements. Also, it was decided at that time to replace subject (b) (6) with alternate subject (b) (6)

**Reviewer's Comment**:

According to the reviewer, the firm's explanation about the withdrawal of subject (b) (6) is adequate. In the original review[3], the reviewer included data from subject (b) (6) and recalculated the pharmacokinetic parameters and 90% confidence intervals for the sprinkled fasting study. The 90% confidence intervals for $\ln AUC_{0-t}$, $\ln AUC_{0-\infty}$, and $\ln C_{max}$ were still within the acceptable limits of 80-125%. The firm's response is acceptable.

**DBE comment #4** (correspondence date: October 3, 2006):

*You submitted only six summary tables electronically. Please submit dissolution data and formulation data in the DBE-specified format. Please submit these tables in Microsoft Word.*

[3] Page 34, DBE review of ANDA #78-003 (\\cdsnas\ogds11\firmsam\ivaxpharm\ltrs&rev\78003n1105.doc)

**Firm's Response**:

The firm submitted the dissolution data and formulation data summary tables in the DBE-specified format as electronic Microsoft Word documents.

**Reviewer's Comment**:

The electronic tables are currently archived in EDR. The firm also submitted paper copies of the two above-mentioned summary tables. The firm's response is acceptable.

**DBE comment #5** (correspondence date: October 3, 2006):

*We have not received your response to the dissolution deficiency communicated to you earlier. Please provide dissolution testing data for the acid stage. In addition, please indicate if you accept the dissolution specification of NLT* (b)(4)*% (Q) in 30 minutes for the buffer stage.*

**Firm's Response**:

The firm provided acid stage dissolution testing data and indicated acceptance of the FDA-recommended dissolution specification of *NLT* (b)(4)*% (Q) in 30 minutes for the buffer stage* (see the firm's response to DBE comment #1 and #2**;** correspondence date: May 5, 2006).

**Reviewer's Comment**:

The firm's response is acceptable.

## IV. Deficiency Comments

1. For the fasting study (#P1BD05001), although the firm provided explanation for the 12 "Discretionary Rejection" reassays, it did not provide any supporting data along with the response. The firm may provide supporting data, such as chromatograms of the original 12 samples showing the abnormal internal standard responses and 12 original assay values. In the response, the firm also stated that visually observed discrepancy in remaining sample volumes in the injection vials subjected to "Discretionary Rejection" were noted. The firm may provide evidence in support of that statement.

2. For the fasting study (#P1BD05001), the firm conducted sample reanalysis based on "Discretionary Rejection", but there is no mention of "Discretionary Rejection" in any of the submitted SOPs. Since all reasons for reanalysis should be included in the SOPs *a priori*, the firm should explain the absence of "Discretionary Rejection", as a cause for reanalysis, in the SOPs.

## V. Recommendations

1. The single-dose, *in vivo* fasting bioequivalence study (#P1BD05001) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **incomplete** pending adequate explanation of the deficiency comments.

2. The single-dose, *in vivo* non-fasting bioequivalence study (#P1BD05002) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable**.

3. The single-dose, *in vivo* sprinkled fasting bioequivalence study (#P1BD05010) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **acceptable**.

4. The *in vitro* dissolution testing conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 20 mg (Lot #Y51231) and 40 mg (Lot # Y51232, same as Lot#Y51286 used in the *in vivo* bioequivalence studies, but different package number), comparing to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 20 mg (Lot#P4879) and 40 mg (Lot #N5819), is **acceptable**.

   The dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b) (4) 0% in 120 minutes<br>Buffer stage: NLT (b) (4) % in 30 minutes |

5. The formulation of the 20 mg strength is proportionally similar to the 40 mg strength of the test product, which underwent *in vivo* bioequivalence testing. Based on 21CFR §320.24 b(6), the Division of Bioequivalence (DBE) may deem the 20 mg strength of the test product to be bioequivalent to the 20 mg strength of the reference listed drug, pending acceptable fasting bioequivalence study on the 40 mg strength of the test product.

   The firm should be informed of the above deficiency comments and recommendations.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-003 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. For the fasting study (#P1BD05001), although you have provided explanation for the 12 "Discretionary Rejection" reassays, you did not provide any supporting data along with the response. Please provide supporting data, such as chromatograms of the original 12 samples showing the abnormal internal standard responses and 12 original assay values. In the response, you have also stated that visually observed discrepancy in remaining sample volumes in the injection vials subjected to "Discretionary Rejection" were noted. Please provide evidence in support of that statement.

2. For the fasting study (#P1BD05001), you have conducted sample reanalysis based on "Discretionary Rejection", but there is no mention of "Discretionary Rejection" in any of the submitted Standard Operating Procedures (SOPs). Since all reasons for reanalysis should be included in the SOPs *a priori*, please explain the absence of "Discretionary Rejection", as a cause for reanalysis, in the SOPs.

The DBE agrees that the dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b) (4)% in 120 minutes<br>Buffer stage: NLT (b) (4)% in 30 minutes |

Sincerely yours,

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

ANDA#: 78-003

**ANDA#: 78-003**

BIOEQUIVALENCE – **INCOMPLETE** Submission Date: **November 13, 2006**

1. **STUDY AMENDMENT** (STA) Strengths: 20 mg and 40 mg
**Outcome: IC**

**Outcome Decisions: IC – Incomplete**

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/s/
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Parthapratim Chandaroy
1/4/2007 11:05:51 AM
BIOPHARMACEUTICS

Kuldeep R. Dhariwal
1/4/2007 02:02:55 PM
BIOPHARMACEUTICS

Barbara Davit
1/4/2007 03:45:25 PM
BIOPHARMACEUTICS

## DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 78-003 |
| **Drug Product Name** | Esomeprazole Magnesium Delayed-Release Capsules |
| **Strength** | 20 mg and 40 mg |
| **Applicant Name** | IVAX Pharmaceuticals, Inc. |
| **Address** | 125 Wells Avenue, Congers, NY |
| **Contact Information** | Patricia Jaworski, Director Regulatory Affairs,<br>Phone: (845) 267-2444 ext. 201 or 200<br>Fax: (845) 268-0117 |
| **Submission Date(s)** | November 23, 2005 |
| **Amendment Date(s)** | N/A |
| **Reviewer** | Parthapratim Chandaroy, Ph.D. |
| **First Generic** | No |
| **File Location** | v:\firmsam\IvaxPharm\ltrs&rev\78003N1105.doc |

## I. Executive Summary

The firm submitted fasting, fed, and sprinkled fasting bioequivalence (BE) studies comparing its test product, Esomeprazole Magnesium Delayed-Release Capsules, 40 mg to the reference listed drug (RLD), AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg. The firm also submitted comparative *in vitro* dissolution data for the 20 mg and 40 mg strengths of the test and reference products, and requested waiver of *in vivo* BE study requirements for the 20 mg strength.

The design for all the three studies is a single-dose two-way crossover in healthy subjects (n=51 for fasting, n=84 for fed, and n=54 for sprinkled fasting). Statistical analyses of the plasma esomeprazole concentration data for all three studies demonstrate bioequivalence. The results for esomeprazole (point estimate, 90% CI) are - for the **fasting** study: $\ln AUC_t$ of 106, 101.6-109.5; $\ln AUC_\infty$ of 105, 100.8-108.4; and $\ln C_{max}$ of 107, 100.2-113.3; for the **fed** study: $\ln AUC_t$ of 104, 96.2-113.4; $\ln AUC_\infty$ of 109, 100.0-118.2; and $\ln C_{max}$ of 102, 92.6-113.1; for the **sprinkled fasting** study: $\ln AUC_t$ of 100, 93.4-106.1; $\ln AUC_\infty$ of 100, 93.9-106.7; and $\ln C_{max}$ of 101, 90.6-111.7. All three BE studies are incomplete due to bio-analytical method deficiencies.

There is no USP method for this product but there is an FDA-recommended method. The dissolution data were reviewed earlier and deficiencies were communicated to the firm. The firm was asked to repeat acid stage dissolution testing using the FDA method and indicate if it accepts the FDA-recommended specification for the buffer stage. The firm has not yet responded to the dissolution deficiencies. The dissolution testing is **incomplete**. The waiver of *in vivo* bioequivalence study requirements for the 20 mg strength is **denied** pending acceptable BE studies and dissolution testing. The application is **incomplete.**

1.1

wg

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## III. Submission Summary

### A. Drug Product Information

| | |
|---|---|
| **Test Product** | Esomeprazole Magnesium Delayed-Release Capsules |
| **Reference Product** | Nexium® (esomeprazole magnesium) Delayed-Release Capsules |
| **RLD Manufacturer** | AstraZeneca |
| **NDA No.** | 21-153 |
| **RLD Approval Date** | February 20, 2001 |
| **Indication** | It is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. |

## B. PK/PD Information[1]

| | |
|---|---|
| **Bioavailability** | At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 μmol*hr/L on day 1 to 11.2 μmol*hr/L on day 5 after 40 mg once daily dosing. The $C_{max}$ increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 μmol/L. |
| **Food Effect** | The AUC after administration of a single 40 mg dose of esomeprazole is decreased by 43-53% after food intake compared to fasting conditions. **Esomeprazole should be taken at least one hour before meals.** |
| **$T_{max}$** | 1.5 hours |
| **Metabolism** | Esomeprazole is extensively metabolized in the liver by the cytochrome P450 enzyme system. The metabolites of esomeprazole lack antisecretory activity. CYP2C19 is responsible for the major metabolites, hydroxy and desmethyl esomeprazole. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed *poor metabolizers*. At steady state, the ratio of AUC in *poor metabolizers* to AUC in the rest of the population (*extensive metabolizers*) is approximately 2. |
| **Excretion** | Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces. |
| **Half-life** | 1-1.5 hours |
| **Relevant OGD or DBE History** | The following documents were reviewed by the Division of Bioequivalence (DBE) for Esomeprazole Magnesium Delayed-Release Capsules:<br><br>**Controlled Documents:**<br>#03-165 (b) (4) #03-443 (Mylan); #03-797 (b) (4) #04-277 (b) (4) #04-319 (b) (4); #04-524 (b) (4) #04-537 (b) (4) #04-545 (b) (4) #04-832 (b) (4); #04-1064 (b) (4) #04-1089 (b) (4) #05-0017 (b) (4) 05-0219 (b) (4); #05-0326 (b) (4) #05-0636 (Reddy); #05-1068 (b) (4); #05-1073 (b) (4); #05-1514 (b) (4) #06-0400 (Hetero); #06-0573 (b) (4)<br><br>**ANDA:**<br>• (b) (4)<br>• #78-003 (Ivax; submitted on November 23, 2005) – current application<br>• #78-279 (Reddy's; submitted on April 25, 2006)<br><br>The DBE currently recommends the following for Esomeprazole Magnesium Delayed-Release Capsules[2]: |

[1] Clinical Pharmacology 2006 entry for Nexium®

[2] Control document #05-0017 (b) (4) replied on April 7, 2005

| | |
|---|---|
| | • A single-dose, two-way crossover fasting *in vivo* bioequivalence study comparing Esomeprazole Magnesium Delayed-Release Capsules, 40 mg, to the reference listed drug (RLD), Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg.<br>• A single-dose, two-way crossover fed *in vivo* bioequivalence study comparing Esomeprazole Magnesium Delayed-Release Capsules, 40 mg, to the RLD.<br>• A single-dose, two-way crossover fasting *in vivo* bioequivalence study comparing Esomeprazole Magnesium Delayed-Release Capsules, 40 mg, to the RLD, sprinkled over a spoonful of applesauce.<br>• Only the parent compound, esomeprazole, in plasma should be measured using an achiral assay.<br>• The 20 mg strength may be considered for a waiver of *in vivo* bioequivalence testing based on 1) acceptable bioequivalence studies on the 40 mg strength, 2) acceptable dissolution testing for both the strengths, and 3) proportional similarity in the formulations of both the strengths.<br>• For dissolution method development, USP 29, "Delayed-Release (Enteric-Coated) Articles-General Drug Release Standard" should be referred. In addition, dissolution testing should be conducted using the following FDA-recommended method:<br>**Acid Stage (acid resistance):**<br>Apparatus: USP Apparatus II (Paddle)<br>Speed: 100 rpm<br>Medium: 0.1N HCl @ 37°C<br>Volume: 300 mL<br>Duration: 2 hours<br><br>Esomeprazole is an acid labile drug substance; therefore, esomeprazole should be measured from the beadlets of the capsule and not from the dissolution medium (0.1N HCl) during the acid stage. Using 12 additional capsules of the test and reference products, the dissolution for the buffer stage should be conducted:<br><br>**Buffer Stage (drug release):**<br>Apparatus: USP Apparatus II (Paddle)<br>Speed: 100 rpm<br>Medium: Sodium phosphate buffer, pH 6.8 @ 37°C<br>Volume: 1000 mL<br>Sampling times: 10, 20, 30, 45 and 60 minutes or until at least 80% of the labeled content is dissolved.<br><br>Dissolution specifications will be set at the time of ANDA review. |
| **Agency Guidance** | None |
| **Drug Specific Issues (if any)** | None |

## C. Contents of Submission

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

## D. Pre-Study Bioanalytical Method Validation

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| | |
|---|---|
| Report location | Volume page |
| Analyte | Omeprazole or Esomeprazole |
| Internal standard (IS) | (b) (4) |
| Method description | liquid extraction of alkalinized plasma with organic solvent, detection by HPLC-MS/MS |
| Lower of quantitation (ng/mL) | 2.57 |
| Average recovery of drug (%) | 84.2 |
| Average recovery of IS (%) | 85.4 |
| Standard curve concentrations (ng/mL) | 2.57, 6.44, 16.09, 40.22, 100.56, 251.40, 628.51, 1382.73 |
| QC concentrations (ng/mL) | 5.36, 70.30, 439.96, 1005.62 |
| QC Intraday precision range (%) | 0.7 to 14.9 |
| QC Intraday accuracy range (%) | -4.4 to 10.4 |
| QC Interday precision range (%) | 2.9 to 7.1 |
| QC Interday accuracy range (%) | -0.9 to 5.7 |
| Bench-top stability (hrs) | 22 hours at room temperature |
| Stock stability (days) | 90 days at 4°C |
| Processed stability (hrs) | 175 hours at room temperature |
| Freeze-thaw stability (cycles) | 4 cycles |
| Long-term storage stability (days) | 110 days at -30°C (nominal) |
| Dilution integrity | acceptable at 2x and 4x |
| Selectivity | No interference detected from endogenous compounds in six lots of blank matrix, from four potentially present exogenous compounds, or in each of the method analyte response channels from the actual presence of another. |

**Reviewer's note:** An achiral assay of omeprazole was used in the study. In order to show that the assay did not differentiate between the isomers of omeprazole, four QC concentrations of omeprazole were compared against a standard curve of esomeprazole in the range of 2.57-1382.73 ng/mL.

**Comments on Pre-Study Bioanalytical Method Validation:**
The pre-study bioanalytical method validation is **acceptable**.

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## E. In Vivo Studies

### 1. Single-dose Fasting Bioequivalence Study

| Study Summary, Fasting Bioequivalence Study | |
|---|---|
| **Study No.** | P1BD05001 |
| **Study Design** | Randomized single-dose, 2-treatment, 2-period, 2-sequence, 2-way crossover bioavailability study under fasting conditions. |
| **No. of subjects enrolled** | 54 + 2 alternates |
| **No. of subjects completing** | 49 + 2 alternates |
| **No. of subjects analyzed** | 51, as per protocol |
| **Subjects (Healthy or Patients?)** | Healthy |
| **Sex(es) included (how many?)** | Male: 33 Female: 18 |
| **Test product** | Esomeprazole Magnesium Delayed-Release Capsules |
| **Reference product** | Nexium® (esomeprazole magnesium) Delayed-Release Capsules |
| **Strength tested** | 40 mg |
| **Dose** | 1 x 40 mg with 240 mL water under fasting conditions. |

**Fasting Study Statistical Summary** (n=51):

| Esomeprazole Magnesium versus Nexium® Dose (1 x 40 mg) Geometric Means, Ratio of Means, and 90 % Confidence Intervals Fasted Bioequivalence Study | | | | |
|---|---|---|---|---|
| Parameter | Test | Reference | Ratio | 90% C.I. |
| AUC$_{(0-t)}$ (ng/mL) | 2613.44 | 2470.43 | 105.8 | 101.2%-109.52 |
| AUC$_{(0-\infty)}$ (ng/mL) | 2623.21 | 2515.29 | 104.5 | 100.7%-108.38 |
| C$_{max}$ (ng/mL) | 1134.96 | 1112.22 | 106.5 | 100.18-113.31 |

**Reviewer's note**: The values presented in above table were calculated by the firm (n=51)

**Fasting Study Sample Reanalysis**:

| Study No. P1BD05001 Additional information in Volume(s) Page(s) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Incomplete Analysis | 3 | 5 | 0.15 | 0.26 | 3 | 5 | 0.15 | 0.26 |
| Chromatography Unacceptable | 2 | 2 | 0.10 | 0.10 | 2 | 2 | 0.10 | 0.10 |
| Above the Upper Limit of Quantitation | 47 | 47 | 2.43 | 2.43 | 47 | 47 | 2.43 | 2.43 |
| Discretionary Rejection | 6 | 6 | 0.31 | 0.31 | 6 | 6 | 0.31 | 0.31 |
| Total | 58 | 60 | 2.99 | 3.10 | 58 | 60 | 2.99 | 3.10 |

* based on 1938 total samples

Total number of samples assayed = **1938**

**Did use of recalculated plasma concentration data change study outcome?** No. There were 118 sample repeat analysis, which were all analytical repeats. But there is no information about the nature of "Discretionary Rejection" for 12 sample repeats.

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2. Single-dose Fed Bioequivalence Study

| Study Summary, Fed Bioequivalence Study | |
|---|---|
| **Study No.** | P1BD05002 |
| **Study Design** | Randomized single-dose, 2-treatment, 2-period, 2-sequence, 2-way crossover bioavailability study under fed conditions. |
| **No. of subjects enrolled** | 84 + 4 alternates |
| **No. of subjects completing** | 81 + 4 alternates |
| **No. of subjects analyzed** | 84, as per protocol |
| **Subjects (Healthy or Patients?)** | Healthy |
| **Sex(es) included (how many?)** | Male: 62 Female: 22 |
| **Test product** | Esomeprazole Magnesium Delayed-Release Capsules |
| **Reference product** | Nexium® (esomeprazole magnesium) Delayed-Release Capsules |
| **Strength tested** | 40 mg |
| **Dose** | 1 x 40 mg with 240 mL water under fed conditions. |

**Fed Study Statistical Summary (n=84):**

| Esomeprazole Magnesium versus Nexium® Dose (1 x 40 mg) Geometric Means, Ratio of Means, and 90 % Confidence Intervals | | | | |
|---|---|---|---|---|
| Fed Bioequivalence Study | | | | |
| **Parameter** | **Test** | **Reference** | **Ratio** | **90% C.I.** |
| $AUC_{0-t}$ (ng·h/mL) | 1425.90 | 1365.57 | 104.4 | 96.15-113.41 |
| $AUC_{0-\infty}$ (ng·h/mL) | 1623.67 | 1490.06 | 108.7 | 100.02-118.23 |
| $C_{max}$ (ng/mL) | 465.94 | 455.37 | 102.3 | 92.56-113.11 |

**Reviewer's note**: The values presented in above table were calculated by the firm (n=84).

**Fed Study Sample Reanalysis:**

| Study No. P1BD05002 Additional information in Volume(s), Page(s) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Reason why assay was repeated | Number of samples reanalyzed[1] | | | | 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 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Above the upper limit of quantitation | 5 | 4 | 0.16 | 0.13 | 5 | 4 | 0.16 | 0.13 |
| Incorrect | 2 | 3 | 0.06 | 0.09 | 2 | 3 | 0.06 | 0.09 |
| Chromatography unacceptable | 1 | - | 0.03 | - | 1 | - | 0.03 | - |
| Total | 8 | 7 | 0.25 | 0.22 | 8 | 7 | 0.25 | 0.22 |

[1] Based on 3192 total samples

Total number of samples assayed = **3192**

**Did use of recalculated plasma concentration data change study outcome?** No. There were fifteen sample repeat analysis, which were all analytical repeats. The reviewer agrees with the reanalysis.

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3. Single-dose Sprinkled Fasting Bioequivalence Study

| Study Summary, Sprinkled Fasting Bioequivalence Study | |
|---|---|
| **Study No.** | P1BD05010 |
| **Study Design** | Randomized single-dose, 2-treatment, 2-period, 2-sequence, 2-way crossover bioavailability study under fasting conditions. |
| **No. of subjects enrolled** | 54 + 4 alternates |
| **No. of subjects completing** | 52 + 3 alternates |
| **No. of subjects analyzed** | 54 (As per protocol, data from 54 subjects were used for the pharmacokinetic analysis. Due to a delayed communication from the firm, samples from subject #5, who was removed from the clinical study, were also analyzed, but not used in the PK analysis, making total number of subjects analyzed 55) |
| **Subjects (Healthy or Patients?)** | Healthy |
| **Sex(es) included (how many?)** | Male: 33 Female: 21 |
| **Test product** | Esomeprazole Magnesium Delayed-Release Capsules |
| **Reference product** | Nexium® (esomeprazole magnesium) Delayed-Release Capsules |
| **Strength tested** | 40 mg |
| **Dose** | 1 x 40 mg, with capsule contents sprinkled over a spoonful of applesauce, followed by 240 mL water under fasting conditions. |

**Sprinkled Fasting Study Statistical Summary** (n=54)**:**

| Esomeprazole Magnesium versus Nexium®<br>Dose (1x 40 mg)<br>Geometric Means, Ratio of Means, and 90 % Confidence Intervals<br>Fasted Bioequivalence Study: P1BD05010 | | | | |
|---|---|---|---|---|
| Parameter | Test | Reference | Ratio | 90% CI |
| $AUC_{0-t}$ (ng·h/mL) | [illegible] | [illegible] | [illegible] | [illegible] |
| $AUC_{0-\infty}$ (ng·h/mL) | [illegible] | [illegible] | [illegible] | [illegible] |
| $C_{max}$ (ng/mL) | [illegible] | [illegible] | [illegible] | [illegible] |

**Reviewer's note**: The values presented in above table were calculated by the firm (n=54)

**Sprinkled Fasting Study Sample Reanalysis**:

| Study No. P1BD05010<br>Additional information in Volume(s), Page(s) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Reason why assay was repeated | Number of samples reanalyzed | | | | Number of recalculated values used after reanalysis | | | |
| | Actual number | | % of total samples * | | Actual number | | % of total samples * | |
| | T | R | T | R | T | R | T | R |
| Pharmacokinetic | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Incomplete Analysis | 0 | 4 | 0 | 0.19 | 0 | 4 | 0 | 0.19 |
| Above the Upper Limit of Quantitation | 38 | 40 | 1.82 | 1.91 | 38 | 40 | 1.82 | 1.91 |
| Unacceptable Internal Standard Response | 0 | 1 | 0 | .05 | 0 | 1 | 0 | .05 |
| Total | 38 | 45 | 1.82 | 2.15 | 38 | 45 | 1.82 | 2.15 |

* based on 2090 total samples

Total number of samples assayed = **2090**

**Did use of recalculated plasma concentration data change study outcome?** No. There were 83 sample repeat analysis, which were all analytical repeats. The reviewer agrees with the reanalysis.

### F. Formulation

| | |
|---|---|
| **Location in appendix** | Section IV.B, page 37 |
| **Are inactive ingredients within IIG limits?** | Yes |
| **If no, list ingredients outside of limits** | N/A |
| **If a tablet, is the product scored?** | N/A |
| **If yes, which strengths are scored?** | N/A |
| **Is scoring of RLD the same as test?** | N/A |
| **Is the formulation acceptable?** | Yes |
| **If not acceptable, why?** | N/A |

### G. In Vitro Dissolution

| | |
|---|---|
| **Source of Method (USP, FDA or Firm)** | FDA |
| **Medium** | Acid stage: 0.1N HCl; Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume (mL)** | Acid stage: 300 mL; Buffer stage: 1000 mL |
| **USP Apparatus type** | II (paddle) |
| **Rotation (rpm)** | 100 rpm |
| **Firm's proposed specifications** | Acid stage: NMT (b)(4)% in 120 minutes; Buffer stage: NLT (b)(4)% in (b)(4) minutes |
| **FDA-recommended specifications** | Acid stage: NMT (b)(4)% in 120 minutes; Buffer stage: NLT (b)(4)% in 30 minutes |
| **F2 metric calculated?** | No (dissolution data incomplete) |
| **Is method acceptable?** | No |
| **If not then why?** | Firm used non-FDA method for the acid stage |

**Reviewer's note**: There is no USP method for this product but there is an FDA-recommended method. The firm conducted dissolution testing at the acid stage with a non-FDA-recommended method (b)(4) 0.1M HCl with a paddle speed of 100 rpm)[3]. The firm's dissolution testing data at the buffer stage with the FDA-recommended method were acceptable (at the L1 level). However, the firm's proposed specification of "NLT (b)(4)% (Q) in (b)(4) minutes" for the buffer stage is different from the FDA-recommended specification. The firm was asked to repeat acid stage dissolution testing using the FDA-recommended method (**300 mL** 0.1N HCl with a paddle speed of 100 rpm). Also, the firm was asked to acknowledge its acceptance of the FDA-recommended specification of "NLT (b)(4)% (Q) in 30 minutes" for the buffer stage. Till date, there is no response from the firm regarding the dissolution deficiencies. The dissolution testing study is **incomplete**.

### H. Waiver Request(s)

| | |
|---|---|
| Strengths for which waivers are requested | 20 mg |
| Regulation cited | 21 CFR §320.22(d)(2) |
| Proportional to strength tested in vivo? | Yes |
| Is dissolution acceptable? | No |
| Waivers granted? | No |

[3] Dissolution review of ANDA #78-003 (v:\firmsam\ivaxpharm\ltrs&rev\78003D1105.doc)

| | |
|---|---|
| If not then why? | Pending acceptable bioequivalence studies on the 40 mg strength and dissolution study. |

### I. Deficiency Comments

1. The firm did not submit any Standard Operating Procedure for sample repeat analysis. The firm should submit all the relevant Standard Operating Procedures and their effective dates.

2. Twelve samples in the fasting study (#P1BD05001) were reassayed due to Discretionary Rejection. The firm should explain the meaning of Discretionary Rejection in this context.

3. Sprinkle study (1BD05010): The firm states that Subject (b)(6) was withdrawn by the investigator due to noncompliance after the completion of the study. Plasma samples of this subject were analyzed. The firm should explain why this subject was withdrawn after completing the study.

4. We have not received firm's response to dissolution deficiency communicate to the firm earlier. The firm should provide dissolution testing data for the acid stage. The dissolution testing should be conducted using 300 mL of 0.1 N HCl and a paddle speed of 100 rpm. In addition, the firm should indicate if it accepts the dissolution specification of NLT (b)(4)% (Q) in 30 minutes for the buffer stage.

5. The firm submitted only 6 electronic summary bio-tables in the DBE-recommended format and did not submit the summary bio-tables for the dissolution and the formulation data. The firm should submit these tables in Microsoft Word.

### J. Recommendations

1. The single-dose, *in vivo* fasting bioequivalence study (#P1BD05001) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **incomplete** due to bioanalytical method deficiencies.

2. The single-dose, *in vivo* non-fasting bioequivalence study (#P1BD05002) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 40 mg (Lot #N5819), is **incomplete** due to bioanalytical method deficiencies.

3. The single-dose, *in vivo* sprinkled fasting bioequivalence study (#P1BD05010) conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 40 mg (Lot #Y51286), comparing it to AstraZeneca's Nexium® (esomeprazole magnesium)

Delayed-Release Capsules, 40 mg (Lot #N5819), is **incomplete** due to bioanalytical method deficiencies.

4. The *in vitro* dissolution testing conducted by IVAX Pharmaceuticals, Inc. on its Esomeprazole Magnesium Delayed-Release Capsules, 20 mg (Lot #Y51231) and 40 mg (Lot # Y51232, same as Lot#Y51286 used in the *in vivo* bioequivalence studies, but different package number), comparing to AstraZeneca's Nexium® (esomeprazole magnesium) Delayed-Release Capsules, 20 mg (Lot#P4879) and 40 mg (Lot #N5819), is **incomplete**

   The dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b)(4)% in 120 minutes<br>Buffer stage: NLT(b)(4)% in 30 minutes |

5. The formulation of the 20 mg strength is proportionally similar to the 40 mg strength of the test product, which underwent *in vivo* bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for the 20 mg strength is **denied** due to deficiencies.

   The firm should be informed of the above deficiency comments and recommendations.

Parthapratim Chandaroy — 9/22/06

Parthapratim Chandaroy, Ph.D. Reviewer, Branch V — Date

KDhariwal — 9/22/06

Kuldeep R. Dhariwal, Ph.D. Team Leader, Branch V — Date

Barbara McDavit — 9/22/06

Dale P. Conner, Pharm.D. — Date
Director, Division of Bioequivalence
Office of Generic Drugs

# IV. Appendix

## A. Individual Study Reviews

### 1. Single-dose Fasting Bioequivalence Study

#### a) Study Design

| Study Information | |
|---|---|
| **Study Number** | P1BD05001 |
| **Study Title** | Comparative Bioavailability Study of Esomeprazole Magnesium 40 mg Capsules (Ivax Pharmaceuticals Inc., USA) vs. Nexium® 40 mg Capsules (AstraZeneca LP, USA) In Healthy Male and/or Female Volunteers Under Fasting Conditions |
| **Clinical Site** | Allied Research International Inc., 4520 Dixie Road, Mississauga, Ontario, Canada L4W 1N2 |
| **Principal Investigator** | Deepen Patel, M.D., CCFP |
| **Study/Dosing Dates** | Period I: July 14, 2005; Period II: July 21, 2005 |
| **Analytical Site** | (b) (4) |
| **Analytical Director** | (b) (6) Hons. B.Sc. |
| **Analysis Dates** | July 26, 2005 – August 15, 2005 |
| **Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)** | 33 days[4] |

| **Treatment ID** | **A** | **B** |
|---|---|---|
| **Test or Reference** | Test | Reference |
| **Product Name** | Esomeprazole Magnesium Delayed-Release Capsules | Nexium® (esomeprazole magnesium) Delayed-Release Capsules |
| **Manufacturer** | Cipla for IVAX Pharmaceuticals, Inc. | AstraZeneca |
| **Batch/Lot No.** | Y51286 | N5819 |
| **Manufacture Date** | 6/2005 | N/A |
| **Expiration Date** | N/A | 11/2006 |
| **Strength** | 40 mg | 40 mg |
| **Dosage Form** | Delayed-Release Capsules | Delayed-Release Capsules |
| **Batch Size** | (b) (4) | N/A |
| **Production Batch Size** | | N/A |
| **Potency** | 100.3% | 100.4% |
| **Content Uniformity (mean, %CV)** | 99.8%, 1.1% | 100.3%, 0.5% |
| **Formulation** | See **Table 34** | N/A |
| **Dose Administered** | 1x40 mg | 1x40 mg |
| **Administration Route** | Oral | Oral |

[4] The firm submitted long-term (freezer) storage stability data for 116 days (at -30°C, nominal)

| | |
|---|---|
| **No. of Sequences** | 2 |
| **No. of Periods** | 2 |
| **No. of Treatments** | 2 |
| **No. of Groups** | 1 |
| **Washout Period** | 7 days |
| **Randomization Scheme** | AB: 03, 06, 07, 08, 11, 13, 17, 18, 21, 22, 24, 25, 26, 28, 32, 33, 35, 37, 39, 40, 41, 42, 45, 47, 49, 52, 54, 55<br>BA: 01, 02, 04, 05, 09, 10, 12, 14, 15, 16, 19, 20, 23, 27, 29, 30, 31, 34, 36, 38, 43, 44, 46, 48, 50, 51, 53, 56 |
| **Blood Sampling Times** | 0 (x2), 0.17, 0.33, 0.5, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 14 hours post-dose |
| **Blood Volume Collected/Sample** | 6 mL collected in Vacutainer™ tubes containing sodium heparin. |
| **Blood Sample Processing/Storage** | Blood samples were collected in Vacutainer™ tubes and immediately placed in an ice bath until centrifugation. Centrifugation was conducted within at most 30 minutes after sample collection. The plasma was separated by centrifugation at 3000 rpm (4±1°C) for a minimum of 10 minutes. Plasma from each sample was equally transferred into two labeled polypropylene tubes and stored below -20°C until analysis. |
| **IRB Approval** | Yes |
| **Informed Consent** | Yes |
| **Subjects Demographics** | See **Table 1** |
| **Length of Fasting** | 10 hours pre-dose until 4 hours post-dose |
| **Length of Confinement** | At least 10 hours pre-dose until 14 hours post-dose |
| **Safety Monitoring** | Seated blood pressure and heart rate were measured prior to dosing, and at the end of confinement (14 hours post-dose) in each period. Adverse events were monitored throughout the study. |

**Comments on Study Design:** The study design is **acceptable**.

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b) Clinical Results

**Table 1: Demographics of Study Subjects**

| Study No. PHH0600[illegible] | | |
|---|---|---|
| | Treatment Groups | |
| | Esomeprazole magnesium 40 mg N = 51 | Nexium® 40 mg N = 51 |
| Age (years) | | |
| Mean ± SD | 37 ± 9 | 37 ± 9 |
| Range | 21 - 53 | 21 - 53 |
| Groups | | |
| < 18 | 0 (0%) | 0 (0%) |
| 18 – 40 | 34 (66.7%) | 34 (66.7%) |
| 41 – 64 | 17 (33.3%) | 17 (33.3%) |
| 65 – 75 | 0 (0%) | 0 (0%) |
| > 75 | 0 (0%) | 0 (0%) |
| Sex | | |
| Female | 18 (35.3%) | 18 (35.3%) |
| Male | 33 (64.7%) | 33 (64.7%) |
| Race | | |
| Asian | 3 (5.9%) | 3 (5.9%) |
| Black | 18 (35.3%) | 18 (35.3%) |
| Caucasian | 24 (47.1%) | 24 (47.1%) |
| Hispanic | 4 (7.8%) | 4 (7.8%) |
| Other | 2 (3.9%) | 2 (3.9%) |
| Other Factors | | |
| Height (cm) | | |
| Mean ± SD | 170.7 ± 8.0 | 170.7 ± 8.0 |
| Range | 152.5 – 187.0 | 152.5 – 187.0 |
| Weight (kg) | | |
| Mean ± SD | 74.1 ± 9.3 | 74.1 ± 9.3 |
| Range | 53.0 – 95.6 | 53.0 – 95.6 |

**Reviewer's note**: Subject BMI (mean, standard deviation) for the study is: 25.2, 2.3

**Table 2: Dropout Information**

| Subject No | Reason | Period | Replaced? |
|---|---|---|---|
| (b) (6) | Voluntarily withdrew from the study due to adverse events | Before II | (b) (6) |
| | Same as above | Before II | |
| | Same as above | Before II | |
| | Voluntarily withdrew from the study due to personal reasons | Before II | |
| | Same as above (b) (6) | Before II | |

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## Table 3: Study Adverse Events

| Body System/Adverse Event | Reported Incidence by Treatment Groups | | | |
|---|---|---|---|---|
| | Fasted Bioequivalence Study Study No. PHB005001 (N = 51)* | | Fed Bioequivalence Study Study No. PHB005002 (N = 84)* | |
| | Esomeprazole magnesium 40 mg | Nexium® 40 mg | Esomeprazole magnesium 40 mg | Nexium® 40 mg |
| Body as a whole | | | | |
| Injection Site Edema | 1 (2.0%) | 1 (2.0%) | 1 (1.2%) | |
| Injection Site Pain | 4 (7.8%) | 1 (2.0%) | 2 (2.4%) | 1 (1.2%) |
| Headache | | 1 (2.0%) | 2 (2.4%) | 3 (3.6%) |
| Asthenia | | | 1 (1.2%) | |
| Abdominal Pain | | | | 2 (2.4%) |
| Accidental Injury | | | | 2 (2.4%) |
| Fever | | | | |
| Heme and Lymphatic System | | | | |
| Ecchymosis | 1 (2.0%) | | | |
| Cardiovascular System | | | | |
| Tachycardia | 1 (2.0%) | | 1 (1.2%) | |
| Hypertension | | | | 1 (1.2%) |
| Nervous System | | | | |
| Dizziness | | 1 (2.0%) | | 1 (1.2%) |
| Respiratory System | | | | |
| Pharyngitis | 1 (2.0%) | | | |
| Rhinitis | | | | |
| Skin and Appendages | | | | |
| Rash | | | 1 (1.2%) | 1 (1.2%) |
| Total | 8 | 4 | 8 | 11 |

*Includes only those subjects that were used in the statistical analysis

**Reviewer's note**: The following part of the table represents adverse events data from subjects not included in the statistical analysis.

| Body System/Adverse Event | Reported Incidence by Treatment Groups | | | |
|---|---|---|---|---|
| | Fasted Bioequivalence Study Study No. PHB005001 (N = 5) | | Fed Bioequivalence Study Study No. PHB005002 (N = 4) | |
| | Esomeprazole magnesium 40 mg | Nexium® 40 mg | Esomeprazole magnesium 40 mg | Nexium® 40 mg |
| Body as a whole | | | | |
| Fever | 1 (20%) | | | 1 (25.0%) |
| Headache | 1 (20%) | | 1 (25.0%) | |
| Asthenia | | 1 (20%) | | |
| Back Pain | | | | 1 (25.0%) |
| Abdominal Pain | 1 (20%) | | | |
| Respiratory | | | | |
| Cough Increased | 1 (20%) | 1 (20%) | | |
| Rhinitis | 1 (20%) | 1 (20%) | | 1 (25.0%) |
| Digestive | | | | |
| Diarrhea | 1 (20%) | | | |
| Nausea | | | | 2 (50.0%) |
| Vomiting | | | 1 (25.0%) | 1 (25.0%) |
| Musculoskeletal | | | | |
| Myalgia | | 1 (20%) | | |
| Total | 6 | 4 | 2 | 6 |

**Table 4: Protocol Deviations**

| Type | Subject #s (Test) | Subject #s (Ref.) |
|---|---|---|
| Samples were not centrifuged within 30 min. in period I | (b) (6) | (b) (6) |
| Unknown sample centrifuge time and duration in period II | many | many |
| Blood sampling time deviations: samples drawn late (early for only subject (b) (6) period I) | many | many |

**Comments on Dropouts/Adverse Events/Protocol Deviations:**

- There were a total of 22 (14: test; 8: reference) post-dose adverse events reported by 8 subjects. All events were "mild" in severity, except one of "moderate" severity. Eighteen of the adverse events (pain/bruising/burning/swelling at the venipuncture site, elevated heart rate, scratchy throat, stuffy nose, fever, intermittent headache, cough, weakness, and aching muscles) were "unlikely" related to the study treatments. The remaining 4 adverse events (stomach ache, diarrhea, headache, and dizziness) were "possibly" related to the study treatments.
- There were several blood draw deviations in the study with a maximum deviation of 4.6 minutes. All the time-points were corrected for any deviation before pharmacokinetic analysis.
- **The adverse events and protocol deviations did not compromise the integrity of the study.**

c) Bioanalytical Results

**Table 5: Assay Quality Control – Within Study**

| | Esomeprazole | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **QC Conc. (ng/mL)** | 5.29 | | 69.42 | | | 433.88 | | 991.74 |
| **Inter day Precision (%CV)** | 12.9 | | 2.8 | | | 2.8 | | 2.2 |
| **Inter day Accuracy (%)** | 104.8 | | 103.0 | | | 103.0 | | 99.4 |
| | | | | | | | | |
| **Cal. Standards Conc. (ng/mL)** | 2.54 | 6.35 | 15.87 | 39.67 | 99.17 | 247.93 | 619.83 | 1363.64 |
| **Inter day Precision (%CV)** | 2.6 | 3.4 | 2.8 | 2.9 | 2.4 | 2.1 | 1.9 | 2.8 |
| **Inter day Accuracy (%)** | 99.7 | 100.4 | 101.6 | 101.1 | 101.2 | 100.2 | 100.0 | 98.1 |
| **Linearity Range (range of r values)** | 0.9982-0.9999 | | | | | | | |

**Comments on Study Assay Quality Control:** None.

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

**Comments on Chromatograms:** None.

**Table 6: SOPs dealing with analytical repeats of study samples**

| SOP No. | Date of SOP | SOP Title |
|---|---|---|
| None provided (NP) | NP | NP |

**Table 7: Additional Comments on Repeat Assays**

| | |
|---|---|
| Were all SOPs followed? | N/A |
| Did recalculation of plasma concentrations change the study outcome? | No |
| Does the reviewer agree with the outcome of the repeat assays? | No |
| If no, reason for disagreement | The firm did not provide any information for 12 sample repeat analysis performed because of "Discretionary Rejection" |

**Summary/Conclusions, Study Assays:**

- There were a total of 1938 study samples analyzed. A total of 118 samples (Test: 58, Reference: 60) were reanalyzed, representing 6.09% of the total study assays. All reanalysis were analytical repeats.
- The analytical method and data are **incomplete** due to deficiencies.

d) Pharmacokinetic Results

**Table 8: Arithmetic Mean Pharmacokinetic Parameters for Esomeprazole (n=51)**

Mean plasma concentrations are presented in **Table 11** and **Figure 1**.

| Parameter | Units | Test | | Reference | | T/R |
|---|---|---|---|---|---|---|
| | | Mean | %CV | Mean | % CV | |
| $AUC_{0-t}$ | ng/mL x hr | 3362.89 | 72.64 | 3215.38 | 74.05 | 1.05 |
| $AUC_{0-\infty}$ | ng/mL x hr | 3413.47 | 73.91 | 3304.84 | 73.53 | 1.03 |
| $C_{max}$ | ng/mL | 1319.72 | 46.34 | 1236.70 | 45.98 | 1.07 |
| $T_{max}$ | hr | 2.45 | 30.32 | 2.27 | 39.65 | 1.08 |
| $K_e$ | $hr^{-1}$ | 0.69 | 41.62 | 0.69 | 40.28 | 1.01 |
| $T_{1/2}$ | hr | 1.19 | 43.47 | 1.19 | 42.62 | 1.00 |

**Table 9: Geometric Means and 90% Confidence Intervals for Esomeprazole (n=51)**

| Parameter | Test | Reference | T/R | 90% CI |
|---|---|---|---|---|
| $AUC_{0-t}$ | 2615.44 | 2479.43 | 1.05 | 101.59-109.53 |
| $AUC_{0-\infty}$ | 2628.20 | 2515.29 | 1.04 | 100.76-108.35 |
| $C_{max}$ | 1184.96 | 1112.22 | 1.07 | 100.18-113.31 |

**Reviewer's note**: The values in the above table were calculated by the reviewer.

**Table 10: Additional Study Information for Esomeprazole**

| | |
|---|---|
| Root mean square error, $\ln AUC_{0-t}$ | 0.113241 |
| Root mean square error, $\ln AUC_{0-\infty}$ | 0.107152 |
| Root mean square error, $\ln C_{max}$ | 0.185514 |
| $K_{el}$ and $AUC_{0-\infty}$ determined for how many subjects? | 50 (test and reference) |
| Do you agree or disagree with firm's decision? | Agree |
| Indicate the number of subjects with the following: | |
| -measurable drug concentrations at 0 hr | None |
| -first measurable drug concentration as $C_{max}$ | None |
| Were the subjects dosed as more than one group? | No |

**Comments on Pharmacokinetic and Statistical Analysis:**

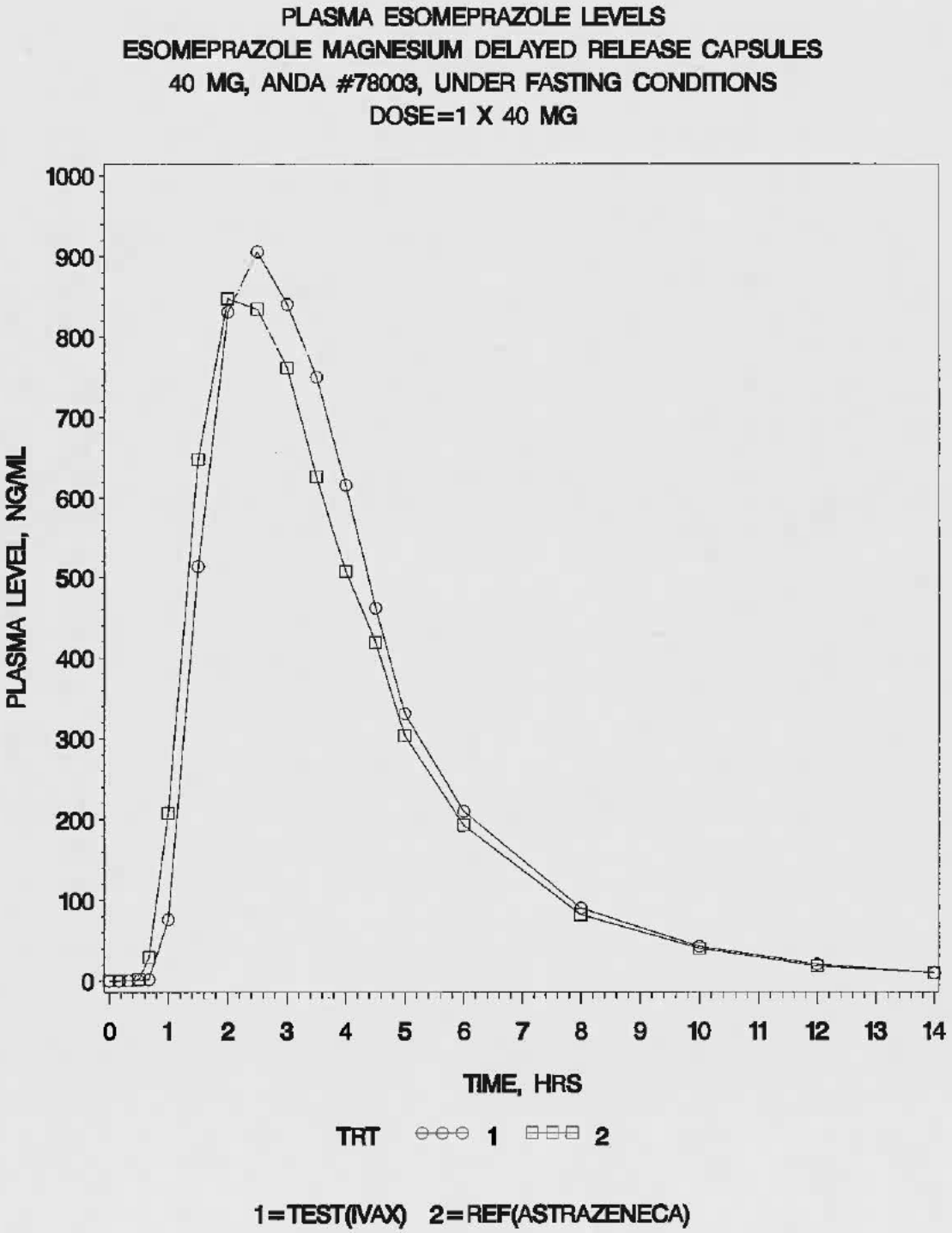
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.
- The 90% confidence intervals for $\ln AUC_{0-t}$, $\ln AUC_{0-\infty}$, and $\ln C_{max}$ are within the acceptable limits of 80-125%.

**Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:** The single-dose fasting study is **incomplete** due to bioanalytical method deficiencies.

**Table 11 Mean Esomeprazole Plasma Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study**

| Time | Test (n=51) | | Reference (n=51) | | T/R |
|---|---|---|---|---|---|
| | Mean Conc. | %CV | Mean Conc. | %CV | |
| 0 | 0.00 | . | 0.00 | . | N/A |
| 0.17 | 0.00 | . | 0.08 | 714.14 | 0.00 |
| 0.33 | 0.00 | . | 0.00 | . | N/A |
| 0.5 | 0.05 | 714.14 | 1.96 | 357.00 | 0.03 |
| 0.67 | 1.89 | 222.10 | 29.12 | 267.97 | 0.06 |
| 1 | 76.06 | 227.14 | 207.48 | 165.47 | 0.37 |
| 1.5 | 513.78 | 127.64 | 648.15 | 82.19 | 0.79 |
| 2 | 830.79 | 92.68 | 847.34 | 74.19 | 0.98 |
| 2.5 | 905.70 | 71.80 | 834.37 | 69.29 | 1.09 |
| 3 | 840.56 | 62.29 | 761.24 | 80.16 | 1.10 |
| 3.5 | 749.87 | 71.68 | 626.53 | 87.51 | 1.20 |
| 4 | 616.13 | 76.51 | 507.63 | 90.84 | 1.21 |
| 4.5 | 461.92 | 87.74 | 419.28 | 98.38 | 1.10 |
| 5 | 330.85 | 96.78 | 303.52 | 106.40 | 1.09 |
| 6 | 209.80 | 114.31 | 192.58 | 124.63 | 1.09 |
| 8 | 89.91 | 145.96 | 81.62 | 155.86 | 1.10 |
| 10 | 42.18 | 169.15 | 40.06 | 181.44 | 1.05 |
| 12 | 20.03 | 200.36 | 17.93 | 215.05 | 1.12 |
| 14 | 9.67 | 227.75 | 9.32 | 244.77 | 1.04 |

**Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (n=51)**



2. Single-dose Fed Bioequivalence Study

a) Study Design

| Study Information | |
|---|---|
| **Study Number** | P1BD05002 |
| **Study Title** | Comparative Bioavailability Study of Esomeprazole Magnesium 40 mg Capsules (Ivax Pharmaceuticals Inc., USA) vs. Nexium® 40 mg Capsules (AstraZeneca LP, USA) In Healthy Male and/or Female Volunteers Under Fed Conditions |
| **Clinical Site** | Allied Research International Inc., 4520 Dixie Road, Mississauga, Ontario, Canada L4W 1N2 |
| **Principal Investigator** | Deepen Patel, M.D., CCFP |
| **Study/Dosing Dates** | Group1: Period I: July 16, 2005; Period II: July 23, 2005<br>Group2: Period I: July 17, 2005; Period II: July 24, 2005 |
| **Analytical Site** | (b) (4) |
| **Analytical Director** | (b) (6) Hons. B.Sc. |
| **Analysis Dates** | August 11, 2005 – August 24, 2005 |
| **Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)** | 40 days[5] |

| Treatment ID | A | B |
|---|---|---|
| **Test or Reference** | Test | Reference |
| **Product Name** | Esomeprazole Magnesium Delayed-Release Capsules | Nexium® (esomeprazole magnesium) Delayed-Release Capsules |
| **Manufacturer** | Cipla for IVAX Pharmaceuticals, Inc. | AstraZeneca |
| **Batch/Lot No.** | Y51286 | N5819 |
| **Manufacture Date** | 6/2005 | N/A |
| **Expiration Date** | N/A | 11/2006 |
| **Strength** | 40 mg | 40 mg |
| **Dosage Form** | Delayed-Release Capsules | Delayed-Release Capsules |
| **Batch Size** | (b) (4) | N/A |
| **Production Batch Size** | | N/A |
| **Potency** | 100.3% | 100.4% |
| **Content Uniformity (mean, %CV)** | 99.8%, 1.1% | 100.3%, 0.5% |
| **Formulation** | See **Table 34** | N/A |
| **Dose Administered** | 1x40 mg | 1x40 mg |
| **Route of Administration** | Oral | Oral |

[5] The firm submitted long-term (freezer) storage stability data for 116 days (at -30°C, nominal)

| | |
|---|---|
| **No. of Sequences** | 2 |
| **No. of Periods** | 2 |
| **No. of Treatments** | 2 |
| **No. of Groups** | 2 |
| **Washout Period** | 7 days |
| **Randomization Scheme** | AB:<br>Group1: 01, 03, 04, 05, 06, 08, 09, 11, 14, 16, 18, 25, 28, 31, 32, 35, 40, 44<br>Group2: 46, 49, 50, 52, 53, 55, 56, 58, 60, 61, 64, 65, 66, 68, 69, 70, 71, 73, 75, 79, 80, 81, 83, 84, 85, 87<br>BA:<br>Group1: 02, 07, 10, 12, 13, 15, 17, 19, 20, 21, 22, 23, 24, 26, 27, 29, 30, 33, 34, 36, 37, 38, 39, 41, 42, 43<br>Group2: 45, 47, 48, 51, 54, 57, 59, 62, 63, 67, 72, 74, 76, 77, 78, 82, 86, 88<br><br>Note: The subjects were divided into two equal groups (Group 1: 1-44; Group 2: 45-88) |
| **Blood Sampling Times** | 0 (x2), 0.17, 0.33, 0.5, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 14 hours post-dose |
| **Blood Volume Collected/Sample** | Same as Fasting study |
| **Blood Sample Processing/Storage** | Same as Fasting study |
| **IRB Approval** | Yes |
| **Informed Consent** | Yes |
| **Subjects Demographics** | See **Table 12** |
| **Length of Fasting before Meal** | After an overnight fast of at least 10 hours, subjects were served with a standardized breakfast 30 minutes before drug administration. Subjects fasted for 4 hours post-dose. |
| **Length of Confinement** | Same as Fasting study |
| **Safety Monitoring** | Same as Fasting study |
| **Standard FDA Meal Used?** | Yes |
| **If no, then meal is listed in table below** | N/A |

**Comments on Study Design:** The study design is **acceptable**.

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b) Clinical Results

**Table 12: Demographics of Study Subjects**

| Study No. PHD06002 | | |
|---|---|---|
| | Treatment Groups | |
| | Esomeprazole magnesium 40 mg N = 84 | Nexium® 40 mg N = 84 |
| Age (years) | | |
| Mean ± SD | 37 ± 8 | 37 ± 8 |
| Range | 20 – 54 | 20 – 54 |
| Groups | | |
| < 18 | 0 (0%) | 0 (0%) |
| 18 – 40 | 51 (60.7%) | 51 (60.7%) |
| 41 – 64 | 33 (39.3%) | 33 (39.3%) |
| 65 – 75 | 0 (0%) | 0 (0%) |
| > 75 | 0 (0%) | 0 (0%) |
| Sex | | |
| Female | 22 (26.2%) | 22 (26.2%) |
| Male | 62 (73.8%) | 62 (73.8%) |
| Race | | |
| Asian | 9 (10.7%) | 9 (10.7%) |
| Black | 18 (21.4%) | 18 (21.4%) |
| Caucasian | 39 (46.4%) | 39 (46.4%) |
| Hispanic | 12 (14.3%) | 12 (14.3%) |
| Other | 6 (7.1%) | 6 (7.1%) |
| Other Factors | | |
| Height (cm) | | |
| Mean ± SD | 170.3 ± 10.0 | 170.3 ± 10.0 |
| Range | 143 – 198.0 | 143 – 198.0 |
| Weight (kg) | | |
| Mean ± SD | 74.8 ± 11.6 | 74.8 ± 11.6 |
| Range | 44.4 – 114.9 | 44.4 – 114.9 |

**Reviewer's note**: Subject BMI (mean, standard deviation) for the study is: 25.6, 2.2

**Table 13: Dropout Information**

| Subject No | Reason | Period | Replaced? |
|---|---|---|---|
| (b) (6) | Voluntarily withdrew from the study due to adverse events | Before II | (b) (6) |
| | Same as above | Before II | |
| | Withdrawn from the study due to non-compliance (unable to complete high-fat breakfast in period 2 and was withdrawn prior to dosing) | II | |

**Table 14: Study Adverse Events**

**Reviewer's note**: Adverse event data from fasting and fed the studies were provided together by the firm (see **Table 3**).

**Table 15: Protocol Deviations**

| Type | Subject #s (Test) | Subject #s (Ref.) |
|---|---|---|
| Samples were not centrifuged within 30 min in period I or II | several | several |
| Blood sampling time deviations (samples drawn late) | many | many |

**Comments on Dropouts/Adverse Events/Protocol Deviations:**

- There were a total of 27 (10: test; 17: reference) post-dose adverse events reported by 17 subjects. All events were "mild" in severity, except one of "moderate" severity. Seventeen of the adverse events (pain/swelling/soreness at the venipuncture site, rash on arms/legs, elevated heart rate, headache, low blood pressure, nausea, **vomiting,** stiff back, nasal congestion, fever and injured/stubbed toe) were "unlikely" related to the study treatments. The remaining 10 adverse events (headache, **vomiting**, tired, dizzy, and abdominal pain/discomfort) were "possibly" related to the study treatments.
- Two subjects (b) (6) vomited during the study. Both subjects voluntarily withdrew from the study.
- Subject (b) (6) took Tylenol during wash-out period due to an adverse event (fever). Subject voluntarily withdrew from the study because of the adverse event. Subject (b) (6) took Flonase approximately 10 days before period I dosing. Subject was deemed acceptable to participate in the study. The reviewer agrees that use of concomitant medication did not affect the integrity of the study.
- There were several blood draw deviations in the study with a maximum deviation of 8.9 minutes. All the time-points were corrected for any deviation before pharmacokinetic analysis.
- **The adverse events and protocol deviations did not compromise the integrity of the study.**

c) Bioanalytical Results

**Table 16: Assay Quality Control – Within Study**

| | Esomeprazole | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **QC Conc. (ng/mL)** | 5.29 | | 69.42 | | | 433.88 | | 991.74 |
| **Inter day Precision (%CV)** | 6.2 | | 6.1 | | | 4.4 | | 4.6 |
| **Inter day Accuracy (%)** | 97.8 | | 99.2 | | | 100.7 | | 98.9 |
| | | | | | | | | |
| **Cal. Standards Conc. (ng/mL)** | 2.54 | 6.35 | 15.87 | 39.67 | 99.17 | 247.93 | 619.83 | 1363.64 |
| **Inter day Precision (%CV)** | 4.1 | 2.6 | 2.7 | 2.8 | 2.5 | 2.3 | 2.4 | 3.1 |
| **Inter day Accuracy (%)** | 99.9 | 100.6 | 100.1 | 98.6 | 99.7 | 100.4 | 101.1 | 99.8 |
| **Linearity Range (range of r values)** | 0.9980-0.9999 | | | | | | | |

**Comments on Study Assay Quality Control: None.**

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

**Comments on Chromatograms:** None.

**Table 17: SOPs dealing with analytical repeats of study samples**

| SOP No. | Date of SOP | SOP Title |
|---|---|---|
| None provided (NP) | NP | NP |

**Table 18: Additional Comments on Repeat Assays**

| | |
|---|---|
| Were all SOPs followed? | N/A |
| Did recalculation of plasma concentrations change the study outcome? | No |
| Does the reviewer agree with the outcome of the repeat assays? | Yes |
| If no, reason for disagreement | N/A |

**Summary/Conclusions, Study Assays:**

- There were a total of 3192 study samples analyzed. 15 samples (Test: 8, Reference: 7) were reanalyzed, representing 0.47% of the total study assays. All reanalysis were analytical repeats.
- The analytical method and data are **incomplete** due to deficiencies.

d) Pharmacokinetic Results

**Table 19: Arithmetic Mean Pharmacokinetic Parameters for Esomeprazole (n=84)**

Mean plasma concentrations are presented in **Table 22** and **Figure 2.**

| Parameter | Units | Test | | Reference | | T/R |
|---|---|---|---|---|---|---|
| | | Mean | %CV | Mean | % CV | |
| $AUC_{0-t}$ | ng/mL x hr | 1889.91 | 78.88 | 1756.48 | 75.95 | 1.00 |
| $AUC_{0-\infty}$ | ng/mL x hr | 2170.80 | 71.45 | 1903.05 | 73.80 | 1.14 |
| $C_{max}$ | ng/mL | 586.34 | 62.99 | 555.51 | 60.81 | 1.06 |
| $T_{max}$ | Hr | 5.50 | 23.39 | 5.43 | 26.52 | 1.01 |
| $K_e$ | $hr^{-1}$ | 0.61 | 28.58 | 0.60 | 25.81 | 1.02 |
| $T_{1/2}$ | Hr | 1.24 | 32.55 | 1.28 | 41.36 | 0.97 |

**Table 20: Geometric Means and 90% Confidence Intervals for Esomeprazole (n=84)**

| Parameter | Test | Reference | T/R | 90% CI |
|---|---|---|---|---|
| $AUC_{0-t}$ | 1446.63 | 1380.78 | 1.05 | 96.23-114.07 |
| $AUC_{0-\infty}$ | 1661.14 | 1526.39 | 1.09 | 99.87-118.59 |
| $C_{max}$ | 473.56 | 461.72 | 1.03 | 92.50-113.72 |

**Reviewer's note:** The values in the above table were calculated by the reviewer and they are different from the corresponding values provided by the firm (see comments below).

**Table 21: Additional Study Information for Esomeprazole (n=84)**

| | |
|---|---|
| Root mean square error, $\ln AUC_{0-t}$ | 0.323369 |
| Root mean square error, $\ln AUC_{0-\infty}$ | 0.287852 |
| Root mean square error, $\ln C_{max}$ | 0.392798 |
| $K_{el}$ and $AUC_{0-\infty}$ determined for how many subjects? | Test: 71; Reference: 73 |
| Do you agree or disagree with firm's decision? | Yes |
| Indicate the number of subjects with the following: | |
| -measurable drug concentrations at 0 hr | None |
| -first measurable drug concentration as $C_{max}$ | None |
| Were the subjects dosed as more than one group? | Yes (2 groups) |

**Comments on Pharmacokinetic and Statistical Analysis:**

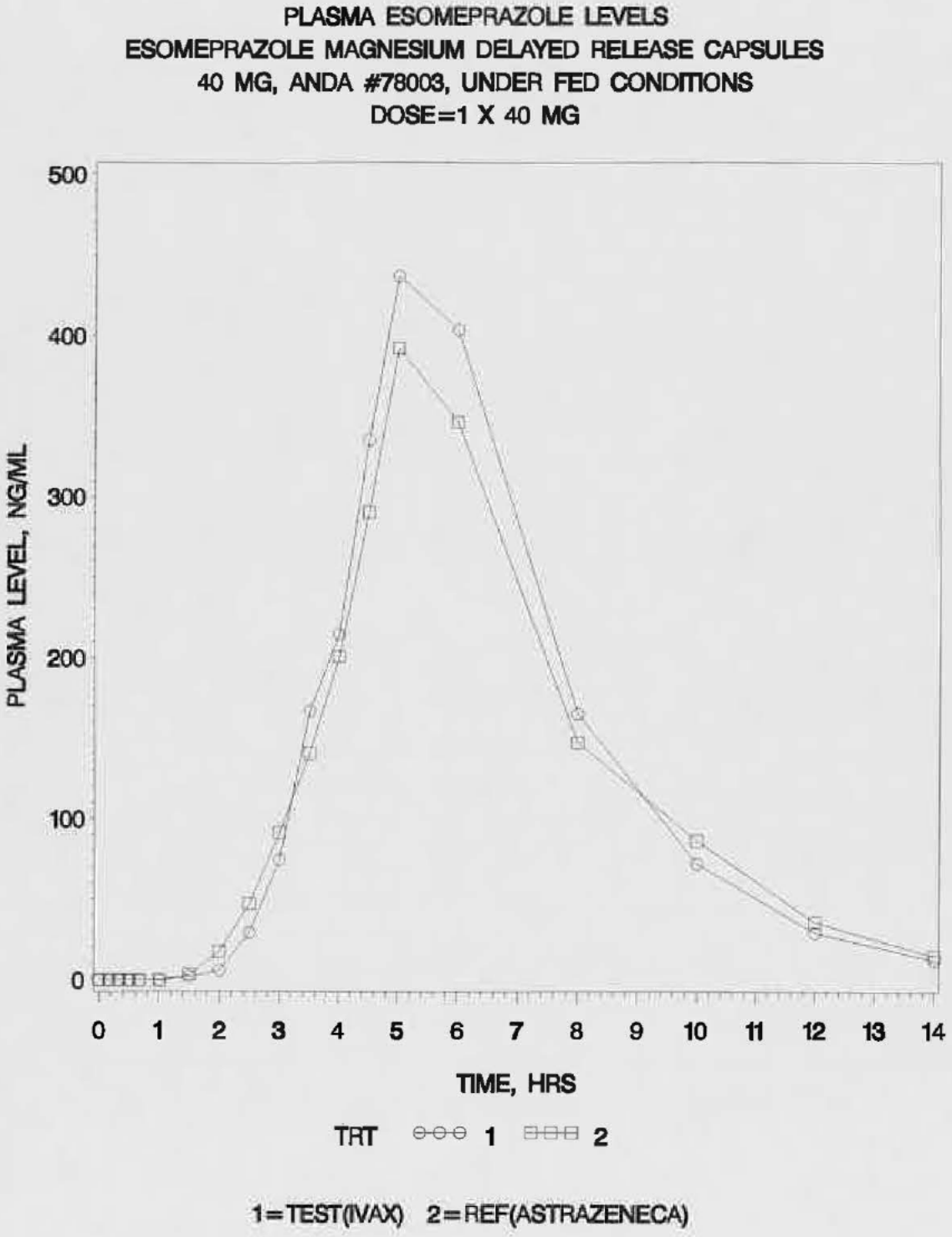
- The fed study was conducted in two groups. When a TRT*GRP effect was used in the SAS model, the following p-values were generated for esomeprazole: $\ln AUC_{0-t}$ 0.5185, $\ln AUC_{0-\infty}$ 0.3795, and $\ln C_{max}$ 0.9367. Since the TRT*GRP effect was not significant ($\alpha$=0.1), the TRT*GRP term was dropped from the analysis as per DBE practice (see attachment).
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer are a little different from the one provided by the firm. This is because the firm dropped GRP term in the model. The reviewer kept GRP term but dropped GRP*TRT.
- The 90% confidence intervals for $\ln AUC_{0-t}$, $\ln AUC_{0-\infty}$, and $\ln C_{max}$, as calculated by the reviewer, are within the acceptable limits of 80-125%.

**Summary/Conclusions, Single-Dose Fed Bioequivalence Study:** The single-dose fed study is **incomplete** due to bioanalytical method deficiencies.

**Table 22: Mean Esomeprazole Plasma Concentrations (ng/mL), Single-Dose Fed Bioequivalence Study**

| Time | Test (n=84) | | Reference (n=84) | | T/R |
|---|---|---|---|---|---|
| | Mean Conc. | %CV | Mean Conc. | %CV | |
| 0 | 0.00 | N/A | 0.00 | N/A | N/A |
| 0.17 | 0.00 | N/A | 0.04 | 916.52 | 0.00 |
| 0.33 | 0.00 | N/A | 0.00 | N/A | N/A |
| 0.5 | 0.00 | N/A | 0.00 | N/A | N/A |
| 0.67 | 0.00 | N/A | 0.00 | N/A | N/A |
| 1 | 0.00 | N/A | 0.16 | 705.50 | 0.00 |
| 1.5 | 2.20 | 525.37 | 3.53 | 507.72 | 0.62 |
| 2 | 6.19 | 358.13 | 17.95 | 342.31 | 0.34 |
| 2.5 | 29.61 | 402.32 | 47.34 | 296.36 | 0.63 |
| 3 | 74.71 | 271.47 | 91.51 | 211.12 | 0.82 |
| 3.5 | 167.01 | 195.52 | 140.56 | 175.15 | 1.19 |
| 4 | 214.73 | 155.56 | 200.90 | 160.58 | 1.07 |
| 4.5 | 335.02 | 107.70 | 290.31 | 118.78 | 1.15 |
| 5 | 436.72 | 80.85 | 392.08 | 78.96 | 1.11 |
| 6 | 403.51 | 68.18 | 345.79 | 76.86 | 1.17 |
| 8 | 165.12 | 98.49 | 147.42 | 104.96 | 1.12 |
| 10 | 72.32 | 125.54 | 86.45 | 131.47 | 0.84 |
| 12 | 29.43 | 152.99 | 35.97 | 174.35 | 0.82 |
| 14 | 12.20 | 190.03 | 14.65 | 202.50 | 0.83 |

**Figure 2: Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study (n=84)**



3. Single-dose Sprinkled Fasting Bioequivalence Study
   a) Study Design

| Study Information | |
|---|---|
| **Study Number** | P1BD05010 |
| **Study Title** | Comparative Bioavailability Study of Esomeprazole Magnesium 40 mg Capsules (Ivax Pharmaceuticals Inc., USA) vs. Nexium® 40 mg Capsules (AstraZeneca LP, USA), with Capsule Contents Sprinkled on Applesauce and Administered In Healthy Male and/or Female Volunteers Under Fasting Conditions |
| **Clinical Site** | Allied Research International Inc., 4520 Dixie Road, Mississauga, Ontario, Canada L4W 1N2 |
| **Principal Investigator** | Deepen Patel, M.D., CCFP |
| **Study/Dosing Dates** | Period I: October 6, 2005; Period II: October 13, 2005 |
| **Analytical Site** | (b) (4) |
| **Analytical Director** | (b) (6) Hons. B.Sc. |
| **Analysis Dates** | October 15, 2005 – October 27, 2005 |
| **Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)** | 22 days[6] |

| **Treatment ID** | **A** | **B** |
|---|---|---|
| **Test or Reference** | Test | Reference |
| **Product Name** | Esomeprazole Magnesium Delayed-Release Capsules | Nexium® (esomeprazole magnesium) Delayed-Release Capsules |
| **Manufacturer** | Cipla for IVAX Pharmaceuticals, Inc. | AstraZeneca |
| **Batch/Lot No.** | Y51286 | N5819 |
| **Manufacture Date** | 6/2005 | N/A |
| **Expiration Date** | N/A | 11/2006 |
| **Strength** | 40 mg | 40 mg |
| **Dosage Form** | Delayed-Release Capsules | Delayed-Release Capsules |
| **Batch Size** | (b) (4) | N/A |
| **Production Batch Size** | | N/A |
| **Potency** | 100.3% | 100.4% |
| **Content Uniformity (mean, %CV)** | 99.8%, 1.1% | 100.3%, 0.5% |
| **Formulation** | See **Table 34** | N/A |
| **Dose Administered** | 1x40 mg, content sprinkled over tablespoon of applesauce | 1x40 mg, content sprinkled over tablespoon of applesauce |
| **Route of Administration** | Oral | Oral |

[6] The firm submitted long-term (freezer) storage stability data for 116 days (at -30°C, nominal)

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| | |
|---|---|
| **No. of Sequences** | 2 |
| **No. of Periods** | 2 |
| **No. of Treatments** | 2 |
| **No. of Groups** | 1 |
| **Washout Period** | 7 days |
| **Randomization Scheme** | AB: 01, 03, 04, 07, 09, 10, 12, 14, 15, 18, 20, 21, 23, 24, 27, 35, 36, 37, 38, 39, 42, 45, 46, 47, 49, 51, 52, 56, 58<br>BA: 02, 05, 06, 08, 11, 13, 16, 17, 19, 22, 25, 26, 28, 29, 30, 31, 32, 33, 34, 40, 41, 43, 44, 48, 50, 53, 54, 55, 57 |
| **Blood Sampling Times** | 0 (x2), 0.17, 0.33, 0.5, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 14 hours post-dose |
| **Blood Volume Collected/Sample** | Same as Fasting study |
| **Blood Sample Processing/Storage** | Same as Fasting study |
| **IRB Approval** | Yes |
| **Informed Consent** | Yes |
| **Subjects Demographics** | See **Table 23** |
| **Length of Fasting before Meal** | Same as Fasting Study |
| **Length of Confinement** | Same as Fasting study |
| **Safety Monitoring** | Same as Fasting study |

**Comments on Study Design:** The study design is **acceptable**.

b) Clinical Results

**Table 23: Demographics of Study Subjects**

| Study No. [illegible] | | |
|---|---|---|
| | Treatment Groups | |
| | [illegible] 40 mg N = 54 | [illegible] 40 mg N = 54 |
| Age (years) | | |
| Mean ± SD | [illegible] | [illegible] |
| Range | [illegible] | [illegible] |
| Groups | | |
| < 18 | [illegible] | [illegible] |
| 18 – 30 | [illegible] | [illegible] |
| 31 – 45 | [illegible] | [illegible] |
| 46 – 65 | [illegible] | [illegible] |
| ≥ 75 | [illegible] | [illegible] |
| Sex | | |
| Female | [illegible] | [illegible] |
| Male | [illegible] | [illegible] |
| Race | | |
| Asian | [illegible] | [illegible] |
| Black | [illegible] | [illegible] |
| Caucasian | [illegible] | [illegible] |
| Hispanic | [illegible] | [illegible] |
| Other | [illegible] | [illegible] |
| Other Factors | | |
| Height (cm) | | |
| Mean ± SD | [illegible] | [illegible] |
| Range | [illegible] | [illegible] |
| Weight (kg) | | |
| Mean ± SD | [illegible] | [illegible] |
| Range | [illegible] | [illegible] |

**Reviewer's note**: Subject BMI (mean, standard deviation) for the study is: 24.0, 2.5

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**Table 24: Dropout Information**

| Subject No | Reason | Period | Replaced? |
|---|---|---|---|
| (b) (6) | Withdrawn by the sponsor due to noncompliance after completing the study | After II | (b) (6) |
| | Voluntarily withdrew from the study due to personal reasons | Before II | |
| | Voluntarily withdrew from the study due to adverse events (intermittent cold) | After I | |

* Subject (b) (6) does not have the same sequence as subject (b) (6)

**Table 25: Study Adverse Events**

| Body System/Adverse Event | Fasted Bioequivalence Study Study No. PHB05010 (N=54)* | |
|---|---|---|
| | Esomeprazole Magnesium 40mg capsules | Nexium® 40mg capsules |
| Body as a whole | | |
| Injection Site Edema | 1 (1.9%) | |
| Injection Site Pain | 3 (5.6%) | 5 (9.3%) |
| Ecchymosis | 2 (3.7%) | 1 (1.9%) |
| Headache | 1 (1.9%) | 1 (1.9%) |
| Accidental Injury | 1 (1.9%) | 1 (1.9%) |
| Fever | | |
| Pain | 1 (1.9%) | |
| Cardiovascular System | | |
| Tachycardia | 1 (1.9%) | 1 (1.9%) |
| Bradycardia | 1 (1.9%) | |
| Hypertension | 1 (1.9%) | 1 (1.9%) |
| Hypotension | 1 (1.9%) | |
| Skin and Appendages | | |
| Rash | | |
| Musculoskeletal | | |
| Twitching | 1 (1.9%) | |
| Total | 14 (25.9%) | 10 (18.5%) |

* Includes only those subjects that were used in the statistical analysis

**Reviewer's note:** The following part of the table represents adverse events data from subjects not included in the statistical analysis.

| Body System/Adverse Event | Fasted Bioequivalence Study Study No. PHB05010 (N=4) | |
|---|---|---|
| | Esomeprazole Magnesium 40mg capsules | Nexium® 40mg capsules |
| Body as a whole | | |
| Infection | | 1 (25%) |
| Total | | 1 (25%) |

**Table 26: Protocol Deviations**

| Type | Subject #s (Test) | Subject #s (Ref.) |
|---|---|---|
| Samples were not centrifuged within 30 min in period I or II | many | many |
| In period I, centrifuged blood samples were stored at temperature above the protocol-specified -20°C for approximately 30 minutes (as high as -17.4°C) | all | all |
| Blood sampling time deviations (samples drawn late) | many | many |

**Comments on Dropouts/Adverse Events/Protocol Deviations:**

- There were a total of 25 (14: test; 11: reference) post-dose adverse events reported by 16 subjects. All events were "mild" in severity, except one of "moderate" severity. 24 of the adverse events (decreased/increased blood pressure, pain/bruising/soreness/ swelling at the venipuncture site, muscle twitch in the neck, right foot pain, elevated heart rate, headache, and cut on finger) were "not" related to the study treatments. The remaining 1 adverse event (elevated blood pressure) was "possibly" related to the study treatments.
- There were two incidents of concomitant medication taken. Subject (b) (6) took acetaminophen approximately 11 days before period I dosing. Subject (b) (6) used Polysporin triple antibiotic ointment topically, approximately 3.5 days after period I dosing, to alleviate pain from a burn. Subject (b) (6) was given 2x500 mg acetaminophen for headache, approximately 10 hours after period II dosing. According to the opinion of the reviewer, none of the concomitant medications would have any significant impact on the study outcome.
- There were several blood draw deviations in the study with a maximum deviation of 12.9 minutes. All the time-points were corrected for any deviation before pharmacokinetic analysis.
- **The adverse events and protocol deviations did not compromise the integrity of the study.**

c) Bioanalytical Results

**Table 27: Assay Quality Control – Within Study**

| | Esomeprazole | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **QC Conc. (ng/mL)** | 5.29 | | 69.42 | | 433.88 | | 991.74 | |
| **Inter day Precision (%CV)** | 4.1 | | 2.8 | | 3.1 | | 3.8 | |
| **Inter day Accuracy (%)** | 102.5 | | 102.0 | | 102.5 | | 101.1 | |
| | | | | | | | | |
| **Cal. Standards Conc. (ng/mL)** | 2.54 | 6.35 | 15.87 | 39.67 | 99.17 | 247.93 | 619.83 | 1363.64 |
| **Inter day Precision (%CV)** | 1.9 | 2.5 | 2.5 | 1.4 | 1.9 | 1.5 | 1.1 | 1.7 |
| **Inter day Accuracy (%)** | 100.0 | 100.0 | 99.8 | 100.4 | 100.5 | 100.4 | 101.0 | 98.9 |
| **Linearity Range (range of r values)** | 0.9994-0.9999 | | | | | | | |

**Comments on Study Assay Quality Control:** None.

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

**Comments on Chromatograms:** None.

**Table 28: SOPs dealing with analytical repeats of study samples**

| SOP No. | Date of SOP | SOP Title |
|---|---|---|
| None provided (NP) | NP | NP |

**Table 29: Additional Comments on Repeat Assays**

| | |
|---|---|
| Were all SOPs followed? | N/A |
| Did recalculation of plasma concentrations change the study outcome? | No |
| Does the reviewer agree with the outcome of the repeat assays? | Yes |
| If no, reason for disagreement | N/A |

**Summary/Conclusions, Study Assays:**

- There were a total of 2090 study samples analyzed. 83 samples (Test: 38, Reference: 45) were reanalyzed, representing 3.97% of the total study assays. All reanalysis were analytical repeats.
- The analytical method and data are **incomplete** due to deficiencies.

d) Pharmacokinetic Results

**Table 30: Arithmetic Mean Pharmacokinetic Parameters for Esomeprazole (n=54)**

Mean plasma concentrations are presented in **Table 33** and **Figure 3.**

| Parameter | Units | Test | | Reference | | T/R |
|---|---|---|---|---|---|---|
| | | Mean | %CV | Mean | % CV | |
| $AUC_{0-t}$ | ng/mL x hr | 2911.60 | 59.24 | 2945.33 | 59.35 | 0.99 |
| $AUC_{0-\infty}$ | ng/mL x hr | 2971.48 | 57.85 | 2957.64 | 59.46 | 1.00 |
| $C_{max}$ | ng/mL | 1214.61 | 39.38 | 1179.02 | 39.91 | 1.03 |
| $T_{max}$ | hr | 2.81 | 37.77 | 2.34 | 36.40 | 1.20 |
| $K_e$ | $hr^{-1}$ | 0.71 | 39.56 | 0.71 | 39.92 | 0.99 |
| $T_{1/2}$ | hr | 1.11 | 31.86 | 1.10 | 33.37 | 1.00 |

**Table 31: Geometric Means and 90% Confidence Intervals for Esomeprazole (n=54)**

| Parameter | Test | Reference | T/R | 90% CI |
|---|---|---|---|---|
| $AUC_{0-t}$ | 2399.85 | 2410.40 | 1.00 | 93.43-106.09 |
| $AUC_{0-\infty}$ | 2424.01 | 2420.86 | 1.00 | 93.99-106.67 |
| $C_{max}$ | 1076.17 | 1069.47 | 1.01 | 90.63-111.73 |

**Reviewer's note:** The values in the above table were calculated by the reviewer.

**Table 32: Additional Study Information for Esomeprazole**

| | |
|---|---|
| Root mean square error, $\ln AUC_{0-t}$ | 0.197013 |
| Root mean square error, $\ln AUC_{0-\infty}$ | 0.196079 |
| Root mean square error, $\ln C_{max}$ | 0.324541 |
| $K_{el}$ and $AUC_{0-\infty}$ determined for how many subjects? | 53 (Test); 54 (Reference) |
| Do you agree or disagree with firm's decision? | Yes |
| Indicate the number of subjects with the following: | |
| -measurable drug concentrations at 0 hr | None |
| -first measurable drug concentration as $C_{max}$ | None |
| Were the subjects dosed as more than one group? | No |

**Comments on Pharmacokinetic and Statistical Analysis:**

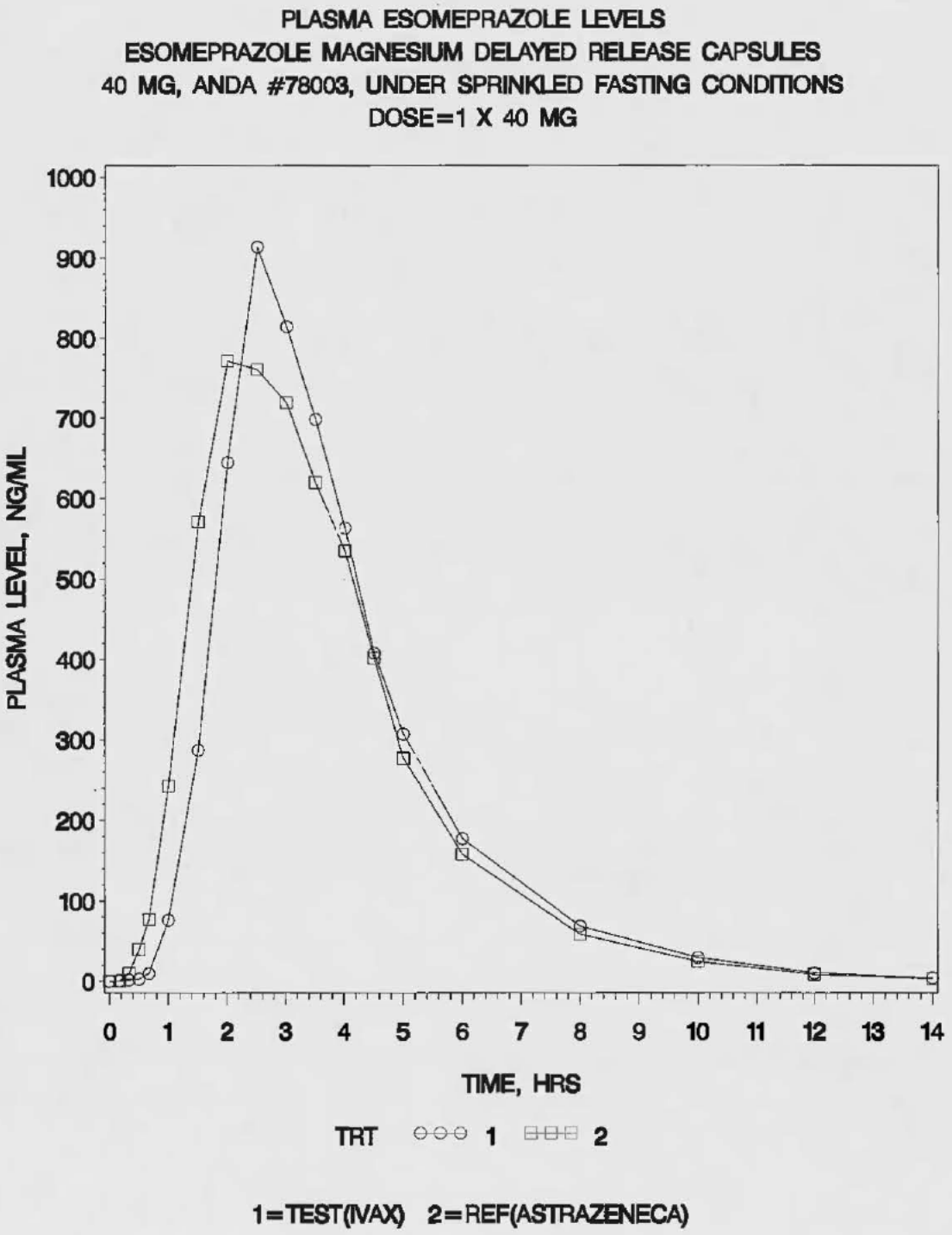
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.
- The 90% confidence intervals for $\ln AUC_{0-t}$, $\ln AUC_{0-\infty}$, and $\ln C_{max}$ are within the acceptable limits of 80-125%.
- Subject (b) (6) was withdrawn by the sponsor after completing the study due to noncompliance. The firm did not provide the explanation of noncompliance. Samples from subject (b) (6) were analyzed, but not used by the firm for the calculation of the pharmacokinetic parameters. The reviewer included data from subject (b) (6) and recalculated the pharmacokinetic parameters and 90% confidence intervals. The 90% confidence intervals for $\ln AUC_{0-t}$, $\ln AUC_{0-\infty}$, and $\ln C_{max}$ were still within the acceptable limits of 80-125%.

**Summary/Conclusions, Single-Dose Sprinkled Fasting Bioequivalence Study:** The single-dose sprinkled fasting study is **incomplete** due to bioanalytical method deficiencies.

**Table 33: Mean Esomeprazole Plasma Concentrations (ng/mL), Single-Dose Sprinkled Fasting Bioequivalence Study**

| Time | Test (n=54) | | Reference (n=54) | | T/R |
|---|---|---|---|---|---|
| | Mean Conc. | %CV | Mean Conc. | %CV | |
| 0 | 0.00 | N/A | 0.00 | N/A | N/A |
| 0.17 | 0.50 | 488.62 | 0.39 | 439.24 | 1.28 |
| 0.33 | 1.78 | 384.21 | 9.90 | 213.27 | 0.18 |
| 0.5 | 2.86 | 260.81 | 39.70 | 188.21 | 0.07 |
| 0.67 | 9.76 | 236.59 | 77.17 | 149.32 | 0.13 |
| 1 | 76.15 | 209.80 | 242.74 | 141.26 | 0.31 |
| 1.5 | 287.12 | 136.49 | 571.46 | 98.30 | 0.50 |
| 2 | 644.69 | 88.66 | 771.67 | 78.18 | 0.84 |
| 2.5 | 913.52 | 66.31 | 760.87 | 69.41 | 1.20 |
| 3 | 814.39 | 62.74 | 719.34 | 64.64 | 1.13 |
| 3.5 | 698.47 | 64.01 | 619.59 | 68.71 | 1.13 |
| 4 | 563.45 | 74.78 | 535.08 | 72.54 | 1.05 |
| 4.5 | 407.95 | 79.19 | 401.82 | 80.29 | 1.02 |
| 5 | 307.01 | 91.43 | 276.98 | 83.24 | 1.11 |
| 6 | 177.40 | 102.81 | 157.83 | 94.77 | 1.12 |
| 8 | 68.70 | 122.74 | 58.50 | 121.23 | 1.17 |
| 10 | 29.48 | 144.61 | 24.60 | 148.61 | 1.20 |
| 12 | 10.34 | 162.60 | 8.48 | 167.59 | 1.22 |
| 14 | 3.98 | 187.52 | 3.45 | 191.39 | 1.15 |

**Figure 3: Mean Plasma Concentrations, Single-Dose Sprinkled Fasting Bioequivalence Study (n=54)**



## B. Formulation Data

**Table 34 Formulation of Esomeprazole Magnesium Delayed-Release Capsules[7]**

| Ingredient | 20 mg (mg/Capsule) | wt/wt (%) 20 mg | 40 mg (mg/Capsule) | wt/wt (%) (40 mg) |
|---|---|---|---|---|
| [redacted] | | | | |

(b) (4)

| Composition | 20 mg Capsule (b) (4) Size 4) | 40 mg Capsule (b) (4) Size 3) |
|---|---|---|
| Body (light turkoise blue opaque) | [redacted] | |
| Cap (light turkoise blue opaque) | | |
| Theoretical Wt. Empty Capsule (mg) | | |
| Gold Ink (spin printing on capsules) | | |

(b) (4)

**Reviewer's note**: The firm did not submit an electronic version of the formulation table.

[7] Modified from the Components and Composition table - Chemistry Review of ANDA #78-003, p.10 (v:\firmsnz\ivaxpharm\ltrs&rev\78003.r01.doc)

### C. Dissolution Data

**FDA METHOD**

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Sampling Times** | Acid stage: 120 minutes<br>Buffer stage: 10, 20, 30, 45 and 60 minutes |
| **Specifications** | Acid stage: NMT (b) (4)% in 120 minutes<br>Buffer stage: NLT (b) (4)% in 30 minutes |

The dissolution review is attached below:

78003D1105.doc

### D. Consult Reviews

None

### E. SAS Output

| | SAS DATA | SAS PROGRAM | SAS OUTPUT |
|---|---|---|---|
| **Single-dose fasting BE study (#P1BD05001)** | ConcPkData.xls | SASprogram.txt | SASoutput.txt |
| **Single-dose fasting BE study (#P1BD05002)** | ConcPkData.xls | SASprogram.txt | SASoutput.txt |
| **Single-dose sprinkled fasting BE study (#P1BD05010)** | ConcPkData.xls | SASprogram.txt | SASoutput.txt |

### F. Additional Attachments

Following is the attachment regarding DBE practice for Group Analysis:

DBE Practice for Group Analysis.pdf

CC: ANDA #78-003
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Reviewer P. Chandaroy
HFD-650/ Project manager C. Thompson
HFD-650/ Team Leader K. R. Dhariwal

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Printed in final on 09/22/06

Endorsements: (Final with Dates)
HFD-650/P. Chandaroy PC 9/22/06
HFD-650/K. R. Dhariwal KRD 9/22/06
HFD-650/D. P. Conner BMD 9/22/06

BIOEQUIVALENCE – **INCOMPLETE** Submission Date: November 23, 2005

✓1. **FASTING STUDY** (STF) Strength: 40 mg
**Clinical:** Allied Research International Inc., 4520 Dixie Road, Mississauga, Ontario, Canada L4W 1N2 **Outcome: IC**

**Analytical:** [redacted] (b) (4)

✓2. **FOOD STUDY** (STP) Strength: 40 mg
**Clinical:** Same as fasting study **Outcome: IC**
**Analytical:** Same as fasting study

✓3. **SPRINKLED FASTING STUDY** (STF-Sprinkled) Strength: 40 mg
**Clinical:** Same as fasting study **Outcome: IC**
**Analytical:** Same as fasting study

✓4. **Dissolution Waiver** (DIW) Strength: 20 mg
**Outcome: IC**

**Outcome Decisions: IC - Incomplete**
WinBio Comments: IC

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-003 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. You did not submit any Standard Operating Procedure for sample repeat analysis. Please submit all relevant Standard Operating Procedures and their effective dates.

2. Twelve samples in the fasting study (#P1BD05001) were reassayed due to Discretionary Rejection. Please explain the meaning of Discretionary Rejection in this context.

3. Sprinkle study (1BD05010): You state that Subject (b) (6) was withdrawn by the investigator due to noncompliance after the completion of the study. Plasma samples of this subject were analyzed. Please explain why this subject was withdrawn after completing the study.

4. You submitted only six summary tables electronically. Please submit dissolution data and formulation data in the DBE-specified format. Please submit these tables in Microsoft Word.

5. We have not received your response to the dissolution deficiency communicated to you earlier. Please provide dissolution testing data for the acid stage. In addition, please indicate if you accept the dissolution specification of NLT (b) (4)% (Q) in 30 minutes for the buffer stage.

The dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b)(4)% in 120 minutes<br>Buffer stage: NLT (b)(4)% in 30 minutes |

Sincerely yours,

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

ANDA: 78-003
Ivax

# DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

| | |
|---|---|
| **ANDA No.** | 78-003 |
| **Drug Product Name** | Esomeprazole Magnesium Delayed Release Capsules |
| **Strength** | EQ 20 mg Base and 40 mg Base |
| **Applicant Name** | IVAX Pharmaceuticals, Inc. |
| **Submission Date(s)** | November 23, 2005 |
| **First Generic** | No |
| **Reviewer** | Yi Zhang, Ph.D. |
| **File Location** | **V:\firmsam\IVAX\ltrs&rev\78003D1105** |
| **Clinical Site** | Allied Research International Inc.<br>4520 Dixie Road<br>Mississauga, Ontario, Canada L4W 1N2 |
| **Analytical Site** | (b) (4) |
| **Dissolution Testing Site** | (b) (4) |

## EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm conducted dissolution testing at the acid stage with a non-FDA-recommended method (b) (4) 0.1M HCl with a paddle speed of 100 rpm). The firm should repeat dissolution testing using the FDA-recommended method (**300 mL** 0.1N HCl with a paddle speed of 100 rpm). The firm's dissolution testing data at the buffer stage with the FDA-recommended method are acceptable (at B1 level). However, the firm's proposed specification of NLT (b) (4) % (Q) in (b) (4) minutes for the buffer stage is not the FDA-recommended specification. The firm should acknowledge its acceptance of the FDA-recommended specification of NLT (b) (4) % (Q) in 30 minutes.

The firm has submitted only 6 electronic summary tables in the Division of Bioequivalence (DBE)-recommended format which are located in the EDR. The firm should submit the summary tables for dissolution data and formulation data electronically.

The dissolution testing is incomplete.

The DBE will review the fasted (Including a sprinkle study) and fed BE studies and the waiver request at a later date.

## RLD METHOD

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl; Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL; Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Sampling Times** | Acid stage: 60, 90 and 120 minutes; Buffer stage: 10, 20, 30, 45 and 60 minutes |
| **Specifications** | Acid stage: NMT (b)(4)% in 120 minutes; Buffer stage: NLT (b)(4)% in 30 minutes |

**Source of Method:** Control documents 05-0636 (06/04), 05-0326 (05/05), 05-1514 (02/06); ANDA (b)(4) DBE Dissolution Database accessed on 03/30/2006.

### Table 1a. Summary of *In Vitro* Dissolution Data at the Acid Stage*

| Product ID | Batch No. | Dosage Form | Conditions | No. of Dosage Units | Collection Times Mean %Dissolved (Range) 120 min | Study Report Location |
|---|---|---|---|---|---|---|
| Esomeprazole Magnesium Delayed Release Capsules | Y51231 | 20 mg Capsules | Dissolution: Apparatus: II Speed of Rotation: 100 rpm Medium: 0.1M HCl Volume: (b)(4) Temperature: 37°C Specification: NMT (b)(4)% (Q) in 120 minutes | 12 | (b)(4) | Section VI (Pages 534-545, Vol. 1.1) |
| Nexium® Capsules | P4879 | | | | | |
| Esomeprazole Magnesium Delayed Release Capsules | Y51232 | 40 mg Capsules | | 12 | | |
| Nexium® Capsules | N5819 | | | | | |

*The reviewer prepared the above table. The firm did not submit the summary table for dissolution data electronically.

## Table 1b. Summary of *In Vitro* Dissolution Data at the Buffer Stage*

| Product ID | Batch No. | Dosage Form | Conditions | No. of Dosage Units | Collection Times Mean %Dissolved (Range) (RSD) | | | | | Study Report Location |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 10 min | 20 min | 30 min | 45 min | 60 min (b) (4) | |
| Esomeprazole Magnesium Delayed Release Capsules | Y51231 | 20 mg Capsules | Dissolution: Apparatus: II Speed of Rotation: 100 rpm Medium: (b)(4) Buffer at pH 6.8 Volume: 1000 mL Temperature: 37°C Specification: NLT (b)(4) % (Q) in (b)(4) minutes. | 12 | | | | | | Section VI (Pages 534-545, Vol. 1.1) |
| Nexium® Capsules | P4879 | | | | | | | | | |
| Esomeprazole Magnesium Delayed Release Capsules | Y51232 | 40 mg Capsules | | 12 | | | | | | |
| Nexium® Capsules | N5819 | | | | | | | | | |

*The reviewer prepared the above table. The firm did not submit the summary table for dissolution data electronically.

## Table 2. SAS Transport Files

| Are the SAS files located in the EDR ? (Yes/No) | |
|---|---|
| **Fasting BE Studies (Including a sprinkle study)** | |
| Plasma Data | Yes |
| PK data | Yes |
| **Fed BE Study** | |
| Plasma Data | Yes |
| PK Data | Yes |

## COMMENTS:

1. Dissolution profiles were generated on 12 capsules each for the test and reference products.

| Drug Product | | Batch No. | Manufacture Date | Expiration Date | Analysis Date |
|---|---|---|---|---|---|
| Esomeprazole Magnesium Delayed Release Capsules | 20 mg | Y51231 | 06/2005 | 06/2007 | 08/19/2005 (Acid stage)<br>08/19/2005 (Buffer stage) |
| | 40 mg | Y51232* | 06/2005 | 06/2007 | 06/03/2005 (Acid stage)<br>07/04/2005 (Buffer stage) |
| Nexium® Capsules | 20 mg | P4879 | | 02/2007 | 08/14/2005 (Acid stage)<br>08/13/2005 (Buffer stage) |
| | 40 mg | N5819 | | 11/2006 | 06/30/2005 (Acid stage)<br>06/30/2005 (Buffer stage) |

* The biolot Y51286 used in the firm's *in vivo* BE studies is packaged from this master lot.

2. The firm conducted the dissolution testing at the acid stage using a non-FDA-recommended method (b) (4) 0.1M HCl with a paddle speed of 100 rpm). The firm's proposed specification of NMT (b) (4)% in 120 minutes for the acid stage is same as the FDA-recommended specification. The firm should repeat dissolution testing using the FDA-recommended method (**300 mL** 0.1N HCl with a paddle speed of 100 rpm) and acknowledge its acceptance of the FDA-recommended method for the acid stage.

3. The firm's dissolution testing data at the buffer stage with the FDA-recommended method are acceptable (at B1 level). However, the firm's proposed specification of NLT (b) (4)% (Q) in (b) (4) minutes for the buffer stage is not the FDA-recommended specification. The firm should acknowledge its acceptance of the FDA-recommended specification of NLT (b) (4)% (Q) in 30 minutes for the buffer stage.

## DEFICIENCY COMMENTS:

1. The firm conducted the dissolution testing at the acid stage using a non-FDA-recommended method. The firm should repeat dissolution testing with the FDA-recommended method (**300 mL** 0.1N HCl with a paddle speed of 100 rpm) and acknowledge its acceptance of the FDA-recommended method for the acid stage.

2. The firm's proposed specification of NLT (b) (4)% (Q) in (b) (4) minutes for the buffer stage is not acceptable. The firm should acknowledge its acceptance of the FDA-recommended specification of NLT (b) (4)% in 30 minutes for the buffer stage.

3. The firm has provided only 6 electronic summary tables in the DBE-recommended format which are located in the EDR and did not submit the summary tables for dissolution data and formulation data. The firm should submit these summary tables electronically.

## RECOMMENDATIONS:

1. The *in vitro* dissolution testing conducted by the firm on its test and reference products is incomplete. The dissolution testing should be conducted using of the following FDA-recommended method:

   **Acid Stage (Acid resistance)*:**

   | | |
   |---|---|
   | Medium: | 0.1N HCl at 37°C |
   | Volume: | 300 mL |
   | Apparatus: | USP Apparatus II (Paddle) at 100 rpm |

   The test products should meet the following specification:

   Not more than (b)(4)% of the labeled amount of the drug in the dosage form is dissolved in 120 minutes.

   *Esomeprazole is an acid labile drug substance. Therefore, at the acid stage, esomeprazole should be measured from the beadlets of the esomeprazole delayed release capsules but not from the dissolution medium of 0.1N HCl. 12 additional capsules of the test products should be tested further at the buffer stage.

   **Buffer Stage (Drug Release):**

   | | |
   |---|---|
   | Medium: | Sodium Phosphate Buffer (pH 6.8) at 37°C |
   | Volume: | 1000 mL |
   | Apparatus: | USP Apparatus II (Paddle) at 100 rpm |

   The test products should meet the following specification:

   Not less than (b)(4)% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

2. The firm conducted the dissolution testing at the acid stage using a non-FDA-recommended method. The firm should repeat dissolution testing with the above FDA-recommended method and acknowledge its acceptance of the FDA-recommended method for the acid stage.

3. The firm's proposed dissolution specification of NLT (b)(4)% (Q) in (b)(4)minutes for the buffer stage is not acceptable. The firm should acknowledge its acceptance of the above FDA-recommended dissolution specification for the buffer stage.

04/24/06

Yi Zhang, Ph.D., Review Branch IV
Division of Bioequivalence
Office of Generic Drugs

Date

4/26/2006

Yih-Chain Huang, Ph.D.
Team Leader, Review Branch IV
Division of Bioequivalence
Office of Generic Drugs

Date

4/29/06

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Date

V:\firmsam\IVAX\ltrs&rev\78003D1105

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-003 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed Release Capsules, 20 mg and 40 mg

The Division of Bioequivalence has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence studies and the waiver request will be conducted later. The following deficiencies have been identified:

1. Your dissolution testing at the acid stage using a non-FDA-recommended method is not acceptable. The dissolution testing should be conducted using the following FDA-recommended method for the acid stage*:

   Medium: 0.1N HCl at 37°C
   Volume: 300 mL
   Apparatus: USP Apparatus II (Paddle) at 100 rpm

   The test products should meet the following specification:

   Not more than (b)(4)% of the labeled amount of the drug in the dosage form is dissolved in 120 minutes.

   *Esomeprazole is an acid labile drug substance. Therefore, at the acid stage, esomeprazole should be measured from the beadlets of the esomeprazole delayed release capsules but not from the dissolution medium of 0.1N HCl.

   Please repeat dissolution testing with the above FDA-recommended method and acknowledge your acceptance of the FDA-recommended method for the acid stage.

2. Your dissolution testing data at the buffer stage with the FDA-recommended method are acceptable. However, your proposed specification of NLT (b)(4)% (Q) in (b)(4) minutes for the buffer stage is not acceptable. The dissolution testing should be conducted using the following FDA-recommended method for the buffer stage:

   Medium: Sodium Phosphate Buffer (pH 6.8) at 37°C
   Volume: 1000 mL

Apparatus: USP Apparatus II (Paddle) at 100 rpm

The test products should meet the following specification:

> Not less than (b) (4) % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please acknowledge your acceptance of the above FDA-recommended specification for the buffer stage.

3. You have provided only 6 electronic summary tables in the DBE-recommended format. Please submit the summary tables for dissolution data and formulation data electronically.

Sincerely yours,

Barbara Dr Savit

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

ANDA 78-003; IVAX Esomeprazole Magnesium Delayed Release Capsules

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Yi Zhang
HFD/650/ Beth Fabian-Fritsch

V:\firmsam\IVAX\ltrs&rev\78003D1105
Printed in final on 04/24/06

Endorsements: (Final with Dates)
HFD-650/ Yi Zhang 04/26/2006
HFD-650/ Yih-Chain Huang 4/26/2006
HFD-650/ D . P. Conner BMD 4/29/06

DISSOLUTION - Incomplete Submission date: November 23, 2005

**[NOTE: The *in vitro* testing is incomplete. The fasted (Including a sprinkle study) and fed BE studies and the waiver request are pending review]**

| | | | |
|---|---|---|---|
| 1. DISSOLUTION (Dissolution Data) | | Strength: | 20 mg |
| | | **Outcome:** | **IC** |
| 2. DISSOLUTION (Dissolution Data) | | Strength: | 40 mg |
| | | **Outcome:** | **IC** |

**Outcome Decisions: IC** – Incomplete
WinBio Comments: IC

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 78003

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

| Food and Drug Administration<br>CDER / Office of Generic Drugs | Document No.:<br>4000-LPS-066 | Version:<br>01 |
|---|---|---|
| **Document Status: Approved** | | |
| **Title:** Approval Routing Summary Form | **Author:** Heather Strandberg | |

**Approval Type:** ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)**

**RPM: EAT Team: TH** **Approval Date: 1/26/2015**

☐ **PI** ☐ **PII** ☐ **PIII** ☒ **PIV** (*eligible for 180 day exclusivity* ☐ **Yes** ☒ **No)** ☐ **MOU** ☒ **RX or** ☐ **OTC**

**ANDA #: 078003 Applicant: IVAX Pharmaceuticals, Inc., an indirect and wholly owned subsidiary of Teva Pharmaceuticals USA Established Product Name: Esomeprazole Magnesium Delayed-release Capsules USP, 20 mg and 40 mg**

**Basis of Submission (RLD): 21153/Nexium/AstraZeneca Pharmaceuticals LP**
*(Is ANDA based on an approved Suitability Petition?* ☐ *Yes* ☒ *No)*

**Does the ANDA contain REMS?** ☐ **Yes** ☒ **No** *(If YES, initiate approval action 6 weeks prior to target action date)*

***Regulatory Project Manager Evaluation:*** **Date: 1/6/2015**

☒ Date last Complete Response (CR) letter was issued -- Date 7/11/2014
☐ Previously reviewed and tentatively approved (if applicable) --- Date N/A

| Date of Application 11/23/2005 | Original Received Date 11/25/2005 | Date Acceptable for Filing 11/25/2005 |
|---|---|---|

| YES | NO | |
|---|---|---|
| ☒ | ☐ | All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)<br>Date of Acceptable Quality 1/5/2015<br>Date of Acceptable Dissolution 1/4/2007<br>Date of Acceptable Bioequivalence 12/4/2014<br>Date of Acceptable Labeling 1/7/2015<br>If applicable:<br>Date of Acceptable Microbiology N/A<br>Date of Acceptable Clinical Review N/A<br>Date of Acceptable REMS N/A |
| ☐ | ☒ | Are consults pending for any discipline? |
| ☐ | ☒ | Has there been an amendment providing for a major change in formulation or new strength since filing?<br>If YES→Verify a second filing review was completed and that all disciplines completed new reviews ☐ |
| ☒ | ☐ | Is there a pending Citizen Petition (CP)? |
| ☒ | ☐ | Overall OC Recommendation is acceptable (EES is acceptable) Date Acceptable: 11/24/2014 Re-evaluation Date: 6/28/2015 |
| ☒ | ☐ | OSI Clinical Endpoint and Bioequivalence Site Inspections are acceptable |
| ☒ | ☐ | Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)?<br>If YES → Email OGD Communications Staff (OGDREQUEST) 30 to 60 days prior to approval, Date emailed 12/1/2014 |
| ***Draft Approval/Tentative Approval Letter*** | | |
| ☒ | ☐ | Approval/Tentative Approval letter is drafted and uploaded to the Final Decision task |
| ***Review Discipline/Division Endorsements*** | | |
| ☒ | ☐ | Division of Legal and Regulatory Support Endorsement completed, Date 1/23/2015 |
| ☒ | ☐ | Paragraph IV Evaluation completed (if applicable), Date 1/22/2015 |
| ☒ | ☐ | Quality Endorsement completed, Date 1/22/2015 |
| ☒ | ☐ | Bioequivalence Endorsement completed, Date 1/15/2015 |
| ☒ | ☐ | Labeling Endorsement completed, Date 1/15/2015 |
| ☐ | ☐ | REMS Endorsement (if applicable), Date N/A |
| ***RPM Team Leader Endorsement and Action Package Verification*** | | |
| ☒ | ☐ | RPM Team Leader Endorsement completed, Date 1/23/2015 |
| ***Final Decision and Letter Sign-off*** | | |
| ☒ | ☐ | Final Decision recommending approval/tentative approval completed, Date 1/26/215 |
| ☒ | ☐ | Approval/Tentative Approval letter electronically signed, Date: 1/26/2015 |
| ***Project Close-Out*** | | |
| ☒ | ☐ | Notify applicant of approval and provide a courtesy copy of the electronically signed letter |
| ☐ | ☒ | Is there a Post Marketing Agreement (PMA)?<br>IF YES → Send email to PMA coordinator, Date emailed _____ |

| ☒ | ☐ | Email OGD Approval distribution list (CDER-OGDAPPROVALS) with approval information |
|---|---|---|

*This page to be completed by the RPM*

***ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION***

***1. Division of Legal and Regulatory Support Endorsement***

**Date:** 1/12/2015
**Name/Title: MHS**

| | |
|---|---|
| Contains GDEA certification: Yes ☒ No ☐ | |
| (required if sub after 6/1/92) | Pediatric Exclusivity System |
| | RLD = _____ NDA# _____<br>Date Checked _____<br>Nothing Submitted ☐<br>Written request issued ☐<br>Study Submitted ☐ |
| Patent/Exclusivity Certification: Yes ☒ No ☐<br>If Para. IV Certification- did applicant:<br>Notify patent holder/NDA holder Yes ☒ No ☐<br>Was applicant sued w/in 45 days: Yes ☒ No ☐<br>Has case been settled: Yes ☒ No ☐<br>Date settled: 1/7/2010<br>Is applicant eligible for 180 day NO<br>Is a forfeiture memo needed: Yes ☒ No ☐<br>If yes, has it been completed | |
| 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:<br>☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH)<br>☐ OTHER: | |

Comments:

ANDA submitted on 11/25/2005, BOS=Nexium NDA 21153, PIII to '974(exp. 3/1/2008), PIII to '505(exp. 10/20/2007), PIII to '230(exp. 10/20/2007), PIV to '960, PIV to '504, PIV to '192(exp. 11/27/2014), PIV to '424, PIV to '103, PIV to '213, PIV to '148, PIV to '085, PIV to '810, PIV to '872(exp. 11/27/2014). ANDA ack for filing with a PIV on 11/25/2005 for the 20 mg and 40 mg strengths(LO dated 1/23/2006).

Patent Amendment rec'd 5/29/2008-PIII to the '974.

Patent Amendment rec'd 8/26/2008-PIV to '070.

Patent Amendment rec'd 8/16/2013-PIV to '960, '504, '192, '424, '103, '213, '148, '085, '810, '872, '070 and '175, PIV to the '175 is a new certification.

Patent Amendment rec'd 4/2/2014-RR from Merck and Co. in Rahway NJ signed but not dated-documentation that this notice was sent on 1/27/2006, notice sent via (b) (4) to AstraZeneca in Newark DE with notice delivered on 8/26/2008, notice sent via (b) (4) to AstraZeneca in Wilmington DE with notice delivered on 8/26/2008, notice sent via (b) (4) to AstraZeneca AB in Sodertaljie Sweden with notice delivered on 8/27/2008, notice sent via (b) (4) to AstraZeneca in Wilmington DE with notice delivered on 8/19/2013, notice sent via (b) (4) to AstraZeneca in Newark DE with notice delivered on 8/19/2013, notice sent via (b) (4) to AstraZeneca AB in Sodertalje Sweden with notice delivered on 8/19/2013

-Cover letter states that TEVA was not sued within 45 days of their 8/16/2013 notice for the '175 patent.
-CA 06 CV 1057 filed in the D of NJ on 3/8/2006 for infringement of the '504, '192, '872, '810, '085,
-TEVA(then IVAX) also filed a DJ in the D of NJ on 4/30/2008 wrt the '960, '424, '103, '213, and '148 patents. This DJ was stayed pending the outcome of CA 2006-CV-1057.
-On 8/28/2008 the D of NJ issued an Order for CA 08-2165
-CA 08 CV 4993 filed in the D of NJ on 10/9/2008 for infringement of the '070 patent
-Consent Judgment entered on 1/7/2010 in CA 08 CV 2165(consolidation of 06 CV 1057, 08 CV 4993 and 05 CV

5553), judgment enjoined TEVA until 5/27/2014 from infringing the '960, '504, '192, '424, '789, '810, '085, '872, '070, '103, '213 and '148 patents, provision #16 of the Judgment indicates that "the above actions, including all counterclaims or affirmative defenses, are dismissed with prejudict and without costs, disbursements or attorneys' fees to any party." Patent Amendment rec'd 12/19/2014-copy of selective waiver of pediatric exclusivity on AstraZeneca letterhead. AZ waives ped exclusivity associated with the '960, '504, '192, '424, '085, '872, and '070 patents.

Current Patents listed in the OB, exp. date with ped ex, outcome:
'960-exp. 5/25/2015, ped waiver granted: not a barrier to AP
'504-exp. 8/3/2015, sued: CA dismissed pursuant to Consent Judgment-not a barrier to AP
'192-exp. 11/27/2014: not a barrier to AP
'424-exp. 11/4/2016, NOT sued: not a barrier to AP
'103-exp. 4/9/2019, NOT sued: not a barrier to AP
'213-exp. 4/9/2019, NOT sued: not a barrier to AP
'148-exp. 4/9/2019, NOT sued: not a barrier to AP
'085-exp. 11/25/2018, sued: CA dismissed pursuant to CJ-not a barrier to AP
'810-exp. 11/3/2019, sued: CA dismissed pursuant to CJ-not a barrier to AP
'872-exp. 11/27/2014, not a barrier to AP
'070-exp. 11/25/2018, sued: CA dismissed pursuant to CJ-not a barrier to AP
'175-exp. 11/25/2018, NOT sued: not a barrier to AP

These drug products-20 mg and 40 mg strengths of Esomeprazole Mg DR Capsules are governed by FDA's post MMA rules as the first ANDA submitted for Esomeprazole was received after the implementation date of MMA -12/9/2003. Therefore, the only applicant that was potentially eligible for 180 day exclusivity for these two drug products was (b) (4) ANDA (b) (4) The OGD is currently completing an evaluation to confirm whether (b) (4) should have precluded the OGD from issuing a timely TA to (b) (4) ANDA on the 30 month anniversary date which had the effect of securing the FTF seat for (b) (4) ANDA. If OGD decides that in retrospect (b) (4) ANDA should not have been TA'd on the 30 month anniversary date then OGD will likely determine that (b) (4) has forfeited their exclusivity seat. Forfeiture of the 180 day exclusivity seat would clear the last barrier to AP for TEVA's ANDA.

Final Recommendation-ANDA is eligible for Full AP due to the selective pediatric waiver granted by AZ. The recommendation for Full AP is contingent on OGD's finalized determination that (b) (4) has forfeited their 180 day exclusivity seat under ANDA (b) (4). OGD is working to issue this Full AP on Friday January 23rd 2015. This will permit completion of the Forfeiture memo and finalization of a related CP response.

2. ***Paragraph IV Evaluation (for ANDAs with PIV certifications or other controversial regulatory issues)***
   **Date: _____Name/Title: _____ Comments:**

   *Or see corresponding endorsement task under the ANDA project within the platform*

3. ***Quality Endorsement by the Office of Pharmaceutical Science***
   **Date: _____Name/Title: _____ Comments:**

   *Or see corresponding endorsement task under the ANDA project within the platform*

4. ***Bioequivalence Endorsement***
   **Date: _____Name/Title: _____ Comments:**

   *Or see corresponding endorsement task under the ANDA project within the platform*

5. ***Labeling Endorsement***
   **Date: _____Name/Title: _____ Comments:**

   *Or see corresponding endorsement task under the ANDA project within the platform*

6. ***REMS Endorsement***
   **Date: _____Name/Title: _____ Comments:**

   *Or see corresponding endorsement task under the ANDA project within the platform*

7. ***RPM Team Leader Endorsement***
   **Date: _____Name/Title: _____ Comments:**

   *Or see corresponding endorsement task under the ANDA project within the platform*

***8. Final Decision***

**Date:** 1/23/2015
**Name/Title: WPR**

Para.IV Patent Cert: Yes ☒ ☐ ☐ No ☐
Pending Legal Action: Yes ☐ ☐ No ☒
Petition: Yes ☒ No ☐
Entered to APTrack database ☐
GDUFA User Fee Obligation Status Met ☒ Unmet ☐
Press Release Acceptable ☒
First Generic Approval ☒
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐

Date PETS checked for first generic drug _____

Comments:

BOS=Nexium NDA 21153. The applicant provided PIV certs to the '504, '424, '103, '213, '148, '085, '810, '070, and '175 patents. Ivax/Teva complied with the notification requirements and litigation was initiated against them for infringement of the '504, '810, '085 and '070 patents within the 45 day period. Ivax/Teva also informed the agency that these cases were dismissed. With regards to the ped exclusivity period still in effect associated with the '960 patent expiring 5/25/2015, Ivax/Teva provided a copy of a letter from AZ that waives this exclusivity period. There is no W/H exclusivity that currently protects the RLD. Full approval is contingent on the determination that (b) (4) has forfeited their 180 day exclusivity seat (b) (4) and completion of a forfeiture memo and finalizing the related CP response. Chemistry acceptable 1/5/2015. Bio acceptable 12/4/2014 (fasting/fed studies and fasting sprinkle study 40 mg). No OSI issues. Labeling acceptable 1/7/2015 TL sign-off and 11/15/2014 AP Summary. EES acceptable till 6/25/2015. Okay for full approval.

EES DATA:

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APPEARS THIS WAY ON ORIGINAL

# Application History:

Click here to enter text.

APPEARS THIS WAY ON ORIGINAL

# Orange Book Report:

Click here to enter text.

APPEARS THIS WAY ON ORIGINAL

**REFERENCES / ASSOCIATED DOCUMENTS**

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

**REVISION HISTORY**

| Version | Effective date | Name | Role | Summary of changes |
|---|---|---|---|---|
| 01 | 10/1/2014 | Heather Strandberg | Author | New Form |

APPEARS THIS WAY ON ORIGINAL

# Internal Meeting Minutes

**Topic**: Esomeprazole Delayed Release Capsules, 20 mg and 40 mg (Control 140139)
**Date:** Friday, April 11th, 2014, 3:30 PM to 4:30 PM
**Meeting Location:** MM2 Third Floor Room 373
**FDA Attendees:** John Peters, Ethan Stier, Xiaojian Jiang, Minglei Cui, Ping Ren, and Nabeel Babaa (meeting recorder)

## Background Summary

This meeting was arranged to discuss issues identified in several applications of the noted drug product and the impact of these findings to the current draft guidance. Control 140139 is intended to revise the current FDA guidance on Esomeprazole Magnesium and request comparative *in vitro* NG tube tests (sedimentation testing, particle size distribution study, recovery testing, and acid resistance stability testing) to compare the performance of the test product to that of the reference product under NG tube administration.

(b) (4) applications in house failed acid resistance test for the reference product. The failed acid resistance data from (b) (4) were summarized and referenced. The ultimate goal of the meeting was to finalize the guidance as there are (b) (4) ANDAs pending its completion, to discuss acid resistance testing condition, and to discuss the allowed difference in particle size between test and reference product if the recovery test passed.

## Discussion

(b) (4)

**ANDA 078003:**

**Acid Resistance Test Data:** It was noted that the firm conducted the acid resistance test in water with pHs of 5.4, 5.9, and 6.4 instead of pH 6, 7 and 8 as recommended. The firm justified this by saying that the former pH values best represent water in hospital setting; however, no reference source for this assertion was provided. For the 20 mg strength, approximately 20% and 80% of reference drug were released from enteric coated pellets after soaking in water (pH 5.4, 5.9 and 6.4) for 30 and 60 minutes, respectively whereas less than (b) (4)% of test product was released under the same conditions. For the 40 mg strength, approximately 90% of reference product was released after soaking in the water for 15, 30 or 60 minutes, whereas less than (b) (4)% of the test product was released under the same treatment conditions.

**Particle Size Microscopy**: It was noted that in the case of the 20 mg and 40 strengths of the reference product, the pellets started to rupture, disintegrate, and were irregular in shape after 30 and 15 minutes of soaking time, respectively. In contrast, for the 20 mg and 40 mg strengths of the test product, the pellets

remained intact throughout soaking and maintained their oval to circular shape. It was noted that if microscopy data are not accurate, particle size data can be measured using laser diffraction. It should be noted that the particle size of the test product is slightly larger than that of reference products based on Microscopy data (approximately $D_{50}$ 0.8 mm reference vs. 0.6 mm test).

(b) (4)

**DBII's Proposal and Discussion:**

1. Based on the above ANDAs, we recommend the in vitro NG tube testing to be conducted in water with pH 5.5, 6.5, and 7.5 at soaking time 0 and 15 min (instead of previous 15, 30 and 60 min).

   Discussion of proposal#1:

   Proposal #1 was agreed upon. It was noted that the pH of tap water ranges from 6.5 to 8.5, and the mean pH value of sterile water pH is 5.5.

2. Discuss with Division of New Drug on issues regarding failed acid resistance test of the RLD after soaking in water for a period of time, e.g. even for 15 min. (note: labeling does indicate immediate delivery)[1]

[1] NDA chemistry indicated that the reference product is stable up to 30 min in tape water with pH 7.8.

Discussion of proposal#2:

Proposal #2 was dismissed. We do not need to discuss with the Division of New Drug on issues regarding failed acid resistance test of the RLD after soaking in water for a period of time, e.g. even for 15 min since the RLD label indicates immediate delivery (the data show acceptable acid resistance at 0 min for the RLD). The in vitro data would be acceptable if the test product shows acid résistance no worse than that of the RLD.

3. How should we evaluate acid resistance testing when the RLD failed acid resistance testing? The acid resistance testing would be acceptable if the test product shows acid résistance no worse than that of the RLD.

   Discussion of proposal#3:

   Proposal #3 pertaining to evaluating acid resistance testing was agreed upon.

4. Ask the FDA lab to conduct the in vitro NG tube study for the reference product and some problematic test product. In history, generic firm submitted acceptable NG tube studies for its product (particle size different, but acceptable recovery and acid resistance test). However, the FDA's lab data showed failed results.

   Discussion of proposal#4:

   It was agreed that the FDA lab conduct the testing on the reference product only and the new guidance not be posted until after the FDA lab completes their analysis. The FDA lab can forward the data on the reference product to the new drug division.

5. How should we evaluate data if the firm does not conduct the pH we recommended for In vitro NG tube testing (such as 78003)

   a. Ask the firm to re-conduct the study in our recommended pH

   b. Further discussion on allowed difference on enteric coated particle size between the test and reference product (include Chemistry division) if recover test is passed.

   c. Studies on NG tube with different material?

   Discussion of proposal#5

   Proposal #5 was agreed upon. We should ask the firm to re-conduct the study in our recommended pH. In this manner, we will accept the test product as long as it doesn't release more than the RLD, even if it technically fails the acid resistance test according to the less than (b)(4)% release criteria.

**Action Items**

1. Deficiency letter can be sent but hold off on posting the new guidance until after the FDA lab conducts its test, per Proposal #4. The new guidance will include our recommended pH values of 5.5, 6.5, and 7.5 for NG tube testing in water, as well as a soaking time of 0 min and 15 min. Ask the FDA lab to conduct the in vitro NG tube study for the reference product and some test product, per Proposal #4. The DB should coordinate with science team on the testing.

2. The drug specific guidance should recommend the laser method for measuring particle size in lieu of microscopy.

3. For ANDA 78003, the firm should conduct the study using our recommended pH. The particle size is acceptable. There is no need to ask for the NG tube study with different materials. The criteria will be: if the test product doesn't release more than the RLD it will pass (even if it technically fails the acid resistance test according to the less than (b)(4)% release criteria).

Draft by: Nabeel Babaa (04/16/2014)

Comments: Minglei Cui (04/18/2014)

Comments: Xiaojian Jiang (04/20/2014)

Comments: Ethan Stier (4/21/2014)

Meeting Minutes concurred by: John Peters (4/28/2014)

---

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

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/s/

---

NABEEL BABAA
04/29/2014

ETHAN M STIER
04/30/2014

# Internal Meeting Minutes

Topic: Nasogastric (NG) Tube In-Vitro Study Requirements

Date: August 7, 2013, 9:30 – 10:30 AM

Attendees: Dale Conner, Ethan Stier, John Peters, Yi Zhang, Aaron Sigler, Kimberly Raines, Xiaojian Jiang, Nitin K. Patel, Chitra Mahadevan

## Inquiry

The Control Team is currently reviewing [redacted] (b) (4) can be administered alternatively by nasogastric (NG) tube or gastric feeding tube. The Division of Bioequivalence II (DBII) has asked sponsors of pending Lansoprazole Delayed-Release Capsules and Orally Disintegrating Tablets (ODT), Esomeprazole DR Capsules, and Omeprazole/Sodium Bicarbonate Oral Suspension ANDAs to perform comparative in vitro tests, including sedimentation testing, particle size distribution study, recovery testing, and acid resistance stability testing, to compare the performance of their test products to that of the RLD. The objectives of this meeting are the following:

1) To determine whether there are any potential safety concerns for NG tube administration, and

2) To develop a policy regarding in vitro testing requirements for products that can be administered via NG tube as per labeling.

## Background

Nasogastric (NG) tubes are sometimes used to administer medication to patients who are unable to safely swallow or tolerate oral intake. One such product that can be administered in this manner is the Proton Pump Inhibitor (PPI), Lansoprazole, which is indicated for active stomach and duodenal ulcers. According to the product labeling, Lansoprazole DR Capsules can be administered alternatively through a combination of syringe and NG tube. Specifically, the label states the following:

Lansoprazole should be taken before eating. Lansoprazole delayed-release capsules SHOULD NOT BE CRUSHED OR CHEWED. Lansoprazole delayed-release capsules – Nasogastric Tube (≥ 16 French) Administration:

For patients who have a nasogastric tube in place, lansoprazole delayed-release capsules can be administered as follows:

- Open capsule.
- Mix intact granules into 40 mL of apple juice. DO NOT USE OTHER LIQUIDS.

- Inject through nasogastric tube into the stomach.
- Flush with additional apple juice to clear the tube.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

Other PPI products, including esomeprazole, omeprazole, and lansoprazole delayed-release orally disintegrating tablets use water instead of apple juice to dissolve the product.

Several FDA adverse event reports have indicated that when dosing Teva's now discontinued ANDA 078730, Lansoprazole Delayed-Release Orally Disintegrating Tablets (LODT) product using an oral syringe or feeding tube, the syringes and feeding tubes (including both G and J tubes) became clogged and blocked. The tablets may not fully disintegrate when water is added to them and/or they may disintegrate but later form clumps. These clumps can adhere to the inside walls of oral syringes and feeding tubes. In some cases, patients have had to seek emergency medical assistance and have their feeding tubes unclogged or removed and replaced.

As a result, an OGD internal meeting was held on March 14, 2011 in response to reports of Teva's LODT clogging feeding tubes. The successful delivery of drug product through a syringe and feeding tube requires that all solid oral dosage form contents are able to safely pass through the tube and not cause occlusions. As a result, DBII has asked (b) (4) sponsors with pending lansoprazole delayed-release capsules, lansoprazole delayed-release orally disintegrating tablets, esomeprazole delayed-release capsules, and omeprazole/sodium bicarbonate oral suspension ANDAs to conduct in vitro tests to compare the performance of their test products to that of the reference product under NG tube administration. Based on the OGD internal meeting, DBII recommends the following comparative in vitro tests:

1) Sedimentation test
2) Particle size distribution study
3) Recovery testing
4) Comparative acid resistance stability testing

At this time, DBII has not asked for in vitro testing for 4 approved lansoprazole delayed-release products (ANDAs 077255, 090331, (b) (4), and 091269).

**Discussion**

In order for a solid oral dosage form to successfully pass through an NG tube, it must possess proper dissolution and physico-chemical characteristics. It must be comprised of small particles and the coating must not become sticky. In addition, the use of some insoluble excipients can lead to stickiness and clumping in the NG tube, potentially leading to a need for replacement of the tube. Therefore, it is very important that a generic product performs the same as, or better than, the RLD. Even though the NG tube administration methods used by nurses and home health care workers cannot be controlled, OGD can standardize in vitro testing methodology in order to ensure equivalence of such products for this approved method of administration.

In vitro testing should be requested if a product is a solid oral dosage form and contains instructions for NG tube administration in the RLD labeling. However, if the product is a BCS Class I (highly permeable and highly soluble) Immediate Release (IR) dosage form, additional in vitro testing is not necessary as the product will disintegrate immediately into a clear solution. If a product does not dissolve immediately, it may lead to blockage of an NG tube. Therefore, test product dissolution is an important consideration. The types of studies that have been requested for the PPI products include sedimentation testing, particle size distribution studies, recovery testing, and comparative acid resistance stability testing. A majority of the time, a 16 French (16F) NG tube should be used for in vitro testing because smaller tubes do not function as well in patients for food or drug administration. In addition, in vitro testing should exhibit non-inferiority rather than equivalence, in the event that the test product performs better than the RLD.

The specific in vitro testing requirements may be different for individual drug products. In order to facilitate developing guidance page language for specific drug products, it is necessary to search databases such as Drugs@FDA, Physician's Desk Reference (PDR), and the American College of Physicians (ACP) to determine which drugs contain NG tube administration in the RLD labeling. Since there is no detailed recommendation of in vitro NG tube testing in the currently posted Product-Specific BE Guidances, such as lansoprazole delayed-release capsules, the identified product guidances will need to be revised. There may be slightly different label instructions based on each individual product, and these differences will need to be considered when drafting guidance revisions.

Currently, only pending ANDA holders of lansoprazole delayed-release capsule, esomeprazole delayed-release capsule, and omeprazole/sodium bicarbonate oral suspension have been asked to submit in vitro NG tube testing. As a result, the sponsors of approved lansoprazole delayed-release capsule ANDAs will be asked to submit in vitro NG tube testing.

**Action Items**

1) Ask sponsors of approved Lansoprazole DR and ODT applications to conduct and submit results of in vitro NG tube studies (DBII Team 7)
2) Determine in vitro study methodology (DBI and DBII)
3) Identify other drugs that require in vitro NG tube testing and determine the model drug to be used for detailed recommendations (Yi/Kim)
4) Revise/create guidance pages for specific drug products requiring in vitro NG tube testing (DBI and DBII)
5) Present topic at bimonthly Safety Meeting

Drafted by Chitra Mahadevan\8/8/13
Revised by Ethan Stier\8/9/13
Revised by John Peters\8/9/13
Revised by Yi Zhang\8/9/13
Revised by Aaron Sigler\8/9/13

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/s/

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CHITRA MAHADEVAN
08/19/2013

ETHAN M STIER
08/30/2013

# BIOEQUIVALENCE AMENDMENT

ANDA 078003

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Teva Pharmaceuticals USA

TEL: (215) 591-3144

ATTN: Robert Vicent

FAX: (201) 489-1403

FROM: Chitra Mahadevan

FDA CONTACT PHONE: (240) 276-8817

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on November 23, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Magnesium Delayed Release Capsules, 20 mg and 40 mg.

Reference is also made to your amendment dated November 13, 2006.

The Division of Bioequivalence II has completed its review of the submissions referenced above and has identified deficiencies which are presented on the attached ____ 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 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 II, 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 is:*

***Office of Generic Drugs***
***Document Control Room, Metro Park North VII***
***7620 Standish Place***
***Rockville, Maryland 20855-2810***

*ANDAs will only be accepted at the new mailing address listed above. 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.*

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 078003

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Esomeprazole Magnesium Delayed Release Capsules, 20 mg and 40 mg

The Division of Bioequivalence II (DB II) has completed its review of your submissions acknowledged on the cover sheet. The following deficiencies have been identified:

**In vitro test for Nasogastric (NG) Tube administration:**

The approved labeling for the reference product states that the product may be administered by a nasogastric tube. Therefore, we request that you perform the following comparative in vitro tests to compare the performance of your test product to that of the reference product.

1. Please determine comparative sedimentation volume and particle size of the granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, in 50 mL of water as follows:

   a) Prepare the catheter tipped syringe (60 mL), remove the syringe plunger, open the capsule and empty the contents of one capsule into the syringe. Insert the syringe plunger, draw up 50 mL of water and shake the syringe vigorously for 15 seconds.

   b) Place the syringe perpendicular to the bench with the tip up and record the sedimentation volume at 0 minutes. Please remove the syringe plunger and determine the particle size of the granules in the syringe.

   c) Using a new set of 12 units, please repeat the process described in step (a) to prepare the granule dispersion, incubate for 15 minutes, and record the sedimentation volume and determine the particle size of granules.

   Please provide all particle size data at the D10, D50, and D90 levels. You may use the markings on the syringe to note the sedimentation volume. Please provide a qualitative description, e.g., particle aggregation and particles

adhering to the syringe walls. Please take photos of the contents of the syringe at various intervals throughout the testing process.

2. Please determine the comparative particle size of the granule dispersion using 12 units each of the test and reference products, 20 mg and 40 mg strengths, after delivery to the container through a combination of syringe and the 8 French nasogastric tube at 0 and 15 minutes as follows:

   a) Prepare the feeding tube according to the manufacturer's directions. Repeat the process described in 1(a) to prepare the granule dispersion.

   b) Attach the syringe to the feeding tube, and using the syringe plunger, push the granule dispersion through the syringe and the feeding tube into a collection container.

   c) Remove the syringe from the feeding tube, draw up additional water, and flush the system by pushing the fluid through the feeding tube into the container. Perform particle size analysis of the collected fluid.

   d) Repeat the testing described above with a fresh set of 12 units. However, after suspending the capsule content in step a, wait 15 minutes prior to injecting the contents into the feeding tube.

   Please visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all observations and submit supporting photographs. Please provide the particle size data at the D10, D50 and D90 levels and report the flush volume used in these studies.

3. Please conduct comparative recovery studies to determine what percentage of the initial dose suspended in water passes through the 8 French nasogastric tubes. Please use 12 units of both strengths of the test and the reference products in 50 mL water and follow the process outlined in #2 (above). Determine the percentage of esomeprazole recovered at the tube exit relative to the initial dose using a validated assay method for both the test and the reference products at 0 and 15 minutes. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. The DB II will set an interim

specification based upon review of the submitted data. If high variability is observed, the number of units used for this test may be increased.

4. Please conduct comparative acid resistance stability testing using 12 units of both strengths of the test and the reference products. Please use the following method:

   a) Prepare the granule dispersion in 50 mL of water (hold for 15 minutes), and collect the contents of the granule dispersion at the tube exit.

   b) Transfer the contents of the granule dispersion into a dissolution vessel containing 300 mL of 0.1 N HCl maintained at 37°C ± 0.5°C.

   c) Flush the nasogastric tube with additional water and transfer any remaining contents into the dissolution media mentioned above.

   d) Acid resistance testing should be conducted using USP Apparatus II at 100 rpm. Analyze the amount of esomeprazole released at 120 minutes.

5. Please submit standard operating procedures for sedimentation, particle size, acid resistance and recovery testing. Please submit individual data, mean values, standard deviations, coefficient of variation (CV%), and plots of percent release of esomeprazole in the acid resistance test. Photographs should be submitted to support your observations and results. Please also provide the pre-study and within-study assay validation report.

   Please conduct all of the above testing on unexpired test and reference batches.

***Please note that the following deficiencies were provided to you in the DB II deficiency letter dated 01/10/2007 after our review of your original application and are provided to you again since a response was never received.***

6. For the fasting study (#P1BD05001), although you have provided an explanation for the 12 "Discretionary Rejection" reassays, you did not provide any supporting data along with the response. Please provide supporting data, such as chromatograms of the original 12 samples showing the abnormal internal standard responses and 12

original assay values. In the response, you also stated that visually observed discrepancy in the remaining sample volumes in the injection vials subjected to "Discretionary Rejection" were noted. Please provide evidence in support of that statement.

7. For the fasting study (#P1BD05001), you have conducted sample reanalysis based on "Discretionary Rejection," but there is no mention of "Discretionary Rejection" in any of the submitted Standard Operating Procedures (SOPs). Since all reasons for reanalysis should be included in the SOPs *a priori*, please explain the absence of "Discretionary Rejection," as a cause for reanalysis, in the SOPs.

8. The DB II agrees that the dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37°C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b)(4)% in 120 minutes<br>Buffer stage: NLT (b)(4)% in 30 minutes |

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

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BARBARA M DAVIT
09/26/2012

** Please email me at chan.park@fda.hhs.gov to confirm that you have received this labeling comment.

**Telephone Fax**

ANDA 078003

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park
North I
7520 Standish Place
Rockville, MD 20855-2773
***240-276-8951***

TO: Teva Pharmaceuticals USA TEL: 201-930-2230

ATTN: Patricia Jaworski FAX: 201-489-1403

FROM: Chan Park

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Osomeprazole magnesium D-R Capsules.

**Pages (including cover): 4**

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**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

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ANDA Number: ANDA 078003 Date of Submission: September 22, 2009

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. It appears that a patent "741170" was granted to the reference listed drug, Nexium Delayed-Release Capsules, per the electronic Orange Book. Please submit your patent certification regarding this patent.

   b. We acknowledge that all labeling pieces will be of actual size, color and clarity when final printed labeling is submitted.

   c. We strongly encourage you to include the point-to-point response to the Agency's comments as it would help expedite the review process.

2. CONTAINER – 30s, 90s, and 1000s

   a. Please revise to read as follows and/or comment:

      20 mg – *Each delayed–release capsules contains 20 mg esomeprazole (present as (b) (4) mg of esomeprazole magnesium dihydrate)

      40 mg - *Each delayed –release capsules contains 40 mg esomeprazole (present as (b) (4) mg of esomeprazole magnesium dihydrate)

   b. We recommend that you include a pharmacist directive regarding the patient information leaflet.

3. (b) (4)

4.

5. INSERT

   a. GENERAL

      Please note that updated Nexium® labeling was approved on January 20, 2012. Please revise your labeling accordingly. Please ensure that the highlight sections and the entire insert of the final printed labeling can easily be read and that the point type not be smaller than 6. We refer you to 21 CFR 201.56(d) regarding PLR format for further guidance..

   b. DESCRIPTION

      As requested in the last deficiency letter, please list the components of the imprinting (b) (4) the dye(s) at a minimum, if there are any.

c. DOSAGE AND ADMINISTRATION

(b) (4)

6. PATIENT INFORMATION LEAFLET

a. See comment 5(a) above.

b. Please describe your plan for supplying the patient information leaflet with your product. (e.g., how many leaflets will you supply for each container size and how will these leaflets be supplied.)

c. We recommend that the font size of the final printed patient information leaflet be 6 pts, at a minimum, for sufficient readability.

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

If you have any questions, please call Chan Park at 240-276-8951 or send e-mail to chan.park@fda.hhs.gov

*{See appended electronic signature page}*

_____

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

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CHAN H PARK
04/02/2012

**QUALITY DEFICIENCY - MINOR**

ANDA 078003

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: IVAX Pharmaceuticals, Inc.

TEL: 215-293-6150

ATTN: Patricia Jaworski

FAX: 201-489-1403

FROM: Frank J. Nice

FDA CONTACT PHONE: (240) 276-8555

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 23, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg.

Reference is also made to your amendment dated August 19, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ 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:*

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***Office of Generic Drugs, CDER, FDA***
***Document Control Room, Metro Park North VII***
***7620 Standish Place***
***Rockville, Maryland 20855***

*All ANDA documents will only be accepted at the new mailing address listed above. 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/*

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ANDA: 078003

APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg

A. The deficiencies presented below represent Minor deficiencies.

1. The amendment for the DMF 18821 has been reviewed and found inadequate. The DMF holder has been notified.

2. (b) (4)

3.

4.

5.

6.

7.

8.

9.

(b) (4)

10.

11.

12.

13.

Sincerely yours,

{See appended electronic signature}

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

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RADHIKA RAJAGOPALAN
03/07/2012
For Glen Smith,

# Telephone Fax

ANDA 78-003

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8995

TO: IVAX Pharmaceuticals, Inc.
An indirect, wholly owned subsidiary of
Teva Pharmaceuticals USA

TEL: 201-293-6150 or 215-293-6151

FAX: 201-489-1403

ATTN: Patricia Jaworski

FROM: Sarah Park

Dear Sir or Madam:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg.

**Pages (including cover):** 8

**SPECIAL INSTRUCTIONS:**

Please see attached.

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**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

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| | |
|---|---|
| ANDA Number: | 78-003 |
| Date of Submission: | May 29, 2008 and September 12, 2008 (Amendments) |
| Applicant's Name: | IVAX Pharmaceuticals, Inc.<br>(An indirect, wholly owned subsidiary of TEVA Pharmaceuticals USA) |
| Established Name: | Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg |
| Proprietary Name: | None proposed |

---

Labeling Deficiencies:

1. CONTAINER [bottles of 30, 90 and 1000]

   a. Please submit final printed labels that are of actual size, color and clarity.

   b. Please revise the expression of quantity to read XX CAPSULES, rather than TABLETS.

   c. Please delete the pictorial of the capsule.

2. (b) (4)

3.

4. INSERT

   a. GENERAL COMMENTS

      i. Please revise your labeling to include a Patient Package Insert in accordance with the approved labeling for the referenced listed drug, Nexium® Delayed-Release Capsules, NDA 21-153/S-029, approved January 11, 2008 (see attachment).

      ii. Please explain why you have revised the description of the drug product in the insert from “pellets” to “granules”.

   b. DESCRIPTION: Please include the components of the imprinting ink in the list of inactive ingredients.

   c. CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption, first paragraph:

i. Revise the first sentence as follows: “Esomeprazole magnesium delayed-release capsules and Esomeprazole magnesium for delayed-release oral suspension contain a bioequivalent enteric-coated granule formulation of esomeprazole magnesium.”

ii. Add the following as the second sentence: “Bioequivalency is based on a single dose (40 mg) study in 94 healthy male and female volunteers under fasting condition.”

d. DOSAGE AND ADMINISTRATION

i. Replace the first paragraph with the following: “The recommended dosages are outlined in the table below. Esomeprazole delayed-release capsules should be taken at least one hour before meals.

ii. Table – Revise the title as follows: “Recommended Dosage Schedule of Esomeprazole”.

iii. Administration Options, third paragraph, first sentence – “Alternatively, for patients…”

iv. Administration Options, fourth paragraph, first sentence – “…60 mL catheter tipped syringe…”

v. Administration Options, fifth paragraph – Delete the fifth paragraph which states, “The suspension must be used immediately after preparation.”

Please revise your labels and labeling as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by- side comparison of your proposed labeling with your last submission with all differences annotated and explained.

*{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

Enclosure: Patient Package Insert

## PATIENT INFORMATION

**NEXIUM®** (nex-e-um) (esomeprazole magnesium)
Delayed-Release Capsules and Delayed-Release Oral Suspension

Read the Patient Information that comes with NEXIUM before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

If you have any questions about NEXIUM, ask your doctor.

**WHAT IS NEXIUM?**
NEXIUM is a prescription medicine called a proton pump inhibitor (PPI).

NEXIUM is used in adults:

- to treat the symptoms of gastroesophageal reflux disease (GERD). NEXIUM may also be prescribed to heal acid-related damage to the lining of the esophagus (erosive esophagitis), and to help continue this healing.

  GERD is a chronic condition (lasts a long time) that occurs when acid from the stomach backs up into the esophagus (food pipe) causing symptoms, such as heartburn, or damage to the lining of the esophagus. Common symptoms include frequent heartburn that will not go away, a sour or bitter taste in the mouth, and difficulty swallowing.

- to reduce the risk of stomach ulcers in some people taking pain medicines called non-steroidal anti-inflammatory drugs (NSAIDs).
- to treat a stomach infection (Helicobacter pylori), along with the antibiotics amoxicillin and clarithromycin.
- for the long-term treatment of Zollinger-Ellison Syndrome. Zollinger-Ellison Syndrome is a rare condition in which the stomach produces a more than normal amount of acid.

For adolescents 12 to 17 years of age, NEXIUM may be prescribed for short-term treatment of GERD.

NEXIUM has not been shown to be safe and effective in children under the age of 12.

**WHO SHOULD NOT TAKE NEXIUM?**
Do not take NEXIUM if you:

- are allergic to any of the ingredients in NEXIUM. See the end of this leaflet for a complete list of ingredients in NEXIUM.
- Are allergic to any other Proton Pump Inhibitor (PPI) medicine

**WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING NEXIUM?**

Tell your doctor about all your medical conditions, including if you:

- have liver problems
- are pregnant, think you may be pregnant, or are planning to become pregnant. It is not known whether taking NEXIUM during pregnancy may harm your unborn baby.
- are breastfeeding or planning to breastfeed. You should not breastfeed while taking NEXIUM. Talk with your doctor about the best way to feed your baby if you take NEXIUM.

Tell your doctor about all of the medicines you take including prescription and non-prescription drugs, vitamins and herbal supplements. NEXIUM may affect how other medicines work, and other medicines may affect how NEXIUM works. Especially tell your doctor if you take:

- warfarin (COUMADIN)
- ketoconazole (NIZORAL)
- voriconazole (VFEND)
- atazanavir (REYATAZ)
- products that contain iron
- digoxin (LANOXIN, LANOXICAPS)

**HOW SHOULD I TAKE NEXIUM?**

- Take NEXIUM exactly as prescribed by your doctor.
- Do not change your dose or stop NEXIUM without talking to your doctor.
- Take NEXIUM at least 1 hour before a meal.
- Swallow NEXIUM capsules whole. Never chew or crush NEXIUM.
- If you have difficulty swallowing NEXIUM capsules, you may open the capsule and empty the contents into a tablespoon of applesauce. Be sure to swallow the applesauce right away. Do not store it for later use.
- If you forget to take a dose of NEXIUM, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose on time. Do not take a double dose to make up for a missed dose.
- If you take too much NEXIUM, tell your doctor right away.
- See the “Patient Instructions for Use” at the end of this leaflet for instructions how to take NEXIUM Delayed-Release Oral Suspension, and how to mix and give NEXIUM Delayed-Release Capsules and NEXIUM For Delayed-Release Oral Suspension, through a nasogastric tube or gastric tube.

**WHAT ARE THE POSSIBLE SIDE EFFECTS OF NEXIUM?**

The most common side effects with NEXIUM may include:

- Headache
- Diarrhea
- Nausea
- Gas
- Abdominal pain
- Constipation
- Dry mouth

Tell your doctor about any side effects that bother you or that do not go away. These are not all the possible side effects with NEXIUM. Talk with your doctor or pharmacist if you have any questions about side effects.

**HOW SHOULD I STORE NEXIUM?**

- Store NEXIUM at room temperature between 59°F to 86°F (15°C to 30°C).
- Keep the container of NEXIUM closed tightly.

Keep NEXIUM and all medicines out of the reach of children.

**GENERAL ADVICE**

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use NEXIUM for a condition for which it was not prescribed. Do not give NEXIUM to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet provides a summary of the most important information about NEXIUM. For more information, ask your doctor. You can ask your doctor or pharmacist for information that is written for healthcare professionals. For more information, go to www.purplepill.com or call toll free 1-800-463-9486.

**PATIENT INSTRUCTIONS FOR USE**

For instructions on taking Delayed-Release Capsules, please see "**HOW SHOULD I TAKE NEXIUM**?"

Take NEXIUM Delayed-Release Oral Suspension as follows:

- Empty the contents of a packet into a container with 1 tablespoon (15 mL) of water
- Stir.
- Leave 2 to 3 minutes to thicken.
- Stir and drink within 30 minutes.

If any medicine remains after drinking, add more water, stir, and drink right away.

NEXIUM Delayed-Release Capsules and NEXIUM for Delayed-Release Oral Suspension may be given through a nasogastric tube (NG tube) or gastric tube, as prescribed by your doctor. Follow the instructions below:

NEXIUM Delayed-Release Capsules:

- Open the capsule and empty the granules into a 60 mL (cc) catheter tipped syringe. Mix with 50 mL (cc) of water. Use only a catheter tipped syringe to give NEXIUM through a NG tube.
- Replace the plunger and shake the syringe well for 15 seconds. Hold the syringe with the tip up and check for granules in the tip.
- Do not give the granules if they have dissolved or have broken into pieces.
- Attach the syringe to the NG tube and give the medicine in the syringe through the NG tube into the stomach.
- After giving the granules, flush the NG tube with more water.

NEXIUM For Delayed-Release Oral Suspension:

- Add 15 mL of water to a catheter tipped syringe and then add the contents of a NEXIUM packet (as instructed by your doctor). Use only a catheter tipped syringe to give NEXIUM through a NG tube or gastric tube.
- Shake the syringe right away and then leave it for 2 to 3 minutes to thicken.
- Shake the syringe and give the medicine through the NG or gastric tube (French size 6 or larger) into the stomach within 30 minutes.
- Refill the syringe with 15 mL (cc) of water.
- Shake and flush any remaining contents from the NG tube or gastric tube into the stomach.

**WHAT ARE THE INGREDIENTS IN NEXIUM?**
Active ingredient: esomeprazole magnesium trihydrate

**Inactive ingredients in NEXIUM Delayed-Release Capsules (including the capsule shells):** glyceryl monostearate 40-55, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, triethyl citrate, gelatin, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C Yellow #10.

**Inactive granules in NEXIUM Delayed-Release Oral Suspension**: dextrose, xanthan gum, crospovidone, citric acid, iron oxide, and hydroxypropyl cellulose.

NEXIUM is a registered trademark of the AstraZeneca group of companies.
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AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

Item number
December 2007

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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.**

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/s/
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Soojung Sarah Park
11/24/2008 06:11:40 PM
For Wm Peter Rickman

**MINOR AMENDMENT**

ANDA 78-003

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: IVAX Pharmaceuticals, Inc. TEL: 215-293-6150

ATTN: Patricia Jaworski FAX: 201-489-1403

FROM: Theresa Liu FDA CONTACT PHONE: (240) 276-8555

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 23, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg.

## ***SPECIAL INSTRUCTIONS:***

## ***Please submit your response in electronic format. This will improve document availability to review staff.***

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.

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address

**CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 78-003 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg

A. The deficiencies presented below represent Minor deficiencies.

(b) (4)

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(b) (4)

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Sincerely yours,

***{electronic signature on file}***

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

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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.**

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/s/
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Damaris Maldonado
8/5/2008 12:09:31 PM

# Telephone Fax

ANDA 78-003

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-7344

TO: IVAX Pharmaceuticals, Inc.

TEL: 845-267-2444 ext. 201

ATTN: Patricia Jaworski

FAX: 845-268-0117

FROM: Sarah Park

Dear Sir or Madam:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg.

**Pages (including cover): __4__**

**SPECIAL INSTRUCTIONS:**

Please see attached.

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**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

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| | |
|---|---|
| ANDA Number: | **78-003** |
| Date of Submission: | **November 23, 2005 (Original)** |
| Applicant's Name: | **IVAX Pharmaceuticals, Inc.** |
| Established Name: | **Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg** |
| Proprietary Name: | **None proposed** |

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Labeling Deficiencies:

(b) (4)

INSERT

GENERAL COMMENTS

a. Due to changes in the insert labeling for the reference listed drug, Nexium® Delayed-Release Capsules, NDA 21-153/S-027, approved April 27, 2007, please revise your labeling to be in accordance with the approved referenced listed drug labeling.

b. You should address all exclusivities and patents listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") and revise your insert labeling accordingly. Specifically, please address the following:

   i. The expiration date for Patent No. 4,738,974*PED has changed from "October 19, 2007" to "March 1, 2008". Please provide a revised patent certification.

   ii. You did not provide an Exclusivity Statement in your original ANDA submission dated November 23, 2005. Exclusivities I-484, I-504 and NPP are now listed in the Electronic Orange Book. Please provide an exclusivity statement.

c. You stated that the (b) (4) However, you did not provide a quantitive composition of the gold ink. Please provide a quantitive composition of the gold ink. (b) (4)

Please revise your labels and labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA. Please ensure that the electronic documents are printable.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by- side comparison of your proposed labeling with your last submission with all differences annotated and explained.

*{See appended electronic signature page}*

_____

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/
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Lillie Golson
5/11/2007 12:07:37 PM
Lillie Golson for Wm. Peter Rickman

# BIOEQUIVALENCY AMENDMENT

ANDA 78-003

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: IVAX Pharmaceuticals, Inc. TEL: 845-267-2444 Ext. 201

ATTN: Patricia Jaworski FAX: 845-268-0117

FROM: Christina Thompson PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on November 23, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg.

Reference is also made to your amendment dated November 13, 2006.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __2__ 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:**

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-003 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. For the fasting study (#P1BD05001), although you have provided explanation for the 12 "Discretionary Rejection" reassays, you did not provide any supporting data along with the response. Please provide supporting data, such as chromatograms of the original 12 samples showing the abnormal internal standard responses and 12 original assay values. In the response, you have also stated that visually observed discrepancy in remaining sample volumes in the injection vials subjected to "Discretionary Rejection" were noted. Please provide evidence in support of that statement.

2. For the fasting study (#P1BD05001), you have conducted sample reanalysis based on "Discretionary Rejection", but there is no mention of "Discretionary Rejection" in any of the submitted Standard Operating Procedures (SOPs). Since all reasons for reanalysis should be included in the SOPs *a priori*, please explain the absence of "Discretionary Rejection", as a cause for reanalysis, in the SOPs.

The DBE agrees that the dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b)(4)% in 120 minutes<br>Buffer stage: NLT (b)(4)% in 30 minutes |

Sincerely yours,

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

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/s/
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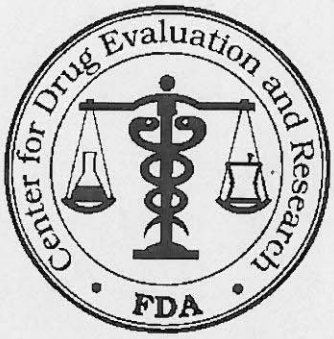
Barbara Davit
1/10/2007 10:22:18 AM
Signing for Dale P Conner

# BIOEQUIVALENCY AMENDMENT

ANDA 78-003

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: IVAX Pharmaceuticals, Inc.

TEL: 845-267-2444 Ext. 201

ATTN: Patricia Jaworski

FAX: 845-268-0117

OCT 0 3 2006

FROM: Christina Thompson

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on November 23, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 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 __2__ 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.

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-003 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. You did not submit any Standard Operating Procedure for sample repeat analysis. Please submit all relevant Standard Operating Procedures and their effective dates.

2. Twelve samples in the fasting study (#P1BD05001) were reassayed due to Discretionary Rejection. Please explain the meaning of Discretionary Rejection in this context.

3. Sprinkle study (1BD05010): You state that Subject #5 was withdrawn by the investigator due to noncompliance after the completion of the study. Plasma samples of this subject were analyzed. Please explain why this subject was withdrawn after completing the study.

4. You submitted only six summary tables electronically. Please submit dissolution data and formulation data in the DBE-specified format. Please submit these tables in Microsoft Word.

5. We have not received your response to the dissolution deficiency communicated to you earlier. Please provide dissolution testing data for the acid stage. In addition, please indicate if you accept the dissolution specification of NLT (b) (4) % (Q) in 30 minutes for the buffer stage.

The dissolution testing should be conducted using the following FDA-recommended method:

| | |
|---|---|
| **Medium** | Acid stage: 0.1N HCl<br>Buffer stage: Sodium Phosphate Buffer, pH 6.8 |
| **Volume** | Acid stage: 300 mL<br>Buffer stage: 1000 mL |
| **Temperature** | 37 °C |
| **Apparatus** | II (Paddle) |
| **Rotational Speed** | 100 rpm |
| **Specifications** | Acid stage: NMT (b) (4) % in 120 minutes<br>Buffer stage: NLT (b) (4) % in 30 minutes |

Sincerely yours,

for Barbara M Sauit

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

ANDA: 78-003
Ivax

# MINOR AMENDMENT

ANDA 78-003

APR 12 2006

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: IVAX Pharmaceuticals, Inc.

TEL: 845-267-2444 Ext. 201

ATTN: Patricia Jaworski

FAX: 845-268-0117

FROM: Yoon Kong

PROJECT MANAGER: (301) 827-5791

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 23, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg.

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.

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YK 4/11/06

## CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-003 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg

A. The deficiencies presented below represent Minor deficiencies.

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7. It is noted that the analytical method and methods validation data for the drug substance provided in this ANDA application is the same as that provided in DMF 18821. We have

provided our concerns in DMF 18821 regarding the analytical methods and the method validation package. Please also address these concerns here and provide updated data as appropriate.

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B. In addition to responding to the deficiencies presented above, please note and acknowledge the following:

1. DMF 18821, Esomeprazole magnesium dihydrate has been reviewed and found inadequate. The DMF holder has been informed. Please indicate in your response that the holder has responded to the deficiencies.

2. Please provide updated data from your on-going stability study.

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

4. A satisfactory CGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

Sincerely yours,

M. Scott Jansen for

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

**ANDA CHECKLIST**
**FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION**

**ANDA Nbr: 78-003** **FIRM NAME**: IVAX PHARMACEUTICALS INC.

**RELATED APPLICATION(S):** NA

**First Generic Product Received? NO**

**DRUG NAME: ESOMEPRAZOLE MAGNESIUM**
**DOSAGE FORM: DELAYED RELEASE TABLETS, 20 MG AND 40 MG**

| **Bio Assignments:** | | ☐ **Micro Review** |
|---|---|---|
| ☒ **BPH** | ☐ **BCE** | |
| ☐ **BST** | ☒ **BDI** | |

**Random Queue: 7**
Chem Team Leader: Scott Furness PM: Yoon Kong Labeling Reviewer: Koung Lee

| | |
|---|---|
| **Letter Date**: NOVEMBER 23, 2005 | **Received Date**: NOVEMBER 25, 2005 |
| **Comments: EC- 2 YES** **On Cards:** YES<br>**Therapeutic Code:** 8015662 PROTON PUMP INHIBITORS | |
| **Archival Format:** PAPER **Sections** I **(356H Sections per EDR Email)**<br>**Review copy**: YES E-Media Disposition: YES SENT TO EDR<br>Not applicable to electronic sections<br>Field Copy Certification (Original Signature) YES | |
| **Methods Validation Package** (3 copies PAPER archive) **YES**<br>(Required for Non-USP drugs) YES | |
| **Cover Letter** YES | **Table of Contents** YES |
| PART 3 Combination Product Category N Not a Part3 Combo Product<br>(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm | |

| | |
|---|---|
| **Reviewing CSO/CST** Stanley Shepperson<br>**Date Stanley Shepperson, 17-Jan-2006** | **Recommendation:**<br>☒ **FILE** ☐ **REFUSE to RECEIVE** |
| **Supervisory Concurrence/Date:** Martin Shimer Date: 23 Jan 2006 | |
| **ADDITIONAL COMMENTS REGARDING THE ANDA:** | |
| **Top 200 Drug Product:** | |

ACCEPTABLE

| | | |
|---|---|---|
| Sec. I | **Signed and Completed Application Form (356h)** YES<br>(Statement regarding Rx/OTC Status) RX YES | ☒ |
| Sec. II | **Basis for Submission** **NDA# : 21-153**<br>Ref Listed Drug: NEXIUM Firm: ASTRA ZENECA<br>ANDA suitability petition required? NO<br>If Yes, then is change subject to PREA (change in dosage form, route, active ingredient)<br>For products subject to PREA a wavier request must be granted prior to approval of ANDA.<br>Wavier Granted: | ☒ |
| Sec. III | **Patent Certification**<br>1. Paragraph: IV<br>2. Expiration of Patent: 5-03-2020<br>A. Pediatric Exclusivity Submitted?<br>B. Pediatric Exclusivity Tracking System checked?<br>**Exclusivity Statement:** YES | ☒ |
| Sec. IV | **Comparison between Generic Drug and RLD-505(j)(2)(A)**<br>1. Conditions of use SAME<br>2. Active ingredients SAME<br>3. Route of administration SAME<br>4. Dosage Form SAME<br>5. Strength SAME | ☒ |
| Sec. V | **Labeling** (Mult Copies N/A for E-Submissions)<br>1. 4 copies of draft (each strength and container) or 12 copies of FPL YES<br>2. 1 RLD label and 1 RLD container label YES<br>3. 1 side by side labeling comparison with all differences annotated and explained YES<br>4. Was a proprietary name request submitted? NO<br><br>HOW SUPPLIED:<br>20 MG AND 40 MG:<br>Bottles of 30s, 90s, and 1000s; (b) (4)<br>(If yes, send email to Labeling Rvwr indicating such.) | ☒ |
| Sec. VI | **Bioavailability/Bioequivalence**<br>**1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES<br>**2. Request for Waiver of In-Vivo Study(ies): YES ON 20 MG**<br>**3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) YES. PROPORTIONAL<br>**4. Lot Numbers of Products used in BE Study(ies):** RLD: N5819 ANDA: Y51232<br>**5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below) | ☒ |

| | | |
|---|---|---|
| Study Type | **IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING , FED AND SPRINKLE ON 40 MG<br>a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC)YES<br>b. EDR Email: Data Files Submitted: YES SENT TO EDR<br>c. In-Vitro Dissolution: YES | ☒ |
| Study Type | **IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO<br>a. Properly defined BE endpoints (eval. by Clinical Team)<br>b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120)<br>c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team)<br>d. EDR Email: Data Files Submitted | ☐ |
| Study Type | **TRANSDERMAL DELIVERY SYSTEMS** NO<br>a. <u>In-Vivo PK Study</u><br>1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC)<br>2. In-Vitro Dissolution<br>3. EDR Email: Data Files Submitted<br>b. <u>Adhesion Study</u><br>c. <u>Skin Irritation/Sensitization Study</u> | ☐ |
| Study Type | **NASALLY ADMINISTERED DRUG PRODUCTS** NO<br>a. <u>Solutions</u> (Q1/Q2 sameness):<br>1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)<br>b. <u>Suspensions</u> (Q1/Q2 sameness):<br>1. In-Vivo PK Study<br>a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC)<br>b. EDR Email: Data Files Submitted<br>2. In-Vivo BE Study with Clinical EndPoints<br>a. Properly defined BE endpoints (eval. by Clinical Team)<br>b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120)<br>c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team)<br>d. EDR Email: Data Files Submitted<br>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<br>a. Pilot Study (determination of ED50)<br>b. Pivotal Study (study meets BE criteria 90%CI or 80-125) | ☐ |
| **Sec. VII** | **Components and Composition Statements**<br>1. Unit composition and batch formulation YES<br>2. Inactive ingredients as appropriate YES. All inactives acceptable per IIG and filing regulations. | ☒ |

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| Sec. VIII | **Raw Materials Controls**<br>1. **Active Ingredients**<br>a. Addresses of bulk manufacturers YES<br>b. Type II DMF authorization letters or synthesis YES. DMF # TBD (9/19/2005)<br>c. COA(s) specifications and test results from drug substance mfgr(s) YES<br>d. Applicant certificate of analysis YES<br>e. Testing specifications and data from drug product manufacturer(s) YES<br>f. Spectra and chromatograms for reference standards and test samples YES<br>g. CFN numbers YES<br>2. **Inactive Ingredients**<br>a. Source of inactive ingredients identified YES<br>b. Testing specifications (including identification and characterization) YES<br>c. Suppliers' COA (specifications and test results) YES<br>d. Applicant certificate of analysis YES | ☒ |
| Sec.IX | **Description of Manufacturing Facility**<br>1. Full Address(es)of the Facility(ies) YES<br>2. CGMP Certification: YES<br>3. CFN numbers YES | ☒ |
| Sec. X | **Outside Firms Including Contract Testing Laboratories**<br>1. Full Address YES<br>2. Functions YES<br>3. CGMP Certification/GLP YES<br>4. CFN numbers YES | ☒ |
| Sec. XI | **Manufacturing and Processing Instructions**<br>1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) YES<br>2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES<br>3.If sterile product: Aseptic fill / Terminal sterilization NA<br>4.Filter validation (if aseptic fill) NA<br>5. Reprocessing Statement YES<br><br>Intended Commercial Batch Sizes:<br>20 mg: (b) (4) capsules<br>40 mg: capsules | ☒ |

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| Sec. XII | **In-Process Controls**<br>1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES<br>2. In-process Controls - Specifications and data YES<br><br>20 mg (Lot # Y51231)<br>TY: (b) (4) CAPSULES<br>AY: CAPSULES<br>PACKAGED:<br>30s- (b) (4) capsules<br>1000s- (b) (4) capsules<br>(b) (4)<br><br>40 mg (Lot # Y51232)<br>TY: (b) (4) CAPSULES<br>AY: CAPSULES<br>PACKAGED:<br>30s- (b) (4) capsules<br>1000s- (b) (4) capsules<br>(b) (4) | ☒ |
| Sec. XIII | **Container**<br>1. Summary of Container/Closure System (if new resin, provide data) YES<br>2. Components Specification and Test Data (Type III DMF References) YES<br>3. Packaging Configuration and Sizes YES<br>4. Container/Closure Testing YES<br>5. Source of supply and suppliers address YES | ☒ |
| Sec. XIV | **Controls for the Finished Dosage Form**<br>1. Testing Specifications and Data YES<br>2. Certificate of Analysis for Finished Dosage Form YES | ☒ |
| Sec. XV | **Stability of Finished Dosage Form**<br>1. Protocol submitted YES<br>2. Post Approval Commitments YES<br>3. Expiration Dating Period YES- 24 MONTHS<br>4. Stability Data Submitted YES<br>a. 3 month accelerated stability data YES<br>b. Batch numbers on stability records the same as the test batch YES | ☒ |
| Sec. XVI | **Samples** - Statement of Availability and Identification of:<br>1. Drug Substance YES<br>2. Finished Dosage Form YES<br>3. Same lot numbers YES | ☒ |

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| Sec. XVII | **Environmental Impact Analysis Statement** YES | ☒ |
| Sec. XVIII | **GDEA (Generic Drug Enforcement Act)/Other**:<br>1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])<br>2. Debarment Certification (original signature): YES<br>3. List of Convictions statement (original signature) YES | ☒ |

**OGD Template Revised 04/01/2004 /T.Hinchliffe**

# FDA FAX

ANDA 78-003

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)

TO: Ivax Pharmaceuticals, Inc.

TEL: 845-267-2444

ATTN: Patricia Jaworski

FAX: 845-268-0117

FROM: Stanley Shepperson

PROJECT MANAGER: 301-827-5830

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 23, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for November 25, 2005.

**Pages (including cover): 4**

**SPECIAL INSTRUCTIONS:**

Acceptable for filing letter.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

ANDA 78-003

IVAX Pharmaceuticals, Inc.
Attention: Patricia Jaworski
125 Wells Avenue
Congers, NY 10920

JAN 23 2006

Dear Madam:

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: Esomeprazole Magnesium Delayed-Release Capsules, 20 mg and 40 mg

DATE OF APPLICATION: November 23, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 25, 2005

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:

Yoon Kong
Project Manager
301-827-5791

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-003
DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610
HFD-143/OIM/DRM

Endorsement:
HFD-615/M.Shimer, Chief, RSB _____ date 23 JAN 2006
HFD-615/S.Shepperson, CSO _____ date 1-23-2006

Word File
V:\CDSNAS\OGDS11\FIRMSAM\IVAXPHARM\LTRS&REV\78003.ACK.DOC

F/T sms 1-23-2006

ANDA Acknowledgment Letter!