CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207920Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**207920**
Submission Date(s)	**02/06/2015**
Brand Name	**Nexium® 24HR Delayed-release Tablets**
Generic Name	**Esomeprazole magnesium**
OCP Reviewer	**Dilara Jappar, Ph.D.**
OCP Team Leader	**Sue-Chih Lee, Ph.D.**
OCP Division	**Division of Clinical Pharmacology 3**
OND Division	**DNDP**
Sponsor	**Pfizer Inc.**
Submission Type	**Original, 505(b)(1),**
Formulation, Strength	**Delayed-release Tablets, 20 mg**
Proposed indication	**Over-the-Counter treatment of frequent heartburn which occurs 2 or more days a week in adults**
Recommended Dosing Regimen	**20 mg Tablets once daily for 14 days**

Table of Contents

1. Executive Summary

The sponsor has developed a delayed release (DR) tablet formulation of esomeprazole magnesium, which is a proton-pump inhibitor (PPI), for the over-the-counter (OTC) treatment of frequent heartburn. The proposed oral dose is one tablet of 20 mg esomeprazole once daily before eating in the morning for 14-Day course of treatment. The proposed regulatory pathway is 505(b)(1). The sponsor (Pfizer) cross references to NDA 204655 for Nexium 24 HR (esomeprazole magnesium) capsule where Pfizer was also the sponsor agent.

In support of this submission, the sponsor has conducted one bioequivalence (BE) study with a partial replicate study design with 6-period cross-over to evaluate the bioequivalence of proposed product of Nexium (b) (4) 20-mg tablet (20 mg esomeprazole delayed-release tablet) relative to the currently available esomeprazole OTC product of Nexium banded OTC 20-mg capsule (20 mg Esomeprazole delayed-release capsule) under both fed and fasted state. This BE study was reviewed by OPQ/Biopharm group. According to the Biopharm reviewer, the proposed delayed-release esomeprazole tablets are bioequivalent to the currently marketed banded OTC capsule in

terms of both peak esomeprazole exposure (C_{max}) and the extent of esomeprazole exposure (AUC) under fasted conditions. This OCP review focused on assessing the effect of food based on the PK parameters obtained in this BE study under fed and fasted conditions.

1.1 Recommendations

The Office of Clinical Pharmacology has found the submission acceptable from a clinical pharmacology standpoint provided a mutual agreement on labeling languages is reached.

1.2 Clinical Pharmacology Highlights

Food Effect:

- Nexium delayed release tablet (proposed product): food reduced the AUC and C_{max} of esomeprazole by 43.7% and 68.3%, respectively, compared to the fasted state.
- Nexium banded OTC capsule (reference product): food reduced the AUC and C_{max} of esomeprazole by 46.1% and 74.5%, respectively, compared to the fasted state.
- The extents of effect of food on these two products were similar.

Labelling recommendation:
Sponsor Proposal: swallow 1 tablet with a glass of water before eating in the morning.
OCP Recommendation: swallow 1 tablet with a glass of water at least one hour before eating in the morning.

2 Question-Based Review

2.1 List of *In-vivo* and *In-vitro* Clinical Pharmacology Studies

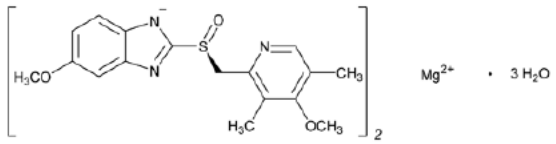
In support of this NDA submission, the sponsor has conducted one BE study in 46 healthy subjects with partial replicated study design with 6-period cross-over to evaluate the bioequivalence of 20 mg of Nexium (b) (4) tablet (20 mg esomeprazole delayed-release tablet) to that of 20 mg of Nexium banded OTC capsule (20 mg Esomeprazole delayed-release capsule) under both fed and fasted states.

Study 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:

2.2 General Attributes of the drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Drug Substance: Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Esomeprazole magnesium trihydrate drug substance is used in this formulation which has a molecular formula of $((C_{17}H_{18}N_3O_3S)_2\ Mg \times 3\ H_2O)$ and molecular weight 767.2 g/mol.



Formulation: The proposed drug product is a delayed released tablet of esomeprazole magnesium which provides a 20 mg dose of esomeprazole as 22.3 mg esomeprazole magnesium trihydrate.

The sponsor is developing only one strength of esomeprazole delayed release tablet to provide 20 mg esomeprazole.

Table 1: Composition of Esomeprazole Magnesium Delayed Release Tablet

Name of Ingredients	Function	Reference to Standard	Unit formula	
			mg/unit	%
Active [a]				
Esomeprazole magnesium trihydrate (corresponding to esomeprazole 20 mg)	Active	USP	22.3	(b) (4)
Excipients [a]				
Cellulose, microcrystalline	(b) (4)	NF	(b) (4)	
Crospovidone (b) (4)		NF		
Glyceryl monostearate (b) (4)		NF		
Hydroxypropyl cellulose		NF		
Hypromellose		USP		
Magnesium stearate		NF		
Methacrylic acid (b) (4) copolymer (b) (4)		NF		
(b) (4)		In-House		
Polysorbate 80		NF		
Sodium stearyl fumarate		NF		
(b) (4)		NF		
(b) (4) Paraffin		NF		
Talc		USP		
Triethyl citrate		NF		
(b) (4)		USP	N/A	- -
		USP	N/A	- -

[a] The normal quantities listed are theoretical and based on a yield corresponding to 100%.
[b] The amount of ingredient is expressed on a (b) (4)
[c] Methacrylic acid (b) (4) copolymer (b) (4) (b) (4) polysorbate 80.
[d] The amount of sucrose (b) (4)
[e] (b) (4)
N/A Not applicable

2.2.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The proposed indication is over-the-counter (OTC) treatment of frequent heartburn which occurs 2 or more days a week in adults 18 years of age and older.

Esomeprazole is a proton pump inhibitor (PPI) that suppresses gastric acid secretion via specific inhibition of the H^+, K^+-ATPase enzyme (proton pump) located in the secretory membrane of the gastric parietal cell. In the acidic compartment of the parietal cell, esomeprazole is protonated

and converted into a pharmacologically active inhibitor that react with luminally accessible cysteines of H^+, K^+-ATPase to form a disulfide bond, thus irreversibly inhibiting H^+, K^+-ATPase activity. Since PPIs block the final common pathway of acid production in the stomach, they inhibit both basal and stimulated gastric acid secretion.

2.2.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose is one tablet (20 mg esomeprazole), once a day for 14 days before eating in the morning.

2.3 General Clinical Pharmacology

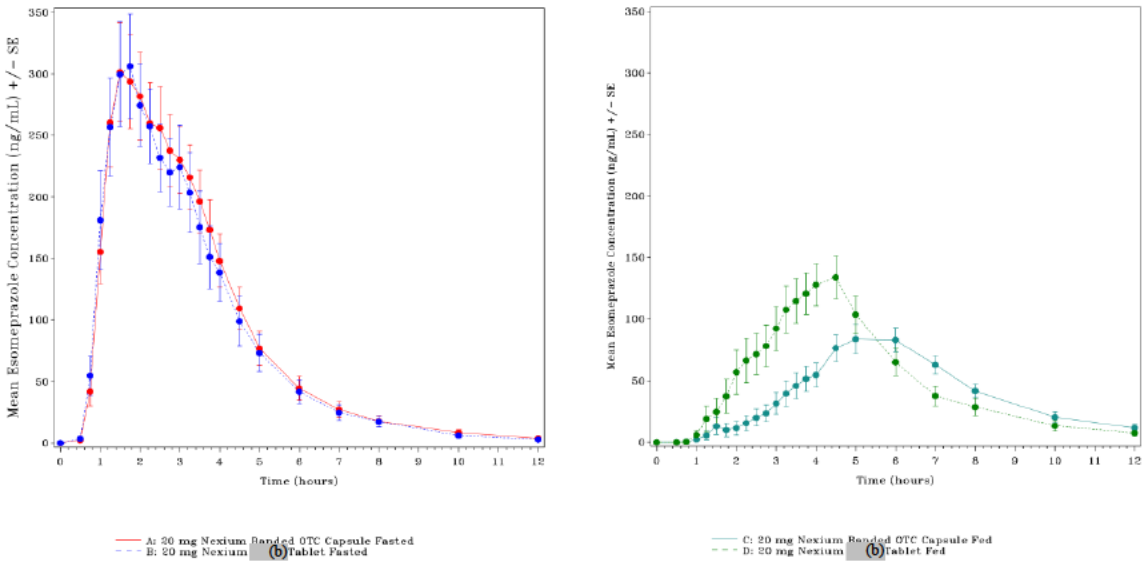
2.3.1 Is the new formulation of 20 mg esomeprazole delayed-release tablet bioequivalence to the reference product 20 mg esomeprazole OTC delayed-release capsule?

In support of this NDA submission, the sponsor has conducted one phase I, randomized, single-dose, 6 period, crossover, partial replicate, open- label BE study (Study B5141002) in 46 healthy subjects to evaluate the bioequivalence of 20 mg of Nexium (b) (4) tablet (20 mg esomeprazole delayed-release tablet) to that of 20 mg of Nexium banded OTC capsule (20 mg Esomeprazole delayed-release capsule) under both fed and fasted state.

- Treatment A: 20 mg Esomeprazole delayed-release capsule in the fasted state (administered in 2 treatment periods)
- Treatment B: 20 mg esomeprazole delayed-release tablet in the fasted state
- Treatment C: 20 mg esomeprazole delayed-release capsule with a high-fat meal (administered in 2 treatment periods)
- Treatment D: 20 mg esomeprazole delayed-release tablet with a high-fat meal

This BE study was reviewed by Biopharm reviewer Dr. Peng Duan in OB/ONDP and the statistical analysis of this BE study was conducted by Biostatistics reviewer Dr. Sungwoo Choi. FDA reviewers obtained similar conclusions as the sponsor's. The 20 mg Nexium (b) (4) tablet is bioequivalent to the currently marketed Nexium banded OTC capsule in terms of both C_{max} and AUCs under fasted conditions. Under fed conditions, the Nexium (b) (4) tablet met bioequivalence criteria to the Nexium banded OTC capsule for AUC; however, for C_{max}, the geometric mean of test/reference ratio was outside bioequivalence criteria (0.80-1.25) where the C_{max} of Nexium (b) (4) tablet was 34.1% higher than that of Nexium banded OTC capsule.

Figure 1: Mean (SE) Plasma Esomeprazole Concentrations (ng/mL) Over Time (h) for 20 mg Nexium Banded OTC Capsule and 20 mg Nexium (b) (4) Tablet in the Fasted and fed State



2.3.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

For proposed product Nexium delayed release tablet, food reduced the AUC and C_{max} of esomeprazole by 43.7% and 68.3%, respectively, compared to the fasted state.
For reference product Nexium banded OTC capsule, food reduced the AUC and C_{max} of esomeprazole by 46.1% and 74.5%, respectively, compared to the fasted state.
The extent of effect of food on these two products was similar.

Labelling recommendation:
Sponsor Proposal: swallow 1 tablet with a glass of water before eating in the morning.
OCP Recommendation: swallow 1 tablet with a glass of water at least one hour before eating in the morning.

Study B5141002 had also evaluated the effect of food on bioavailability of esomeprazole from Nexium banded OTC capsule or (b) (4) tablet where these products were given under fasting conditions in treatment A and B and under fed conditions under treatment C and D in 46 healthy subjects. Please refer to Biopharm review for detailed study design. In all treatment groups of both fed and fasted states, the subjects underwent an overnight fasting of at least 10 hours before the dose administration. In treatment A and B under fasting conditions, a single dose of 20 mg Nexium OTC banded capsule or Nexium (b) (4) tablet were given orally with 200 mL of water and subjects had to fast 4 additional hours post-dose. In treatment C and D under fed conditions, a single dose of 20 mg Nexium OTC banded capsule or Nexium (b) (4) tablet were given orally with 200 mL of water 30 minutes after administration of standardized high-fat breakfast and no food was allowed for 4 hours post-dose.

Co-administration of high fat breakfast had similar effect on and Nexium (b) (4) tablet and Nexium OTC capsule where food reduced the AUC and C_{max} of esomeprazole by 43.7% and 68.3% for (b) (4) tablet and by 46.1% and 74.5% for Nexium OTC capsule product, respectively. In addition, co-administration of food delayed t_{max} by 2.5 hr for (b) (4) tablet and 3.5 Nexium OTC capsule.

Figure 2: Mean (SE) Plasma Esomeprazole Concentrations Over Time (h) under fed and fasted states for 20 mg Nexium (b) (4) Tablet and 20 mg Nexium banded OTC capsule

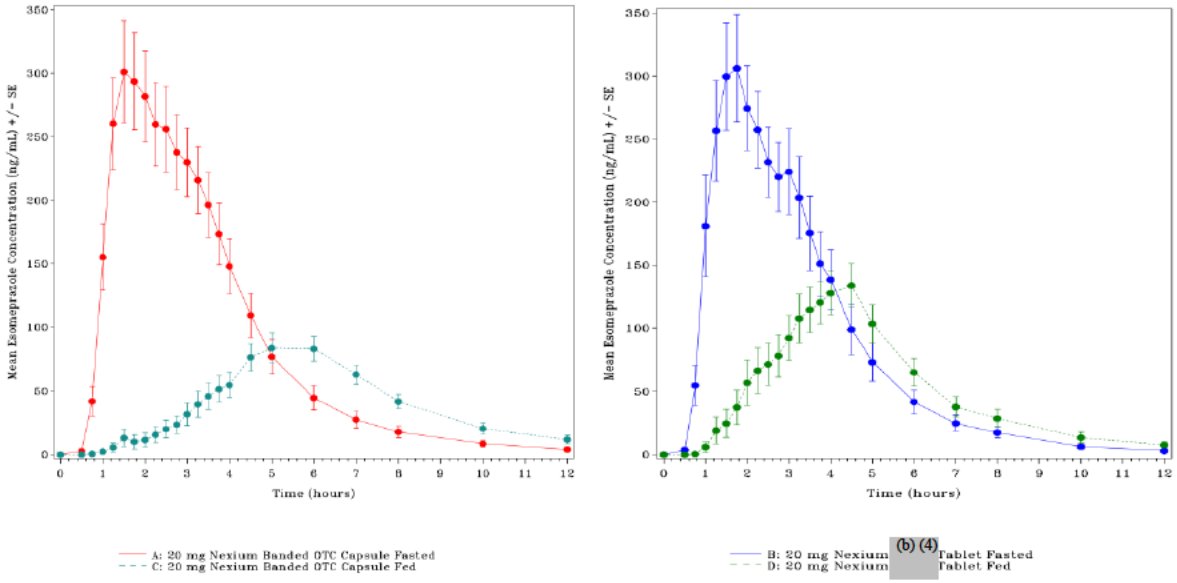


Table 3: Summary of the Mean (SD) Pharmacokinetic Parameters of Plasma Esomeprazole Following a Single Dose Administered as a 20 mg Nexium Banded OTC Capsule or 20 mg Nexium (b) (4) Tablet under Fasted or Fed Conditions

	20 mg Nexium (b) (4) Tablet		20 mg Nexium Banded OTC Capsule	
Parameters (unit)	Fasted Treatment B	Fed Treatment D	Fasted Treatment A	Fed Treatment C
C_{max} (ng/mL)	985.5 (802.1)	637.1 (586.8)	1035.5 (925.7)	537.9 (538.2)
$AUC_{0-\infty}$ (ng/mL·h)	976.2 (789.1)	567.1 (535.9)	1012.0 (906.6)	448.6 (359.3)
AUC_{0-t} (ng•h/mL)	528.3 (292.1)	217.9 (162.0)	511.3 (287.5)	154.5 (109.7)
Median T_{max} (h) [min, max]	1.8 (1.0 – 4.5)	4.5 (1.3 – 10.0)	1.9 (0.8 – 6.3)	5.5 (2.9 – 12.0)
t1/2 (h)	1.1 (0.5)	2.0 (4.5)	1.3 (2.1)	2.0 (3.0)
Cl (L/h)	37.3 (35.2)	74.0 (85.3)	37.5 (29.1)	73.9 (63.6)

Table 4: 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**
20 mg Nexium (b) (4) Tablet Fed vs. Fast (D vs B)	AUCinf (ng*h/mL)	0.563
	Cmax (ng/mL)	0.317
20 mg Nexium Banded OTC Capsule Fed vs. Fast (C vs A)	AUCinf (ng*h/mL)	0.539
	Cmax (ng/mL)	0.255

Reviewer's Comment:

First prescription (Rx) esomeprazole product Nexium (esomeprazole magnesium) delayed release capsule was approved in Feb of 2001 (NDA 21153). The prescription product has two strength, 20 mg and 40 mg, both administered once daily. In food effect studies with 40 mg dose of Nexium capsule, food decreased AUC by 33-53% and C_{max} by 56-79% after single dose administration. Those PK differences between fasting and fed state were similar after multiple dosing, where AUC decreased by 26-50% and C_{max} decreased by 53-68% (please refer to clinical pharmacology review by Dr. Suliman Al-Fayoumi for NDA 21153 for further detail). In the Nexium Rx label for capsule and oral suspension, Nexium is recommended to be taken at least one hour before meal.

The first OTC esomeprazole product, Nexium 24 HR OTC capsule 20 mg that is used as the reference product in this BE study, was approved in March 28th of 2014 for indication of treatment of frequent heartburn (NDA 204655). As the manufacture and composition/formulation of the OTC Nexium 24HR Delayed Release 20 mg capsules (b) (4) *that the OTC Nexium 24HR capsule is required to be sealed by a tamper band (please refer to CMC review by Dr. Sheldon Markofsky for NDA 204655 dated 03/05/2014 for further detail), no new clinical pharmacology studies (e.g., BE study and food effect study) were conducted in that submission. In support of the OTC indication, the sponsor conducted two replicate phase III efficacy and safety trials with Nexium 24 HR OTC 20 mg capsule in which the patients were instructed to swallow Nexium 24 HR OTC 20 mg capsule with a glass of water once a day before eating in the morning for 14 days. Therefore, in the Nexium 24 HR OTC capsule label, it recommends to take one capsule with a glass of water before eating in the morning based on the phase III trial design. Nonetheless, the response rate in these phase III trials, defined as % of heartburn-free 24 hour days during 14 days of treatment, were only 46.13% in treatment vs. 33.07% in placebo in one study and 48.00% in treatment vs. 32.75% in second study (Please refer to Medical review by Dr. Farrokh Sohrabi for NDA 204655 date 02/21/2014 for further detail on Phase III study design and results). As there is a clear food effect on esomeprazole exposure based on the food effect study in Nexium Rx capsule, this low response rate in these phase III studies with Nexium 24 HR OTC 20 mg capsule could be due to reduced esomeprazole exposure from the food effect if subjects took the Nexium 24 HR OTC 20 mg capsule right before eating as the study design did not specify timing of food in regard to drug administration. It is possible these response rates could have been improved by specifying the timing of food in regard to drug administration* (b) (4) (b) (4)

In the current study, for proposed product Nexium delayed release tablet, food reduced the AUC and C_{max} of esomeprazole by 43.7% and 68.3%, respectively, compared to the fasted state. For reference product Nexium banded OTC capsule, food reduced the AUC and C_{max} of esomeprazole by 46.1% and 74.5%, respectively, compared to the fasted state. The magnitudes of food effect on these two Nexium OTC 20 mg products were similar to each other and also similar to that of Nexium 40 mg Rx capsule. Based on the result of this food effect study, we recommend that both Nexium OTC capsule and Nexium OTC tablet products (b) (4)

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/s/

DILARA JAPPAR
10/16/2015

SUE CHIH H LEE
10/17/2015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**207920**	**Brand Name**	**Nexium 24 HR DR Tablet**
OCP Division (I, II, III, IV, V)	**DCP 3**	**Generic Name**	**Esomeprazole Magnesium**
Medical Division	**DGIEP**	**Drug Class**	**Proton Pump Inhibitor (PPI)**
OCP Reviewer	**Dilara Jappar**	**Indication(s)**	**Treat frequent heartburn which occurs 2 or more days a week in adults 18 Years of age and older**
OCP Team Leader	**Sue Chih Lee**	**Dosage Form**	**Delayed-release Tablet**
Pharmacometrics Reviewer		**Dosing Regimen**	**22.3 mg Tablets once daily for 14 days**
Date of Submission	**2/06/2015**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Pfizer Inc on behalf of AstraZeneca**
Medical Division Due Date		**Priority Classification**	**505(b)(1)**
PDUFA Due Date	**12/4/2015**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:	**X**	**1**		**Study B5141002, ONDQA will review**
Food-drug interaction studies	**X**			**Effect of food will be assessed based on the obtained PK parameters from the BE studies under fasting and fed conditions**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				**Sponsor states that in vitro assessment of alcohol induced dose dumping is not feasible for this dosage form [defer to ONDQA]**
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**Requesting waiver for <18 y/o**
Literature References				
Total Number of Studies				
		1		

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements

No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			Reference drug Nexium 24HR Capsule
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	This is an 505(b)(1) application.
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?		X		Missing validation report
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?			X	Dose and schedule relies on NDA 204655
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

	6 above (in .xpt format if data are submitted electronically)?				
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes provided that the sponsor submit the bioanalytical validation report for the BE study.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issued to be forwarded to the Application for the 74-day letter.
N/A

Clinical Pharmacology Filing Memo:

The sponsor has developed a delayed release (DR) tablet formulation of esomeprazole magnesium for the over-the-counter (OTC) treatment of frequent heartburn. The proposed regulatory pathway is 505(b)(1). The sponsor (Pfizer) cross references to NDA 204655 for Nexium 24HR (esomeprazole magnesium) capsule where Pfizer was also the sponsor agent.

The sponsor has conducted one BE study with partial replicated study design with 6-period cross over to evaluate the bioequivalence of 20 mg of Nexium (b) (4) tablet (20 mg esomeprazole delayed-release tablet) to that of 20 mg of Nexium banded OTC capsule (20 mg Esomeprazole delayed-release capsule) under both fed and fasted state.

Study 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*

Treatment A: 20 mg Esomeprazole delayed-release capsule in the fasted state (administered in 2 treatment periods)
Treatment B: 20 mg esomeprazole delayed-release tablet in the fasted state
Treatment C: 20 mg esomeprazole delayed-release capsule with a high-fat meal (administered in 2 treatment periods)
Treatment D: 20 mg esomeprazole delayed-release tablet with a high-fat meal

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Pending review, study B5141002 demonstrated that the esomeprazole tablets are bioequivalent to the currently marketed banded OTC capsule in terms of both peak esomeprazole exposure (Cmax) and the extent of esomeprazole exposure (AUC) under fasted conditions. ONDQA will review this study. OCP will assess the effect of food based on the PK parameters obtained in this BE study under fed and fasted condition.

Sponsor states that in vitro assessment of alcohol induced dose dumping is not feasible for this dosage form. ONDQA will review this issue.

Bioanalytical validation report could not be located in the submission. This was communicated to the ONDQA team and the sponsor on 4/14/2015 via email.

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

/s/

DILARA JAPPAR
04/14/2015

SUE CHIH H LEE
04/14/2015