CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207920Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207920 SUPPL # N/A HFD # 560

Trade Name: Nexium 24HR

Generic Name: esomeprazole (b) (4) delayed-release tablets, 20 mg

Applicant Name: Pfizer, Inc.

Approval Date, If Known: November 19, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

NDA 207920 is a bioequivalence study for a new dosage form only (tablets), relying upon NDA 204655 Nexium 24HR (esomeprazole magnesium) capsules which was approved March 28, 2014.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	204655	Nexium 24HR (esomeprazole magnesium) delayed-release capsules, 22.3 mg
NDA#	021689	Nexium IV; (esomeprazole sodium for injection), 20 or 40 mg IV
NDA#	022101	Nexium (esomeprazole magnesium) delayed-release oral suspension, 10 mg
NDA #	021153	Nexium (esomeprazole magnesium) delayed-release capsules, (b)(4), 20, and 40 mg

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☐
Explain:

Investigation #2

IND # YES ☐ NO ☐
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Jeffrey Buchanan
Title: Regulatory Health Project Manager
Date: 10/27/15

Name of Office/Division Director signing form: Karen Murry Mahoney, MD
Title: Deputy Director, DNDP

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

/s/

JEFFREY A BUCHANAN
10/27/2015

KAREN M MAHONEY
11/03/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207920 BLA #	NDA Supplement # N/A BLA Supplement #	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Nexium 24HR Established/Proper Name: esomeprazole Dosage Form: delayed-release tablets, 20 mg		Applicant: Pfizer Agent for Applicant (if applicable):
RPM: Jung Lee, DNDP		Division: Division of Nonprescription Drug Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 12/06/15	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists documents to be included in the Action Package.

[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Proton Pump Inhibitor (PPI)
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☒ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s): Approval Letter dated 11/23/15
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letter: 04/14/15 Review: 04/02/15
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: ☐ None 06/19/15 DMPP/PLT (DRISK): ☒ None OPDP: ☒ None SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None DNDP: 10/23/15; 11/19/15
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	Filing Review: 04/16/15 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 11/04/15 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	IR 03/25/15; Proprietary Name Conditionally Acceptable 04/14/15; 74-Day Letter 04/21/15; IR 05/28/15; IR 06/18/15; IR 07/16/15; IR 10/06/15; IR 11/03/15
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	TCON minutes 10/05/15 PeRC PREA Template 10/21/15 MTF 10/26/15
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 1/28/14
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	None
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 11/23/15
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11/05/15
PMR/PMC Development Templates *(indicate total number)*	☒ None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 11/05/15
• Clinical review(s) *(indicate date for each review)*	MO 10/26/15; 11/23/15
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	10/26/15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None Biometrics 08/03/15; ClinPharm 10/17/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 08/03/15
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 10/17/15
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested Data accepted without on-site inspection

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 10/27/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☐ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 10/15/15 (multiple reviews); 10/16/15; 10/20/15; 10/21/15; 10/23/15
Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	10/16/15
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☐ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

From:	Buchanan, Jeffrey A.
To:	christine.chirdo@pfizer.com
Cc:	Ross, Kevin (Kevin.Ross@pfizer.com); Ross, Kevin (Kevin.L.Ross@pfizer.com); Buchanan, Jeffrey A.
Subject:	URGENT > NDA 207920 Nexium 24HR tablets - request for revised labeling
Date:	Tuesday, November 03, 2015 9:38:26 AM
Importance:	High

Dear Ms. Chirdo,

Please see the labeling comments below and respond with revised labeling formally submitted to your application by close of business Friday, November 6, 2015. Please email to me a courtesy copy of the formal submission once it is complete. Feel free to contact me with any questions you may have. Thank you.

Make the following revisions:

i. Non Drug Facts Labeling

a. Revise the established name to read "esomeprazole delayed-release tablets 20mg" wherever it appears on the carton and immediate container labels.

b. Configure the 2-ct carton to include the full Drug Facts Label on the carton similar to the configuration approved for Nexium capsules.

ii. Drug Facts Label

a. ***Directions*** section, "14-Day Course of Treatment," first bullet: revise the statement "swallow 1 tablet with a glass of water before eating in the morning" to "swallow 1 tablet with a glass of water at least 1 hour before eating in the morning".

b. ***Other Information*** section, third bullet: revise the storage statement to "Store at 20°C - 25°C (68° - 77°F)".

c. ***Other Information*** section, fourth bullet, "[bullet] (b) (4) provide a rationale for the deviation from the Nexium capsule label or remove the statement.

We also recommend you make the following revisions:

iii. Drug Facts label:

a. ***Questions or comments*** section: include the time that the toll-free number is in operation.

In addition to these changes, we remind you to submit all labeling with the (b) (4) statement removed to reflect the July 31, 2015 amendment to the application.

Jeffrey Buchanan

U.S. Food and Drug Administration
FDA/OMPT/CDER/OND/ODE IV/DNDP
White Oak Building 22, Room 5461
10903 New Hampshire Avenue
Silver Spring, Maryland

Use zip code **20903** *if shipping via United States Postal Service (USPS).*

Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, FedEx, etc.).*

Phone: (301) 796-1007 Fax: (301) 796-9899

Email: jeffrey.buchanan@fda.hhs.gov

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

/s/

JEFFREY A BUCHANAN
11/03/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 19, 2015 2-2:30p, WO 75 RM 3400

Application Number: NDA 207920
Product Name: Nexium (esomeprazole) (b) (4) mg
Sponsor/Applicant Name: Pfizer Inc.

Subject: To clarify CMC questions for the IR sent on October 16, 2015

FDA Participants :

Danae Christodolou, Ph.D	Branch Chief VI, Acting
Ubrani Venkataram, Ph.D	Branch Chief VI Drug Process, Acting
Daniel Peng, Ph.D	Drug Process Reviewer
Thao M. Vu, Rph	Regulatory Business Process Manager
Swapan De, Ph.D	Quality Assessment Lead

Sponsor Participants :

Roger Wilson,	CMC
James Fort,	Product design
Thomas Garcia,	Pharm Science Global CMC
Kim Vukovinsky,	Pharm Science Analytical R&D
Nils Ahlgren,	GI Product Design
William Bubnis,	GI Product Design
Christine Chirdo,	Regulatory
Kevin Ross,	Regulatory

1.0 BACKGROUND:

FDA sent out an information request to Pfizer regarding (b) (4) manufacture site. This site was included in DMF (b) (4) as an analytical stability testing site, but was not included in the NDA. In addition, information in table 2, page 10-11 in module 1.11.1 Qualify information amendment previously submitted on October 14, 2015 need to be updated with the acceptance criteria of PTOSTI 90/97% protocol and submit with the supportive sample data in the NDA's first annual report.

2.0 DISCUSSION:

Question #1-facility- Pfizer confirms that DMF (b) (4) includes (b) (4) as an analytical stability testing site. Pfizer confirmed that this site is not included in the NDA and is not used for stability studies submitted in the NDA. This site was used for historical stability data.

Question #2-Pfizer agrees to evaluate intra and inter-batch variability in the content uniformity of (b)(4) commercial batches, with appropriate sampling plan for Content Uniformity across the compression run, and to implement additional controls if deemed necessary after analysis of the data; the sampling will be per the protocol submitted in the 10/06/2015 amendment; the protocol will be updated as per the 10/21/2015 amendment, and will be submitted with supportive sample data in the NDA Annual report.

Pfizer requested that the above agreement be documented. The review team stated that the agreement will be documented in the CMC NDA review and communicated in the action letter.

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

/s/

THAO M VU
10/26/2015

Note: The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission.*

Definitions:

Deferral *– A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.*

Full Waiver *– On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information MUST be included in the pediatric use section of labeling.*

Partial Waiver *– FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.*

Pediatric Assessment *– The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.*

Pediatric Plan *– A pediatric plan is the applicant's statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.*

Pediatric Population/Patient*- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.*

PREA Pediatric Record/Pediatric Page *– The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.*

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☒ **Full Waiver** ☐ **Partial Waiver** ☐ **Pediatric Assessment** ☐ **Deferral/Pediatric Plan**

BLA/NDA#: NDA 207920

PRODUCT PROPRIETARY NAME: Nexium 24HR Tablets **ESTABLISHED/GENERIC NAME: Esomperazole magnesium**

APPLICANT/SPONSOR: AstraZeneca

PREVIOUSLY APPROVED INDICATION/S:
(1) Treatment of frequent heartburn (occurs 2 or more days a week) (OTC)
(2) Risk reduction of NSAID-associated gastric ulcer (Rx)
(3) Treatment of gastroesophageal reflux disease (GERD) (Rx)
(4) H. pylori eradication to reduce the risk of duodenal ulcer recurrence (Rx)
(5) Pathological hypersecretory conditions, including Zollinger-Ellison syndrome (Rx)

PROPOSED INDICATION/S:
(1) Treatment of frequent heartburn (occurs 2 or more days a week) (OTC)
(2) _____
(3) _____
(4) _____

BLA/NDA STAMP DATE: 02/06/15

PDUFA GOAL DATE: 12/04/15

SUPPLEMENT TYPE: N/A

SUPPLEMENT NUMBER: N/A

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?

Did the sponsor submit an Agreed iPSP? Yes ☒ No ☐

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ☒ No ☐

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ No ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ No ☒

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes ☐ No ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☒ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1. Pediatric age group(s) to be waived. *Children 0 to less than 18 years of age.*

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   ☐ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.

   ☒ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

   ☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

   ☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted***. (This reason is for Partial Waivers Only)***

3. *Provide justification for Waiver:*

Pediatric gastroenterologists recommend that children with symptoms of heartburn should be under the direction of a physician. Furthermore, pediatric gastroenterology guidelines emphasize the importance of evaluating infants and older children/adolescents with reflux symptoms that is sufficient to diagnose GERD, in addition to recognize any complications before symptom and/or disease management is initiated. As a result, a physician should be consulted before use in children under 18 years of age. This is consistent with the Agency's position that treatment of heartburn in a pediatric population is not appropriate in an OTC setting and consistent with the OTC proton pump inhibitor (PPI) products currently approved and marketed in the United States (e.g., omeprazole and lansoprazole).

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*

The proposed Drug Facts language is the same as other PPIs approved for OTC use: "Children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition."

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

- actinic keratosis
- adjunctive treatment of major depressive disorder
- age-related macular degeneration
- Alzheimer's disease
- amyloidosis
- amyotrophic lateral sclerosis
- androgenic alopecia
- atherosclerotic cardiovascular disease
- autosomal dominant polycystic kidney disease (ADPKD)
- benign monoclonal gammopathy
- benign prostatic hyperplasia
- cancer:
  - basal cell and squamous cell skin cancer
  - bladder
  - breast
  - cervical
  - colorectal
  - endometrial
  - esophageal
- cancer (continued):
  - follicular lymphoma
  - gastric
  - hairy cell leukemia
  - hepatocellular
  - indolent non-Hodgkin lymphoma
  - lung (small & non-small cell)
  - multiple myeloma
  - oropharynx (squamous cell)
  - ovarian (non-germ cell)
  - pancreatic
  - prostate
  - refractory advanced melanoma
  - renal cell
  - uterine
- chronic lymphocytic leukemia
- chronic obstructive pulmonary disease
- cryoglobulinemia
- diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)

dry eye syndrome (keratoconjunctivitis sicca)

erectile dysfunction

essential thrombocytosis

Huntington's chorea

infertility & reproductive technology

ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke

memory loss

menopause and perimenopausal disorders

mesothelioma

myelodysplasia

myelofibrosis & myeloproliferative disorders

osteoarthritis

overactive bladder

Parkinson's disease

paroxysmal nocturnal hemoglobinuria

plasma cells and antibody production disorders

polycythemia vera

postmenopausal osteoporosis

prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis

reduction of thrombotic cardiovascular events in patients with coronary artery disease

replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

retinal vein occlusions

stress urinary incontinence

temporary improvement in the appearance of caudal lines

treatment of incompetent great saphenous veins and varicosities

type 2 diabetic nephropathy

vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST – N/A

Please attach:

☐ ***Pediatric Record***

1. **Age groups included in the deferral request:**

2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**

3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:** (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   a. Adult studies are completed and ready for approval
   b. Additional safety or effectiveness data needed (**describe**)
   c. Other (**specify**)

4. **Provide projected date for the submission of the pediatric assessment (deferral date):**

5. **Did applicant provide certification of grounds for deferring assessments?** ☐ **Yes** ☐ **No**

6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** ☐ **Yes** ☐ **No**

SPONSOR'S PROPOSED PEDIATRIC PLAN N/A

1. **Has a pediatric plan been submitted to the Agency?** ☐ **Yes** ☒ **No**

2. Does the division agree with the sponsor's plan? ☐ **Yes** ☒ **No**

3. **Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?** ☐ **Yes** ☒ **No**

a. **Protocol Submission: N/A**
b. **Study Completion: N/A**
c. **Study Submission: N/A**

4. **Has a Written Request been issued? ☐ Yes ☒ No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)**

5. **Has a PPSR been submitted? ☐ Yes ☒ No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)**

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFTEY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design: N/A

Nonclinical Studies: N/A

Clinical Studies: N/A

Age group and population (indication) in which study will be performed: N/A
This section should list the age group and population exactly as it is in the plan.

Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Number of patients to be studied or power of study to be achieved: N/A

Example:
Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

Entry criteria: N/A
This section should list pertinent inclusion/exclusion criteria.

Example:
Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients must have a negative pregnancy test if female..

Clinical endpoints: N/A

Example:
Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

Timing of assessments: N/A

Example :baseline, week 1, 4, and 6

Statistical information (statistical analyses of the data to be performed): N/A
Example:
Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.

Division comments on product safety: N/A
Are there any safety concerns currently being assessed? ☐ **Yes** ☒ **No**

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? ☐ **Yes** ☒ **No**

Will a DSMB be required? ☐ **Yes** ☒ **No**

Other comments:

Division comments on product efficacy: N/A

Division comments on sponsor proposal to satisfy PREA: N/A

PeRC ASSESSMENT TEMPLATE

Please attach:

- ☐ ***Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.***
- ☐ ***Pediatric Record***

Date of PREA PMR: N/A
Description of PREA PMR: N/A ***(Description from the PMC database is acceptable)***

Was Plan Reviewed by PeRC? ☐ **Yes** ☐ **No** If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied: N/A
This section should list the indication(s) exactly as written in the *protocols.*

Example:
DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information: N/A

Examples in italics

- **Route of administration**: *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/ Study Design: N/A

Example:
Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.
Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study/ies was/were performed: N/A

Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved: N/A

Example:
Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .

Entry criteria: N/A

This section should list pertinent inclusion/exclusion criteria.

Example:
Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients had a negative pregnancy test if female.

Clinical endpoints: N/A

Example:
Study 1: Clinical outcome and safety were the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

Statistical information (statistical analyses of the data performed): N/A
This section should list the statistical tests conducted.

Example:
Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.

Timing of assessments: N/A
Example:
Baseline, week 2, week, 6, and end of treatment

Division comments and conclusions (Summary of Safety and Efficacy): N/A
Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language. N/A

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JEFFREY A BUCHANAN
10/21/2015

From: Buchanan, Jeffrey A.
To: christine.chirdo@pfizer.com
Cc: Buchanan, Jeffrey A.
Subject: NDA 207920 Nexium 24HR tablets - Information Request
Date: Tuesday, October 06, 2015 3:53:09 PM

Dear Ms. Chirdo,

We acknowledge your reference to a study related to the use of acid-suppressing drugs in pregnancy and childhood asthma requested by MHRA in your ISS to NDA 207920 submitted with your original application (p. 33/79).

Refer to the Periodic Benefit-Risk Evaluation Report (PBRER) submitted under NDA 204655 (Nexium 24HR Capsules) on June 12, 2015, which states the following:

> 1) "AstraZeneca has been requested by MHRA to perform an observational study on the association between acid-suppressing drugs in pregnancy and asthma in the offspring" (page 29/960).
>
> 2) "Based upon the results of the study D9612N00018 which showed that there is no association between prenatal exposure to PPIs and asthma in childhood, see Section 8.1, and taking into account the cumulative experience, (b) (4) (page 29/960).
>
> 3) "This safety topic will continue to follow AstraZeneca's routine safety surveillance process" (page 30/960).

Although a synopsis of the study results is included in the PBRER (page 22/960) for NDA 204655, a final study report has not been submitted under NDA 204655 or NDA 207920.

Submit the full report for the above-referenced study and reports for any other clinical studies you have conducted (ongoing and completed) or any additional findings from your safety surveillance program that address the use of acid-suppressing drugs in pregnancy and childhood asthma. We request you submit this information by COB Friday, October 16, 2015. Feel free to contact me at will with any questions you may have. Thank you.

Jeffrey Buchanan

U.S. Food and Drug Administration
FDA/OMPT/CDER/OND/ODE IV/DNDP
White Oak Building 22, Room 5461
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, FedEx, etc.).*

Phone: (301) 796-1007 Fax: (301) 796-9899

Email: jeffrey.buchanan@fda.hhs.gov

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/s/

JEFFREY A BUCHANAN
10/06/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 30, 2015, 4:00-4:30pm, WO 75 RM 4400

Application Number: NDA 207920
Product Name: Nexium **(**esomeprazole) (b) (4)
Sponsor/Applicant Name: Pfizer Inc.

Subject: To clarify CMC questions for the IR sent on September 28, 2015

FDA Participants :

Danae Christodolou, Ph.D	Branch Chief VI, Acting
Ubrani Venkataram, Ph.D	Drug Process, Lead
Daniel Peng, Ph.D	Drug Process Reviewer
Thao M. Vu, Rph :	Regulatory Business Process Manager

Sponsor Participants :

James Murphy	Pfizer CMC
Roger Wilson	Pfizer CMC
James Fort	Product Design
Nils Ahlgren	Product Design
Judy Firor	AstraZeneca Regulatory
Mike Bailey	Pfizer Regulatory
Kevin Ross	Pfizer Regulatory
Doreen Franks	Pfizer Regulatory
Sudar Alagarsamy	Pfizer Project Management

1.0 BACKGROUND:

FDA sent out an information request to Pfizer regarding manufacturing process pertaining to intra-batch variability, (b) (4) uniformity (b) (4) and sampling plan. Pfizer requested a Tcon to discuss and clarify their responses to the questions.

2.0 DISCUSSION:

Question #1- Intra-batch variablility-Pfizer indicated that data readily available to address intra-batch variability for content uniformity was from a validation exercise performed many years ago. Thus, the raw data supporting minimum, maximum and RSD values are no longer available. Pfizer proposed to provide any available data from the validation exercise into the response submitted on 06-October. In addition, Pfizer proposed to provide a testing protocol which would be implemented as a post-approval commitment

on commercial batches to include intra-batch sampling for content uniformity on bulk tablets sampled from across the compression run for a specified number of batches. The data generated from the post-approval testing protocol would be provided in an Annual Report.

Question #2 (b) (4) uniformity (b) (4) - Pfizer proposed to provide a testing protocol which would be implemented as a post-approval commitment on commercial batches to perform additional testing of content uniformity on bulk tablets sampled from across the compression run for a specified number of batches. The data generated from the post-approval testing protocol would be provided in an Annual Report. Based on the results of the data analysis an in-process control for content uniformity on bulk tablets would be implemented or content uniformity testing of the finished product at release would be further justified. Additionally, Pfizer agreed to provide additional detail on the (b) (4) process parameters in P.3.3 as part of the response to be submitted on 06-October.

Pfizer understands the adequacy of the sampling plan in place for release of drug product based on Assay, particularly what procedures are in place to ensure acceptable drug product is released to market if assay values are considerably off target. Thus, Pfizer agreed to address this as part of the response to be submitted on 06-October.

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/s/

THAO M VU
10/05/2015

From:	Buchanan, Jeffrey A.
To:	christine.chirdo@pfizer.com
Cc:	Ross, Kevin (Kevin.Ross@pfizer.com); Buchanan, Jeffrey A.
Subject:	NDA 207920 Nexium 24HR tablets - Information Request (07/16/15)
Date:	Thursday, July 16, 2015 2:13:46 PM
Importance:	High

Dear Ms. Chirdo,

Please see the following requests for information and respond by close of business Friday, July 31, 2015. Please formally submit your response to your application and provide me with a courtesy copy/PDF via email at your earliest convenience. Thank you.

1) Submit 3 tablets of the to-be-marketed formulation.

2) Submit data that supports the labeling claim [redacted] (b) (4) to include [redacted] (b) (4), and identify the comparer that will support this claim.

3) Provide an analysis of the ECGs done for study subjects in BE Study B5141002. In your analysis, indicate any abnormal findings compared to baseline, and indicate method of interpretation (e.g., machine read, physician interpretation, cardiologist interpretation, etc.). In addition to ECG interpretation, include analyses of the three parameters listed below. For each parameter, include mean change from baseline for the treatment for the overall treatment group:

a) QTc interval

b) PR interval

c) QRS complex

4) According to your protocol (Table 2), ECGs were done at screening and in the case of subject withdrawal or early discontinuation from study. However, in section 12.5 of your protocol, you state that an ECG was only performed at Screening and at the end of the study (or at the time of early discontinuation from the study). Furthermore, you provided Case Report Forms (CRFs) for the five subjects that discontinued due to adverse events. The CRFs indicate that for three of the subjects, the ECGs were “normal” at screen and at termination; however, ECGs for subject ID 10032 [10011065] and subject ID 10009 [10011169] were not done at termination. Clarify if ECGs were done on all subjects at end of study.

If any of the requested information is available in your February 6, 2015 submission, please direct us to its location in your application. Thank you.

Jeffrey Buchanan
U.S. Food and Drug Administration
FDA/OMPT/CDER/OND/ODE IV/DNDP
White Oak Building 22, Room 5461

10903 New Hampshire Avenue
Silver Spring, Maryland

Use zip code **20903** *if shipping via United States Postal Service (USPS).*

Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, FedEx, etc.).*

Phone: (301) 796-1007 Fax: (301) 796-9899

Email: jeffrey.buchanan@fda.hhs.gov

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/s/

JEFFREY A BUCHANAN
07/16/2015

From:	Bhandari, Navi
To:	"kevin.ross@pfizer.com"
Cc:	Shiber, Andrew J
Bcc:	Chen, Tien Mien; Duan, Peng
Subject:	Information Request NDA 207920
Date:	Thursday, June 18, 2015 7:16:00 AM
Importance:	High

Good morning Kevin,

Please respond to the following information request regarding your statistical analysis of BE study (B5141002).

Please confirm receipt of this message and submit an official response to the FDA document room.

FDA Request:

To facilitate the review process for NDA 207920, please submit the following information by COB of June 25, 2015.

1. ***In your Analysis Dataset for PK Parameters (ADPP) data set, the sequence number is not correctly coded. Please resubmit your ADPP.xpt dataset with the correct sequence assignment coded as 1, 2, 3, 4, 5, or 6 for each subject. Please also specify the sequence for each assignment (for example, sequence = 1 for B-A-C-D-A-C);***

2. ***Please submit the complete SAS code for all analyses (start with the data set import), including the BE studies under both fasted and fed conditions for both AUC_{inf} and C_{max} as well as the analyses for the food effect. Please also clearly list which subjects were not included in each of the analyses.***

Thank you,

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
240-402-3815

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/s/

NAVDEEP BHANDARI
06/18/2015

From:	Salvatore, Alina
To:	"Christine.Chirdo@pfizer.com"
Cc:	Salvatore, Alina; Buchanan, Jeffrey A.
Subject:	NDA 207920 Nexium tablets - Information Request
Date:	Wednesday, May 27, 2015 10:30:00 AM

Hi Christine,

Please respond to the following information request by COB Friday, June 5th. Please reply to this email and submit an official response to the document room.

Please provide the Adverse Event Forms for:

1) all reported deaths from the AstraZeneca database [Global and U.S.]; and

2) all Serious Adverse Events that are not labeled reported from the AstraZeneca [Global and U.S.] and Pfizer [U.S.] databases

or direct us to where this information can be found in your Interim Update of Safety [module 5.3.5.3 in your submission of 2/06/2015]

Thank you,

Alina

Alina W. Salvatore, R.Ph., M.S.

CDR, United States Public Health Service

Regulatory Project Manager

Division of Nonprescription Drug Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

Food and Drug Administration

Phone: 240-402-0379

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/s/

ALINA W SALVATORE
05/28/2015

From:	Buchanan, Jeffrey A.
To:	Chirdo, Christine
Cc:	Buchanan, Jeffrey A.
Subject:	RE: NDA 207920 Nexium 24HR tabs - 74-day letter - Filing Review Issues Identified
Date:	Tuesday, April 28, 2015 10:51:59 AM
Importance:	High

Hi Christine,

Your proposal to submit the information requested in the 74-Day Letter by COB May 15, 2015 is fine. Thank you.

Jeff

-----Original Message-----
From: Chirdo, Christine [mailto:Christine.Chirdo@pfizer.com]
Sent: Monday, April 27, 2015 1:26 PM
To: Buchanan, Jeffrey A.
Subject: RE: NDA 207920 Nexium 24HR tabs - 74-day letter - Filing Review Issues Identified

Good afternoon Jeff,
I just wanted to give you an update on the Information Request per the Day 74 Letter. As we are working closely with our Alliance Partner, AstraZeneca, we are finding that the 1-May 2015 date may be difficult to achieve. While we can provide responses to some of the identified issues, we will still need more time for others - and rather than providing it piece meal fashion, the team was hoping for an extension of 2 weeks (15-May 2015).
Would it be possible to provide the Agency with the entire response no later than 15-May 2015?

Thanks so much!
Christine

Christine D. Chirdo | Director, US Regulatory Strategy Category Lead: GI/Respiratory/Personal Care | Worldwide Regulatory Strategy - Pfizer Consumer Healthcare | One Giralda Farms, Madison, New Jersey 07940 | Tel: 973.660.5602| Cell: (b) (6)

-----Original Message-----
From: Buchanan, Jeffrey A. [mailto:Jeffrey.Buchanan@fda.hhs.gov]
Sent: Tuesday, April 21, 2015 6:14 PM
To: Chirdo, Christine
Subject: NDA 207920 Nexium 24HR tabs - 74-day letter - Filing Review Issues Identified

Hi Christine,

Attached is your 74-Day Letter. Please contact me if you have questions.

Jeff

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/s/

JEFFREY A BUCHANAN
04/28/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207920

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Pfizer, Inc.
Attention: Christine D. Chirdo
Director, U.S. Regulatory Strategy Category Lead
1 Giralda Farms
Madison, NJ 07940

Dear Ms. Chirdo:

Please refer to your New Drug Application (NDA) dated February 6, 2015, received February 6, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Nexium 24HR (esomeprazole magnesium) delayed-release tablets, 22.3 mg.

We also acknowledge your amendment dated February 25, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 6, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 6, 2015.

During our filing review of your application, we identified the following potential review issues:

1. The bioanalytical method validation report associated with Protocol B5141002, "A Phase I, Randomized, Single-Dose, 6-Period, Crossover, Partial Replicate, Open-Label Study to Assess the Bioequivalence of Esomeprazole Banded OTC Capsule and (b) (4) Tablet in Healthy Volunteers Under Fed and Fasted Conditions" was not included in your NDA.

2. The safety profile of the inactive ingredient, [redacted], will be assessed during the review cycle.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Submit the bioanalytical method validation report for Protocol B5141002, "A Phase I, Randomized, Single-Dose, 6-Period, Crossover, Partial Replicate, Open-Label Study to Assess the Bioequivalence of Esomeprazole Banded OTC Capsule and [redacted] Tablet in Healthy Volunteers Under Fed and Fasted Conditions."

2. The proposed acceptance criterion of NMT [redacted]% for "any other individual unspecified impurity" is inconsistent with the ICH threshold of "NMT 0.2%" for identified impurities and is not acceptable. Provide revised drug product specifications with the acceptance criterion for "any other individual unspecified impurity" of "NMT [redacted]%" both at release and stability.

3. You did not propose specifications for [redacted] in the drug product. Based on the composition of your drug product (e.g., relative amounts of excipients compared to the active), the level [redacted] (based on the information on excipient manufacture) should be controlled in the drug product. Provide revised drug product specifications that also include specification for appropriate [redacted]

4. Provide specifications for [redacted] in the tablet drug product.

5. Provide specifications for inorganic impurities in the tablet drug product.

6. [redacted] conforms to 21 CFR [redacted] The regulation states that the "Mica may be safely used in amounts consistent with good manufacturing practice [redacted] The regulation does not specifically provide for [redacted] mica, as would be the case for the tablet dosage form. Provide information that supports the use of mica as proposed in your drug product.

7. We acknowledge that the manufacturing process was developed to support marketing of the Rx tablet product in the EU. Provide the detailed process development section 3.2.P.2.3 to support marketing of the OTC tablet product in the USA.

8. In the provided executed batch record (Batch # BDLK), the API quantity dispensed was [redacted] kg, which is enough for approximate [redacted] tablets based on the drug product composition (22.3 mg /tablet); however, you stated the batch size for this stability batch

is [redacted] tablets. Explain the discrepancy of all the raw material dispensed for this batch and compare to its theoretical amount needed for [redacted] tablets. In addition, provide the executed batch record for batches # BDLD and BDLG. Furthermore, provide the equipment model, full capacity, and actual capacity used for the [redacted] and comment on how many sub-lots are needed for each unit operation of the proposed commercial batch size [redacted] tablets).

9. The proposed dissolution acceptance criterion in buffer stage, Q=[redacted]% at 30 min, needs to be revised. A minimum of Q=[redacted]% at X time point should be employed. The final decision on the acceptance criterion, however, will be made after reviewing the totality of the dissolution profile data in the NDA submission.

Please respond only to the above requests for information by close of business Friday, May 1, 2015. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We reference the waiver granted on February 27, 2014, for the pediatric study requirement for this application.

If you have questions, contact Jeffrey Buchanan, Regulatory Health Project Manager, at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Theresa Michele, M.D.
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

THERESA M MICHELE
04/21/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207920

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Pfizer, Inc.
1 Giralda Farms
Madison, NJ 07940

ATTENTION: Christine D. Chirdo
Director, US Regulatory Strategy Lead

Dear Ms. Chirdo:

Please refer to New Drug Application (NDA) dated and received February 6, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Esomeprazole Magnesium, tablets, 22.3 mg.

We also refer to your correspondence, dated and received February 25, 2015, requesting review of your proposed proprietary name, Nexium 24HR.

We have completed our review of the proposed proprietary name, Nexium 24HR and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your February 25, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abiola M. Olagundoye-Alawode, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982.

For any other information regarding this application, contact Jeffrey Buchanan, Regulatory Project Manager in the Office of New Drugs, at 796-1007.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
04/14/2015

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDER
Division: OTS/OB/DBVI
Mail Code: HF
Consulting Reviewer Name: Yi Tsong
Building/Room #: Building 21 Room 4628
Phone #: 301-796-1013
Fax #: 301-796-9976
Email Address:
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER
Division: OPQ/ONDP
Mail Code: HF
Requesting Reviewer Name: Peng Duan
Building/Room #: WO BLDG 21, RM 2627
Phone#: 301-796-1609
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Andrew Shiber
Requesting Reviewer's Concurring Supervisor's Name: Tien Mien Chen

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: March 26, 2015

Requested Completion Date: August 1, 2015

Submission/Application Number: 207920
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☐ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☑ Not a combination product

Submission Receipt Date: February 6, 2015

Official Submission Due Date: December 6, 2015

Name of Product: esomeprazole

Name of Firm: Astra Zeneca

Intended Use: Treatment of frequent heartburn

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

NDA

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

We need assistance from your group on the BE study Report-5141002 under NDA 207920 (Synopsis attached). We need your help on the analysis of the submitted clinical data with SAS. Specifically we are looking for help to answer

1. Is the Applicant s statistics analysis plan for Protocol B5141002 adequate to meet its goal (primary and secondary objectives)?
2. From their data presentation in this BE report, is it appropriate to conduct analyses on the fast data and fed data separately?

CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc.

Investigational Product: PF-00579913

Clinical Study Report Synopsis: Protocol B5141002

Protocol Title: A Phase I, Randomized, Single-Dose, 6-Period, Crossover, Partial Replicate, Open-Label Study to Assess the Bioequivalence of Esomeprazole Banded OTC Capsule and (b) (4) Tablet in Healthy Volunteers Under Fed and Fasted Conditions

Investigators: Dr Thomas J. Legg

Study Center(s): 1 study center in the United States

Publications Based on the Study: None

Study Initiation and Completion Dates: The study initiation date was 05 April 2014 and the study completion date was 31 May 2014.

Date of Report: 18 December 2014

Phase of Development: Phase 1

Study Objective(s):

Primary Objectives

- To demonstrate bioequivalence of Nexium banded over-the-counter (OTC) capsule compared to the Nexium (b) (4) tablet under fasted conditions
- To demonstrate bioequivalence of Nexium banded OTC capsule compared to the Nexium (b) (4) tablet under fed conditions

Secondary Objective

- To assess the effect of co-administration with a high fat meal on the relative bioavailability of esomeprazole when administered as the Nexium banded OTC capsule or (b) (4) tablet

METHODS

Study Design: This was an open-label, randomized, single-dose, 6-period, partial replicate, crossover study to assess the bioequivalence of Nexium banded OTC capsule and Nexium (b) (4) tablet in healthy volunteers under fed and fasted conditions.

CLINICAL STUDY REPORT SYNOPSIS

Subjects were randomly assigned to receive a single dose of 1 of the following treatments during each of the 6 treatment periods:

Treatment A: 20 mg of Nexium banded OTC capsule in the fasted state (administered in 2 treatment periods)

Treatment B: 20 mg of Nexium [redacted] (b) (4) tablet in the fasted state

Treatment C: 20 mg of Nexium banded OTC capsule with a high-fat meal (administered in 2 treatment periods)

Treatment D: 20 mg of Nexium [redacted] (b) (4) tablet with a high-fat meal

Reference treatments (Treatment A and Treatment C) were administered in 2 separate treatment periods within each subject. The minimum washout between treatment periods was 7 days.

The subjects were randomly assigned to 1 of the following 6 treatment sequences (approximately 9 subjects per sequence):

1. B-A-C-D-A-C
2. A-D-B-C-C-A
3. D-C-A-A-B-C
4. C-A-D-C-A-B
5. A-C-C-B-D-A
6. C-B-A-A-C-D

Diagnosis and Main Criteria for Inclusion: This study included healthy male and/or female subjects between the ages of 18 and 55 years, inclusive, with a body mass index (BMI) of 17.5 to 29.9 kg/m^2 and a total body weight >50 kg (110 lbs).

Study Treatment: Lot and formulation identification is presented in Table S 1**.**

CLINICAL STUDY REPORT SYNOPSIS

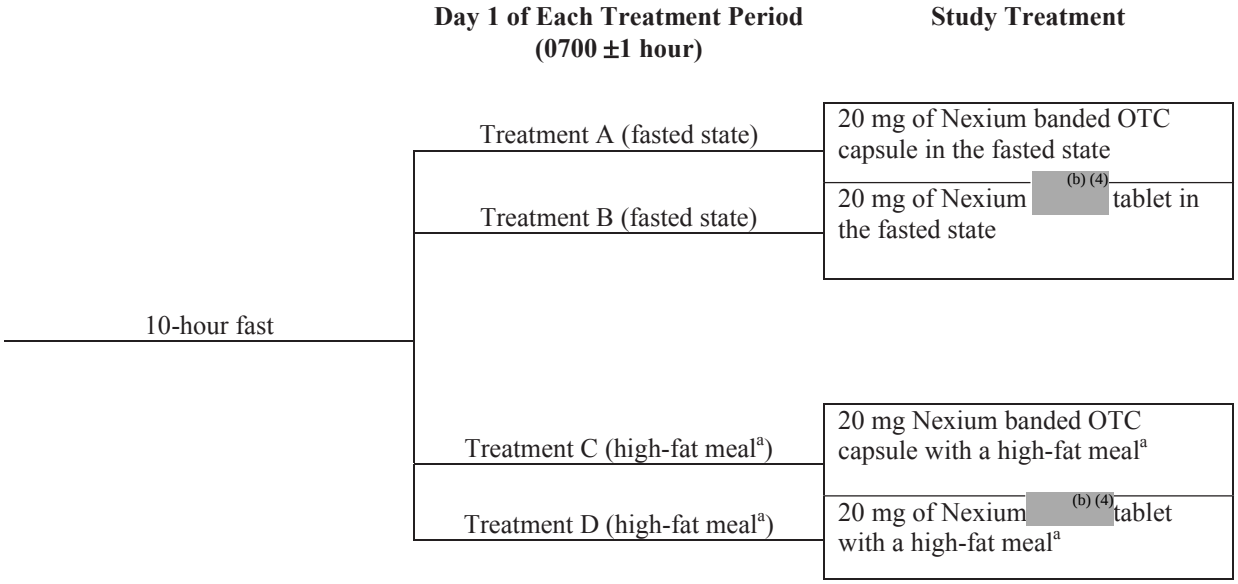
Table S 1. Lot and Formulation Identification/Dosage Material Numbers

Study Drug	Dosage Form	Lot Number	DMID Number
Nexium	20 mg OTC hard gelatin banded capsules	1569-0001-003	Not Applicable
Nexium	20 mg (b) (4) tablets	1587-0003-004	Not Applicable

DMID = dosage material identification number; (b) (4); OTC = over-the-counter.

Treatments administered during each treatment period are presented in Figure S 1.

Figure S 1. Treatments Administered During Each Treatment Period



Note: The 2 reference treatments (Treatment A and Treatment C) were administered in 2 separate treatment periods within each subject. There were 6 treatment periods during the study. The minimum washout between treatment periods was 7 days.
(b) (4) OTC = over-the-counter.
[a] Treatment C and Treatment D were administered 30 minutes after administration of a standardized high-fat meal.

Efficacy Evaluations: Not applicable

Pharmacokinetic and Other Evaluations: Pharmacokinetic (PK) blood samples were collected serially for 12 hours after dosing during each treatment period. Plasma concentrations of esomeprazole were measured with a validated LC-MS/MS assay. PK parameters following single-dose administration were derived from the concentration-time data. The primary PK parameters for the study were area under the drug concentration-time curve from time zero to infinity (AUC_{inf}) and maximum observed drug concentration (C_{max}). Pharmacodynamic evaluations were not done for the study.

CLINICAL STUDY REPORT SYNOPSIS

Safety Evaluations: Subject safety was periodically monitored by blood and urine samples for safety laboratory tests and pregnancy tests; full physical examination; blood pressure, pulse rate, and respiratory rate; electrocardiogram; and adverse events (AEs).

Statistical Methods:

The following were evaluated as primary comparisons:

1. Treatment B: 20 mg Nexium (b) (4) tablet in the fasted state (test) vs
   Treatment A: 20 mg Nexium banded OTC capsule in the fasted state (reference).

2. Treatment D: 20 mg Nexium (b) (4) tablet in the fed state (test) vs
   Treatment C: 20 mg Nexium banded OTC capsule in the fed state (reference).

In addition, the following secondary comparisons were evaluated:

3. Treatment C: 20 mg Nexium banded OTC capsule in the fed state (test) vs
   Treatment A: 20 mg Nexium banded OTC capsule in the fasted state (reference).

4. Treatment D: 20 mg Nexium (b) (4) tablet in the fed state (test) vs
   Treatment B: 20 mg Nexium tablet in the fasted state (reference).

A reference scaled average bioequivalence (RSAB) approach was utilized to test the primary comparisons (1 and 2). For the comparisons, and AUC_{inf} and C_{max}, within-subject standard deviation (SD) of the reference product (s_{wr}) estimated from the study was determined. If s_{wr} was ≥0.294 for the PK parameter, then bioequivalence was declared if both of the following conditions were met:

- The 95% upper confidence bound for $(\mu_T - \mu_R)^2 - \theta s_{wr}^2 \leq 0$, where μ_T was the average bioavailability on the natural log scale for the test products, μ_R was the average bioavailability on the natural log scale for the reference products, and
  $\theta = \left[\frac{\ln(1.25)}{0.25}\right]^2$ (scaled average bioequivalence limit);

  and

- The point estimate of the Test/Reference geometric mean ratio (GMR) fell within [0.80, 1.25].

For any other comparison for which s_{wr} was <0.294, the unscaled bioequivalence testing approach was utilized to test for bioequivalence. For Comparisons 1 and 2, bioequivalence was declared if the estimated 90% confidence interval (CI) for the ratio (Test/Reference) of adjusted geometric means for AUC_{inf} or C_{max} fell within [80%, 125%].

Safety data were summarized using descriptive statistics.

CLINICAL STUDY REPORT SYNOPSIS

RESULTS

Subject Disposition and Demography: Subject disposition is presented in Table S 2. A total of 60 subjects were randomized (10 subjects were randomized to each of the 6 treatment sequences). Forty-six (46, 76.7%) subjects completed all 6 treatment periods of the study and 14 (23.3%) subjects discontinued from the study.

Table S 2. Subject Disposition and Evaluation Groups

	Total N (%)	ACCBDA N (%)	ADBCCA N (%)	BACDAC N (%)	CADCAB N (%)	CBAACD N (%)	DCAABC N (%)
Randomized	60	10	10	10	10	10	10
Completed	46 (76.7)	6 (60.0)	8 (80.0)	9 (90.0)	8 (80.0)	7 (70.0)	8 (80.0)
Discontinued	14 (23.3)	4 (40.0)	2 (20.0)	1 (10.0)	2 (20.0)	3 (30.0)	2 (20.0)
After Period 1	8 (13.3)	2 (20.0)	1 (10.0)	1 (10.0)	2 (20.0)	2 (20.0)	0 (0.0)
Adverse Event	4 (6.7)	0 (0.0)	1 (10.0)	1 (10.0)	1 (10.0)	1 (10.0)	0 (0.0)
Protocol Violation	1 (1.7)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No Longer Willing	3 (5.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (10.0)	0 (0.0)
After Period 2	4 (6.7)	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)
No Longer Willing	4 (6.7)	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)
After Period 3	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
No Longer Willing	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
After Period 4	1 (1.7)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse Event	1 (1.7)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Safety Set	60 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)
Pharmacokinetic Set	60 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)

Note: The percentages are based on the number of randomized subjects.
Safety set consists of all subjects who took study medication.
Pharmacokinetic set consists of all subjects who provide evaluable data in the statistical analysis of pharmacokinetic parameters.
Treatments: A: 20 mg of Nexium banded OTC capsule fasted; B: 20 mg of Nexium [redacted] tablet fasted; C: 20 mg of Nexium banded OTC capsule fed; D: 20 mg of Nexium [redacted] tablet fed.
[redacted] OTC = over-the-counter.

A total of 41 (68.33%) subjects were male and 19 (31.67%) subjects were female. The mean age (SD) was 31.00 (8.97) years with a range of 18.00 to 51.00 years; and the mean BMI (SD) was 25.58 (2.82) kg/m^2. The majority of the study population was White (51, 85.00%). The remaining subjects were of Black (8, 13.33%) and Other (1, 1.67%) race.

Efficacy Results: Not applicable.

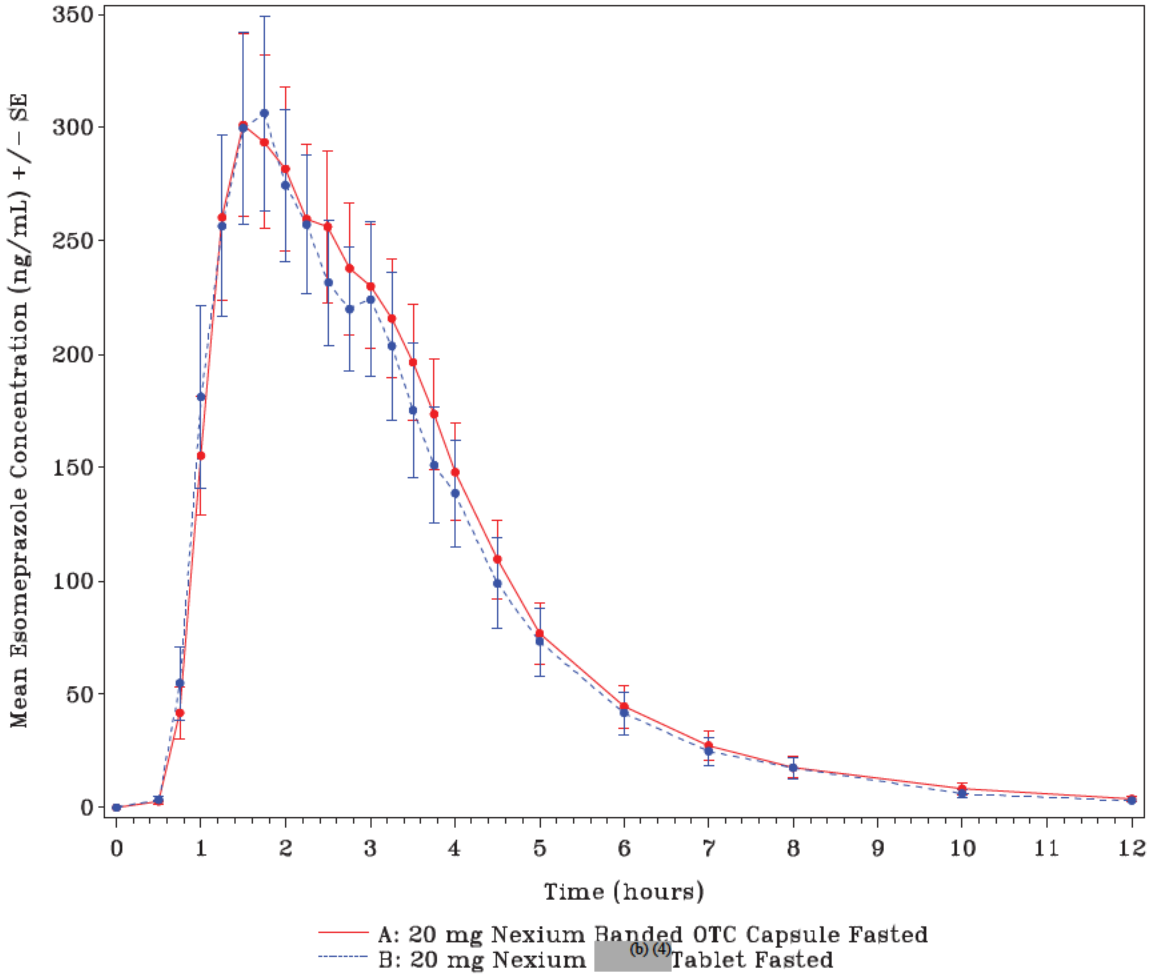
Pharmacokinetic Results:

Esomeprazole Plasma Concentrations:

As shown in Figure S 2, under fasting conditions, the PK profile of the 20 mg Nexium [redacted] tablet was similar to that of the 20 mg Nexium banded OTC capsule.

CLINICAL STUDY REPORT SYNOPSIS

Figure S 2. Mean (SE) Plasma Esomeprazole Concentrations (ng/mL) Over Time (h) – 20 mg Nexium Banded OTC Capsule (A) and 20 mg Nexium (b) (4) Tablet (B) in the Fasted State

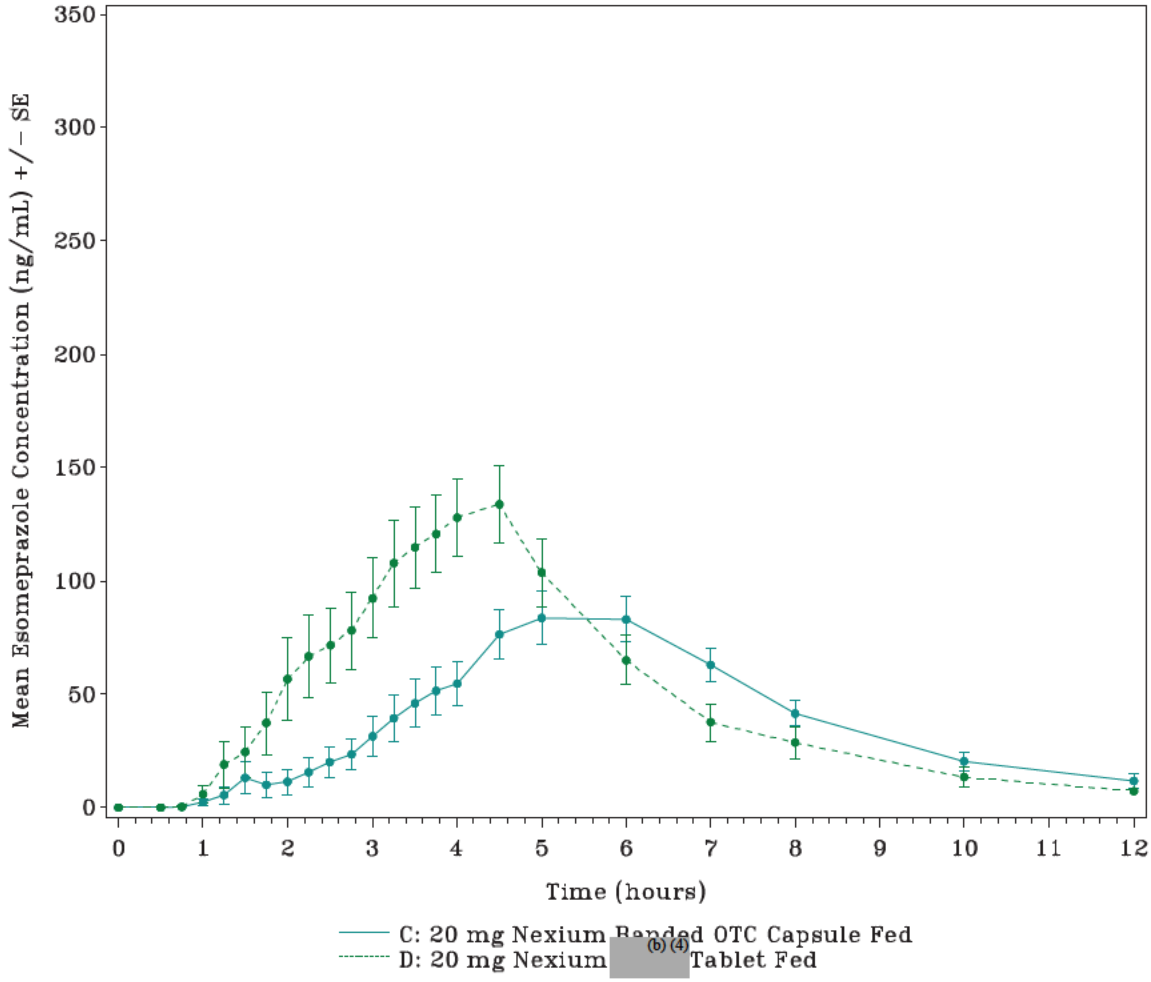


(b) (4) ;OTC = over-the-counter; SE = standard error.

As shown in Figure S 3, after administration with a standardized high-fat breakfast, plasma concentrations were markedly lower during the absorption phase for the 20 mg Nexium banded OTC capsule as compared to the 20 mg Nexium (b) (4) tablet.

CLINICAL STUDY REPORT SYNOPSIS

Figure S 3. Mean (SE) Plasma Esomeprazole Concentrations (ng/mL) Over Time (h) – 20 mg Nexium Banded OTC Capsule (C) and 20 mg Nexium (b) (4) Tablet (D) in the Fed State



(b) (4); OTC = over-the-counter; SE = standard error.

A comparison of the mean esomeprazole plasma concentrations for the 20 mg Nexium (b) (4) tablet in the fed and fasted state showed that after administration with a standardized high-fat breakfast, plasma concentrations were markedly lower during the absorption phase in the fed state as compared to the fasted state. Further, co-administration with food delayed the attainment of maximal plasma concentrations by several hours. Co-administration with food had a similar effect on the pharmacokinetics of the 20 mg Nexium banded OTC capsule.

Pharmacokinetic Parameters of Esomeprazole:

A summary of the mean PK parameters of plasma esomeprazole following a single dose of 20 mg Nexium banded OTC capsule or 20 mg Nexium (b) (4) tablet under fasted or fed conditions are presented in Table S 3. The PK results demonstrated that under fasted

CLINICAL STUDY REPORT SYNOPSIS

conditions, both the 20 mg Nexium banded OTC capsule and 20 mg Nexium [(b) (4)] tablet had numerically similar AUC_{inf}, AUC_{last}, and C_{max} values. Further, peak esomeprazole concentrations were observed approximately 2 hours after administration declining thereafter with an elimination half-life ($t_{½}$) of 1.1 to 1.3 hours for both formulations. Under fed conditions, both formulations exhibited markedly reduced AUC_{inf}, area under the drug concentration-time curve from time zero to time of last measurable concentration (AUC_{last}), and C_{max} values. Similarly, both the 20 mg Nexium banded OTC capsule and 20 mg Nexium [(b) (4)] tablet exhibited delayed time to maximum observed drug concentration (T_{max}) values as well as a slightly prolonged $t_{½}$ in the fed state.

Table S 3. Summary of the Mean (SD)[a] Pharmacokinetic Parameters of Plasma Esomeprazole Following a Single Dose Administered as a 20 mg Nexium Banded OTC Capsule or 20 mg Nexium [(b) (4)] Tablet under Fasted or Fed Conditions

Formulation	AUC_{inf} (ng*h/mL)	AUC_{last} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	Cl (L/h)
20 mg Nexium Banded OTC Capsule (Fasted)	1035.5 (925.7) [53]	1012.0 (906.6) [53]	511.3 (287.5) [53]	1.9 (0.8 – 6.3) [53]	1.3 (2.1) [53]	37.5 (29.1) [53]
20 mg Nexium [(b) (4)] Tablet (Fasted)	985.5 (802.1) [49]	976.2 (789.1) [49]	528.3 (292.1) [49]	1.8 (1.0 – 4.5) [49]	1.1 (0.5) [49]	37.3 (35.2) [49]
20 mg Nexium Banded OTC Capsule (Fed)	537.9 (538.2) [50]	448.6 (359.3) [55]	154.5 (109.7) [55]	5.5 (2.9 – 12.0) [55]	2.0 (3.0) [50]	73.9 (63.6) [50]
20 mg Nexium [(b) (4)] Tablet (Fed)	637.1 (586.8) [46]	567.1 (535.9) [49]	217.9 (162.0) [49]	4.5 (1.3 – 10.0) [49]	2.0 (4.5) [46]	74.0 (85.3) [46]

AUC_{inf} = area under the drug concentration time curve from time zero to infinity; AUC_{last} = area under the drug concentration-time curve from time zero to time of the last measurable concentration; Cl (also referred to as CL/F) = volume cleared by the system; C_{max} = maximum observed drug concentration; [(b) (4)] [(b) (4)] OTC = over-the-counter; SD = standard deviation; $t_{½}$ = elimination half-life; T_{max} = time to maximum observed drug concentration.

[a] All values presented as mean (SD) [n] with the exception of Tmax which is presented as median (range) [n].

Statistical Comparisons of Esomeprazole Pharmacokinetic Parameters:

A summary of statistical comparisons for the primary comparisons is presented in Table S 4. The Nexium [(b) (4)] tablet was bioequivalent to the Nexium banded OTC capsule in terms of both peak esomeprazole exposure (C_{max}) and the extent of esomeprazole exposure (AUC) under fasted conditions. An RSAB criterion was applied for C_{max} as a result of the observed high within-subject variability in the reference product. Under fed conditions, both AUC and C_{max} exhibited high within-subject variability, and RSAB testing approach was applied. The Nexium [(b) (4)] tablet met criteria for bioequivalence to the Nexium banded OTC capsule for AUC, but was not bioequivalent for C_{max}, due to the GMR of test vs reference products being

CLINICAL STUDY REPORT SYNOPSIS

outside of the prescribed range of (0.80, 1.25). Under fed conditions, C_{max} for Nexium (b) (4) tablet was 34.1% higher compared to the Nexium banded OTC capsule.

Table S 4. Summary of the Statistical Comparisons of the Pharmacokinetic Parameters of Esomeprazole Following a Single Dose Administered as a 20 mg Nexium Banded OTC Capsule or 20 mg Nexium (b) (4) Tablet under Fasted or Fed Conditions

Comparison	Parameter	S_{wr}[a]	Test/ Reference GMR	90% Confidence Interval	95% Criteria Bound	Method Used
B vs A	AUC_{inf} (ng*h/mL)	0.202	0.948	(0.890, 1.010)	---	Unscaled
	C_{max} (ng/mL)	0.304	1.009	---	-0.050	Scaled
D vs C	AUC_{inf} (ng*h/mL)	0.351	0.994	---	-0.061	Scaled
	C_{max} (ng/mL)	0.763	1.341	---	-0.156	Scaled

Note: Treatments: A: 20 mg of Nexium banded OTC capsule fasted; B: 20 mg of Nexium (b) (4) tablet fasted; C: 20 mg of Nexium banded OTC capsule fed; D: 20 mg of Nexium (b) (4) tablet fed.
AUC_{inf} = area under the drug concentration time curve from time zero to infinity; C_{max} = maximum observed drug concentration; GMR = geometric mean ratio; (b) (4)
OTC = over-the-counter; s_{wr} = within-subject standard deviation of the reference product
[a] If s_{wr} is ≥0.294 then a reference scaled average bioequivalence approach is applied. Bioequivalence is declared if 95% criteria bound <0 and the Test/Reference geometric mean ratio is between (0.80, 1.25).

A summary of statistical comparisons for the secondary comparisons is presented in Table S 5. Co-administration with a high-fat meal had a pronounced effect on the relative bioavailability of both the Nexium banded OTC capsule and Nexium (b) (4) tablet formulations. For the Nexium banded OTC capsule, AUC_{inf} and C_{max} were reduced by approximately 46.1% and 74.5% respectively in the fed state as compared to the fasted state. Similarly, for the Nexium (b) (4) tablet, AUC_{inf} and C_{max} were reduced by approximately 43.7% and 68.3 % respectively in the fed state as compared to the fasted state.

CLINICAL STUDY REPORT SYNOPSIS

Table S 5. Summary of Test/Reference GMRs Following a Single Dose Administered as a 20 mg Nexium Banded OTC Capsule or 20 mg Nexium (b) (4) Tablet under Fasted or Fed Conditions

Comparison	Parameter	Test/Reference GMR
D vs B	AUC_{inf} (ng*h/mL)	0.563
	C_{max} (ng/mL)	0.317
C vs A	AUC_{inf} (ng*h/mL)	0.539
	C_{max} (ng/mL)	0.255

Note: Treatments: A: 20 mg of Nexium banded OTC capsule fasted; B: 20 mg of Nexium (b) (4) tablet fasted; C: 20 mg of Nexium banded OTC capsule fed; D: 20 mg of Nexium (b) (4) tablet fed.
AUC_{inf} = area under the drug concentration time curve from time zero to infinity; C_{max} = maximum observed drug concentration; GMR = geometric mean ratio; (b) (4)
OTC = over-the-counter.

Pharmacodynamic evaluations were not done.

Safety Results: A summary of all-causality treatment-emergent AEs is presented in Table S 6. Twelve (12, 20.0%) subjects experienced a total of 29 treatment-emergent AEs (all causality). All treatment-emergent AEs were mild or moderate in severity. One (1) serious adverse event (SAE) was reported; the subject reported a wrist fracture after receiving the 20 mg of Nexium (b) (4) tablet in the fasted state. The SAE was considered unrelated to the study medication.

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Table S 6. Summary of Adverse Events

	Total N=60 n (%)	A N=53 n (%)	B N=49 n (%)	C N=55 n (%)	D N=49 n (%)
Number of Treatment Emergent AEs - All Causality	29	6	9	8	6
Number of Subjects with Treatment Emergent AEs - All Causality	12 (20.0)	4 (7.5)	5 (10.2)	4 (7.3)	3 (6.1)
Number of Subjects with Treatment Related[a] AEs	6 (10.0)	2 (3.8)	3 (6.1)	1 (1.8)	3 (6.1)
Number of Subjects with Mild AEs	12 (20.0)	4 (7.5)	5 (10.2)	4 (7.3)	3 (6.1)
Number of Subjects with Moderate AEs	2 (3.3)	0	1 (2.0)	1 (1.8)	0
Number of Subjects with Severe AEs	0	0	0	0	0
Number of Subjects with Serious AEs	1 (1.7)	0	1 (2.0)	0	0
Number of Subjects with AEs Leading to Discontinuation	5 (8.3)	1 (1.9)	2 (4.1)	2 (3.6)	0
Number of Subjects Who Died	0	0	0	0	0

A: 20 mg of Nexium banded OTC capsule fasted; B: 20 mg of Nexium (b) (4) tablet fasted; C: 20 mg of Nexium banded OTC capsule fed; D: 20 mg of Nexium (b) (4) tablet fed.
AE = adverse event, (b) (4) = multiple unit pellet system, OTC = over-the-counter.
[a] Related: related/unknown.

Nausea (n=5, 8.3%) and headache (n=5, 8.3%) were the most frequently reported AEs. Nausea was considered related in 2 of 5 subjects who reported the AE and headache was considered related in 4 of 5 subjects who reported the AE. The incidences of both nausea and headache were numerically similar across formulation and administration conditions. In general, AEs were similar across formulation and administration conditions.

Five (5) subjects discontinued study treatment due to AEs summarized in Table S 7. Of those subjects, 4 discontinued study treatment due to AEs not related to study treatment (vessel puncture site pain, nausea/vomiting, wrist fracture/excoriation, and influenza-like illness) and 1 discontinued study treatment due to a related AE (swollen tongue).

Table S 7. Discontinuations Due to Adverse Events

Event (Severity)	Relatedness to Study Treatment	Serious Adverse Event
Vessel puncture site pain (Mild)	Not related	No
Nausea (Mild)	Not related	No
Vomiting (Mild)	Not related	No
Wrist fracture (Moderate)	Not related	Yes
Excoriation (Mild)	Not related	No
Influenza-like illness (Mild)	Not related	No
Swollen tongue (Mild)	Related[a]	No

[a] Related: Related/Unknown.

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Pharmacokinetic Conclusions: The results of this study provide evidence that the 20 mg Nexium (b) (4) tablet is bioequivalent to the currently marketed Nexium banded OTC capsule in terms of both peak esomeprazole exposure (C_{max}) and the extent of esomeprazole exposure (AUC) under fasted conditions. Under fed conditions, the Nexium (b) (4) tablet met criteria for bioequivalence to the Nexium banded OTC capsule for AUC; however, the Test/Reference geometric mean ratio for C_{max} was 34.1% higher for the Nexium (b) (4) tablet than the Nexium banded OTC capsule, thus not meeting the criteria for bioequivalence.

Co-administration with a high-fat meal had a pronounced effect on the relative bioavailability of both the Nexium banded OTC capsule and Nexium (b) (4) tablet formulations. For the Nexium banded OTC capsule, AUC_{inf} and C_{max} were reduced by approximately 46.1% and 74.5%, respectively, in the fed state as compared to the fasted state. Similarly, for the Nexium (b) (4) tablet, AUC_{inf} and C_{max} were reduced by approximately 43.7% and 68.3%, respectively, in the fed state as compared to the fasted state.

The results of this study also confirmed the well-characterized effect that food has on the bioavailability of esomeprazole. The magnitude reduction in the measured primary PK parameters is consistent with that observed in prior esomeprazole food effect studies. Further, the observed delay in time to peak concentrations is consistent with delayed gastric emptying and decreased absorption that results from co-administration with food. The delayed T_{max} can explain the decreased bioavailability under the fed conditions. The acid-labile nature of esomeprazole would result in increased degradation with increased time in the stomach. The reduction in bioavailability, however, does not affect clinically relevant acid suppression, as it has been shown that food has no significant effect on percentage of time that intragastric pH >4, even though AUC and C_{max} are decreased.

Safety Conclusions: Both Nexium 20 mg banded OTC capsule and Nexium 20 mg (b) (4) tablet formulations, under fed and fasted conditions, were well-tolerated with no unexpected safety findings. No deaths occurred during this study. Twelve (12, 20.0%) subjects experienced a total of 29 treatment-emergent AEs. Four (4, 7.5%) subjects reported an AE after receiving the 20 mg Nexium banded OTC capsule (fasted), 5 (10.2%) after receiving the 20 mg Nexium (b) (4) tablet (fasted), 4 (7.3%) after receiving the 20 mg Nexium banded OTC capsule (fed), and 3 (6.1%) after receiving the 20 mg Nexium (b) (4) tablet (fed). All AEs were mild or moderate in severity. Of the 12 (20.0%) subjects who reported treatment-emergent AEs, 6 (10.0%) subjects had treatment-related AEs. The most frequently reported all-causality treatment-emergent AEs were nausea (n=5, 8.3%) and headache (n=5, 8.3%). There was 1 SAE; the subject reported a wrist fracture after receiving Nexium (b) (4) tablet (fasted). The SAE was considered not related to the study medication.
Five (5) subjects discontinued study treatment due to AEs. Of those subjects, 4 discontinued study treatment due to AEs not related to study treatment (vessel puncture site pain, nausea/vomiting, wrist fracture/excoriation, and influenza-like illness) and 1 discontinued study treatment due to a related AE (swollen tongue).

The observed safety results were consistent with the known safety profile of the study drug and as outlined in the product label.

CLINICAL STUDY REPORT SYNOPSIS

Overall Conclusions: The results from this study support the conclusion that the Nexium 20 mg (b) (4) tablet is bioequivalent to the currently marketed Nexium 20 mg banded OTC capsule under fasted conditions. The results further support the interchangeability of the 2 formulations and OTC marketing of the Nexium (b) (4) tablet formulation with the same directions and usage information as the Nexium banded OTC capsule.

Both Nexium 20 mg banded OTC capsule and Nexium 20 mg (b) (4) tablet formulations (under fed and fasted conditions) were well-tolerated with no unexpected safety findings.

The observed safety results were consistent with the known safety profile of the study drug and as outlined in the product label.

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

/s/

ANDREW J SHIBER
03/26/2015

From:	Buchanan, Jeffrey A.
To:	christine.chirdo@pfizer.com
Cc:	Buchanan, Jeffrey A.
Subject:	NDA 207920 Nexium 24HR DR tablets - Information/Sample Request
Date:	Wednesday, March 25, 2015 2:53:13 PM

Hi Christine,

In order to facilitate the review of the above-referenced application, please submit the following by close of business, Friday, April 3, 2015:

- One exact-size model of the proposed 2-count sample carton with peel-back Drug Facts label

Please send the requested item directly to me at the address below and feel free to contact me should you have questions or concerns. Thank you.

Jeffrey Buchanan

U.S. Food and Drug Administration
FDA/OMPT/CDER/OND/ODE IV/DNDP
White Oak Building 22, Room 5461
10903 New Hampshire Avenue
Silver Spring, Maryland

Use zip code **20903** *if shipping via United States Postal Service (USPS).*

Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, FedEx, etc.).*

Phone: (301) 796-1007 Fax: (301) 796-9899

Email: jeffrey.buchanan@fda.hhs.gov

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

/s/

JEFFREY A BUCHANAN
03/25/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207920

NDA ACKNOWLEDGMENT

Pfizer, Inc.
Attention: Christine D. Chirdo
Director, U.S. Regulatory Strategy Category Lead
1 Giralda Farms
Madison, NJ 07940

Dear Ms. Chirdo:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Nexium® 24HR (esomeprazole magnesium) delayed-release tablets, 22.3 mg

Date of Application: February 6, 2015

Date of Receipt: February 6, 2015

Our Reference Number: NDA 207920

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 7, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Drug Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have questions, contact me at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Jeffrey Buchanan
Regulatory Health Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

JEFFREY A BUCHANAN
02/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 118964

MEETING MINUTES

AstraZeneca, LP
Attention: Judy W. Firor
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Firor:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Nexium 24HR (esomeprazole magnesium) delayed-release tablets, 20 mg.

We also refer to the meeting between representatives of your firm and the FDA on January 28, 2014. The purpose of the meeting was to discuss the content and format of an NDA for over-the-counter Nexium 24HR (esomeprazole magnesium) delayed-release tablets, 20 mg.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have questions, contact Jeffrey Buchanan, Regulatory Health Project Manager, at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Theresa Michele, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	January 28, 2014 at 10:00 to 11:00 AM
Meeting Location:	WO22 Rm 1309
Application Number:	PIND 118964
Product Name:	Nexium 24HR (esomeprazole magnesium) delayed-release tablets, 20 mg
Indication:	Treats frequent heartburn (occurs 2 or more days a week)
Sponsor/Applicant Name:	AstraZeneca, LP
Meeting Chair:	Theresa Michele, M.D.
Meeting Recorder:	Jeffrey Buchanan

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation
Theresa Michele, M.D., Acting Division Director
Lesley Furlong, M.D., Medical Team Leader
Jane Filie, M.D., Medical Officer
Cindy Li, Ph.D., Pharmacology/Toxicology Reviewer
Dan Brum, Pharm.D., M.B.A., B.C.P.S., R.A.C., Chief, Project Manager Staff
Jeffrey Buchanan, Regulatory Health Project Manager

Division of Nonprescription Regulation Development
Ruth E. Scroggs, Pharm.D., IDS Team Leader

Division of Gastroenterology and Inborn Errors Products
Robert Fiorentino, M.D., Medical Team Leader
Farrokh Sohrabi, M.D., Medical Officer

Office of New Drug Quality Assessment
Sheldon Markofsky, Ph.D., Chemistry Reviewer
Tien-Mien (Albert) Chen, Ph.D., Biopharmaceutics Reviewer

Office of Clinical Pharmacology
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

AstraZeneca
Charlotta Klockare, M.Sc. Pharm., Associate Director, Global Regulatory Affairs

Pfizer
Christine Chirdo, Director, Worldwide Regulatory Strategy
Josephine Fubara, Ph.D., Global R&D Franchise Lead, GI
William Bubnis, Ph.D., Director, Product Design
Nandita Mukherjee, M.D., M.P.H., Director, Safety Risk Lead
Sebastian Moreira, Pharm.D., Director, Clinical Research & Development
Charles Pollack, M.D., Ph.D., Senior Director, Franchise Medical Lead
Roger Wilson, M.Sc., Associate Director, Chemistry, Manufacturing and Controls
Steve Teo, Ph.D., DAPB, ERT, Director, Nonclinical Lead
Mark A. Wingertzahn, Ph.D., Head of Global Clinical Research
Doreen Frank, Regulatory Consultant
Naman Shah, Pfizer GI Franchise Intern

1.0 BACKGROUND

AstraZeneca, L.P. (AstraZeneca) proposes to market a new drug product, Nexium 24HR (esomeprazole magnesium) delayed-release tablets, 20 mg, as an over-the-counter (OTC) drug product for the treatment of frequent heartburn in patients 18 years of age and older. The proposed tablet dosage form contains 22.3 mg esomeprazole magnesium trihydrate which is equivalent to 20 mg esomeprazole. Esomeprazole magnesium is a proton pump inhibitor (PPI) intended to be dosed once daily.

Pfizer Consumer Health (Pfizer), having entered into a marketing agreement with AstraZeneca, will have the OTC marketing rights and intends to submit a 505(b)(1) new drug application (NDA) for the tablet dosage form pending the approval of the same OTC indication for esomeprazole magnesium delayed-release capsules currently under review by FDA as NDA 204655, submitted May 30, 2013. Pfizer intends to rely on the nonclinical studies conducted with esomeprazole and omeprazole, the clinical pharmacology data submitted in AstraZeneca's prescription NDA 021153, and the clinical efficacy and safety data in support of the OTC indication submitted in NDA 204655. No new nonclinical or clinical data have been generated in support of the proposed OTC esomeprazole tablets. As such, Pfizer intends to submit previously conducted bioequivalence studies with the esomeprazole tablet and the clinical trial esomeprazole (b) (4) clinical capsule ("esomeprazole clinical capsule") to bridge to the existing data submitted in these NDA applications. Based on this bridging strategy, Pfizer plans to cross-reference the cumulative review of nonclinical pharmacology/toxicology and clinical pharmacology data submitted in NDA 021153, and the most recent integrated summary of safety as well as the clinical efficacy studies for the OTC indication for the treatment of frequent heartburn submitted in NDA 204655. The PDUFA user fee goal date for NDA 204655 is March 30, 2014. The prescription NDA 021153 was approved October 3, 2000.

AstraZeneca and Pfizer requested a Type B pre-NDA meeting with the Division of Nonprescription Clinical Evaluation on August 14, 2013. Pfizer is seeking agreement from FDA that the proposed bridging strategy, based on the bioequivalence studies and the proposed content and format of the NDA, will support the safety and efficacy of OTC esomeprazole magnesium delayed-release tablets for the treatment of frequent heartburn.

2. DISCUSSION

The sponsor's questions are in **bold type**, and FDA's preliminary responses are in *italics*. Minutes of the discussion are in regular font.

1. Does the Agency agree with the proposed presentation of data and cross-referencing strategy to support the nonclinical review of the OTC esomeprazole tablets NDA?

FDA Preliminary Response:
Yes, it appears acceptable. The adequacy of the data to support your submission will be a review issue.

2. Does the Agency agree with the proposed bridging and cross-referencing strategy to support the Clinical review of the NDA?

FDA Preliminary Response:
Refer to our responses to Questions 3, 4, and 5.

3. Pfizer intends to request a bioequivalence waiver for the OTC esomeprazole tablets based upon the proposed bridging strategy from the bioequivalence studies, does the Agency agree?

FDA Preliminary Response:
No, we do not agree. Because the esomeprazole 20 mg DR tablet dosage form has not been approved in the United States, you will need to provide bioequivalence (BE) bridging with an approved product as well as an in vitro alcohol dose dumping study for this DR tablet dosage form.

Bioequivalence Bridging Study: *A new BE study between the proposed OTC 20 mg DR tablet and the OTC 20 mg DR capsule product (NDA 204655, currently under review) is required. We are unable to rely upon the findings of QBE-033 (pharmacokinetic (PK) bioequivalence study) previously submitted to NDA 021153 for the following reasons:*

- *The study was not conducted with the reference product for the proposed OTC indication.*
- *The study was conducted in 1998, and inspections of the clinical trial and bioanalytical sites which are typically required for pivotal BE studies will pose a challenge.*
- *The study utilized statistical approaches that are not standard practice in evaluating bioequivalence (e.g., use of 94 % confidence intervals).*

- *Single dose BE studies are considered most appropriate for establishing bioequivalence between formulations, unlike the multiple dose regimen evaluated in QBE-033.*

- *It is not clear if the manufacturing site, equipment, process, and personnel have changed since this study was conducted.*

In Vitro Alcohol-Induced Dose Dumping: *Evaluate the alcohol-induced dose dumping of your modified-release (MR) product, by first conducting an in vitro alcohol dose dumping test. Depending on the result of the in vitro testing, you may have to follow-up with an in vivo alcohol dose dumping study. Note that if the results show an interaction of your MR product with alcohol, we recommend you discuss these results with FDA prior to NDA submission.*

Consider the following points during the evaluation of the in vitro alcohol-induced dose dumping study of your MR product:

- *Conduct dissolution testing for all the proposed strengths using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.*

- *The following alcohol concentrations for the in vitro dissolution studies are recommended: 0%, 5%, 10%, 20%, and 40%.*

- *In general;*
    - *If the optimal dissolution medium is 0.1N HCl, dissolution profiles in 0.1N HCl (pH 1.2) containing the above range of alcohol concentrations would be sufficient.*
    - *If the optimal dissolution medium is NOT 0.1N HCl, dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal dissolution medium are recommended.*
    - *If the optimal dissolution medium has not been identified, dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH* (b) (4) *, and 6.8) are recommended.*
    - *If the dissolution of the MR product is pH independent, then dissolution data in 0.1N HCl with the above range of alcohol concentrations is sufficient.*

- *Compare the shape of the dissolution profiles to determine if the modified-release characteristics are maintained, especially in the first 2 hours.*

- *The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).*

- *The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol-induced dose dumping study should be provided to us for review and comment.*

Discussion
The Sponsor acknowledged the Agency's request to conduct a BE study for the tablet dosage form and requested clarification regarding its design.

FDA confirmed that the new BE study should compare the proposed OTC 20 mg delayed-release tablet and the OTC 20 mg delayed-release capsule (NDA 204655, currently under review), noting this is contingent upon approval of the latter. FDA recommended that the new BE study be a 2-way crossover study conducted under fasting conditions. FDA also requested that the Sponsor provide data characterizing the effect of food on the pharmacokinetics of the proposed OTC 20 mg delayed-release tablet. The Sponsor agreed and will submit the protocol for FDA review.

Regarding the *in vitro* alcohol induced dose-dumping study, FDA stated it is a relatively new requirement for all modified-release dosage forms. FDA agreed the Sponsor has the option to submit a justification for why such a study would not be feasible for this product.

4. Does the Agency agree with the proposed presentation of data and cross-referencing strategy to support the clinical pharmacology review of the NDA?

FDA Preliminary Response:
Yes, we agree that it is reasonable to cross-reference the clinical pharmacology information generated for esomeprazole in NDA 021153, with the exception of food-effect on PK. You should address the food-effect on PK for your proposed tablet formulation.

In addition, see FDA response to Question 3 regarding the need for an additional bioequivalence study.

Discussion
The Sponsor acknowledged FDA's request to address the food-effect on pharmacokinetics for the proposed tablet and agreed to provide this information.

5. Does the Agency agree that existing safety and efficacy data are sufficient to support the submission and review of an NDA for an OTC esomeprazole tablet?

FDA Preliminary Response:
Contingent upon the approval of your OTC esomeprazole capsule, your safety and efficacy data may be supportive of the NDA for OTC esomeprazole 20 mg tablet, provided you demonstrate that the tablet formulation is bioequivalent to the capsule formulation.

6. Does the Agency agree with the proposed strategy to cross-reference the ISS submitted in the OTC esomeprazole delayed-release capsule NDA for the safety review of the OTC esomeprazole tablet NDA submission?

FDA Preliminary Response:
We agree that you may cross reference the ISS submitted in the NDA for OTC esomeprazole magnesium 20 mg capsules (NDA 204655) up to the cut-off date of April 30, 2013. However, we

expect you to provide, at the time of the NDA submission, an interim update of safety from May 1, 2013 up to a cut-off date as close as possible to the submission date.

Discussion
Given that the NDA submission would be delayed because of the need to conduct a BE study, the Sponsor asked if it was still acceptable to reference the ISS submitted in NDA 204655 for OTC esomeprazole magnesium 20 mg capsules and provide an interim update of safety from AstraZeneca's safety database, the BE study, and a literature review from May 1, 2013, up to a cut-off date as close as possible to the filing date of the OTC tablet NDA submission date. The Agency agreed that an interim update was acceptable as long as the NDA submission occurred within a reasonable time period (a year or two).

7. Does the Agency agree with the proposed outline of content and data cut-off dates for the 4MSU?

FDA Preliminary Response:
We do not agree with your proposed outline of the content of the 4-month safety update. Include all adverse events, serious and non-serious, from the post-marketing database and from the literature in the 4-month safety update. For cut-off dates see the response to Question 6.

8. Does the Agency agree to the proposed cross-referencing strategy to support the review of drug substance information in the NDA?

FDA Preliminary Response:
We agree that you may cross-reference NDA 021153 for the drug substance information in your proposed NDA.

9. Does the Agency agree a future change in color of the non-functional tablet coating is eligible for a biowaiver if these criteria are met?

FDA Preliminary Response:
We are unable to answer your question based on the information provided. Submit for review the complete CMC data/information on the component of the proposed color to be used for tablet coating.

10. Does the Agency agree that, in accordance with currently approved labeling directions for PPIs for OTC use in adults 18 years of age and older, a waiver request for pediatric studies for the proposed OTC esomeprazole tablets is appropriate for submission and review in the NDA?

FDA Preliminary Response:
Yes, we agree that a waiver request for pediatric studies seems appropriate for your NDA submission and our review.

11. Does the Agency agree with the format of the proposed datasets to be provided in the NDA?

FDA Preliminary Response:
Refer to responses to Questions 3 and 4 above. Include the following:

1. *An in vitro alcohol-induced dose dumping study.*

2. *A new head-to-head 2-way crossover BE study comparing the proposed OTC 20 mg DR tablet and the OTC 20 mg DR capsule product (currently under review, NDA 204655).*

3. *The SAS transport file for the individual PK dataset and mean PK parameters of the above new BE study in a reviewable format to allow FDA to reassess the BE results and validate your BE conclusions.*

4. *Complete comparative dissolution profile/data (individual and mean (and standard deviation in electronic format); n=12 tablets/batch) between the proposed OTC DR 20 mg tablet and the proposed OTC DR 20mg capsule (currently under review, NDA 204655).*

5. *Dissolution profile/data of at least three stability batches of the proposed OTC DR 20 mg tablets for verifying your proposed acceptance criterion of dissolution for esomeprazole.*

Discussion
The Sponsor requested clarification regarding FDA's request to conduct comparative dissolution profile/data [individual and mean (and standard deviation in electronic format); n=12 tablets/batch] between the proposed OTC delayed-release 20 mg tablet and the proposed OTC delayed-release 20 mg capsule (currently under review, NDA 204655). FDA recommended the Sponsor provide comparative dissolution data between the tablet to be used in the bioequivalence study and tablet stability samples. The Sponsor took FDA's request under advisement.

12. Does the Agency agree with the proposed table of contents for the NDA submission?

FDA Preliminary Response:
Generally speaking, the proposed table of contents appears acceptable. The contents of the submission, as well as the functionality and navigability of the electronic submission, will be assessed at the time of submission.

If you intend to market the proposed product with a consumer information leaflet, then the eCTD labeling folder would include the draft consumer information leaflet labeling.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End-of-Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, submit the initial PSP as early as practicable but before the initiation of any phase 3 studies, or any combined phase 2 and phase 3 study, of the drug that is the subject of the initial PSP. If a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, submit the initial PSP no later than 210 calendar days before a marketing application or supplement is submitted. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach), any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and MSWord format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, "Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans," located at the following web address: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The page may be found at the following web address: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	*Site Address*	*Federal Establishment Indicator (FEI) or Registration Number (CFN)*	*Drug Master File Number (if applicable)*	*Manufacturing Step(s) or Type of Testing [Establishment function]*
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	*Site Address*	*Onsite Contact (Person, Title)*	*Phone and Fax number*	*Email address*
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Post Meeting Addendum:

Regarding the Biopharmaceutics requirement for the *in vitro* alcohol dose-dumping study, consider the following items as you develop your justification:

1. The proposed formulation of the drug product (drug name) does not contain any extended release component. The delayed-release (DR) component (b) (4) (drug name) which is labile in the acid stage/environment.

2. In the buffer stage (pH XX), the drug product of (drug name) behaves as an immediate release product showing dissolution of >YY% at ZZ min.

Submit your justification with supportive *in vitro* dissolution profile data. FDA will review and consider your request for waiving the *in vitro* alcohol dose-dumping study for this particular drug formulation.

5.0 ACTION ITEMS

- The Sponsor aligned with FDA's request to conduct a 2-way crossover study under fasting conditions between the proposed OTC 20 mg delayed-release tablet and the OTC 20 mg delayed-release capsule product (NDA 204655, currently under review).

- FDA asked the Sponsor to submit the protocol for the new BE study and inform the Agency of the initiation date.

- FDA agreed that the Sponsor could submit a justification for not conducting an alcohol-induced dose dumping study due to the inherent characteristics of the PPIs; the Sponsor acknowledged the Agency's feedback.

- Sponsor agreed to provide characterization of food-effect on the pharmacokinetics of the proposed OTC tablet.

- FDA agreed the Integrated Summary of Safety provided in NDA 204655 (currently under review) may be cross-referenced and supplemented with updated safety information from the time of the OTC 20 mg delayed-release capsule NDA submission. FDA agreed with the Sponsor's proposal to conduct an interim update as long as the NDA submission for the proposed OTC 20 mg delayed-release tablet occurs within one to two years.

- FDA requested dissolution profiles on the bio-study tablet and tablet stability samples; Sponsor stated that this feedback will be taken under advisement.

6.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

THERESA M MICHELE
03/25/2014