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RESEARCH**

*APPLICATION NUMBER:*

**204655Orig1s000**

**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA 204655  
Supporting document/s: 003  
Applicant's letter date: May 30, 2013  
CDER stamp date: May 30, 2013  
Product: Nexium 24HR (esomeprazole magnesium)  
Delayed-Release Capsules, 20 mg  
Indication: Treatment of frequent heartburn that occurs two  
or more days a week  
Applicant: AstraZeneca LP  
Review Division: Division of Nonprescription Clinical Evaluation  
(DNCE) (HFD-560)  
Reviewer: Robert T. Dorsam, Ph.D.  
Secondary Reviewer: Paul Brown, Ph.D.  
Division Director: Theresa Michele, M.D.  
Project Manager: Jeffrey Buchanan

*Template Version: September 1, 2010*

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# 1 Executive Summary

## 1.1 Introduction

The applicant submitted NDA 204655 as a partial Rx-to-OTC switch for Nexium 24HR (esomeprazole magnesium) Delayed-Release Capsules for the indication: “treats frequent heartburn that occurs 2 or more days a week.” The recommended dosing for consumers 18 years of age or older is a single 20 mg Nexium 24HR capsule daily for 14 days with an option to repeat a 14-day course every 4 months. The sponsor did not submit nonclinical studies in the current application; however they cross-reference information on the pharmacology and toxicology of esomeprazole magnesium from prior regulatory submissions.

In this review, the drug product will be identified as “Nexium 24HR.” This is an abbreviation of Nexium 24HR Delayed-Release Capsules and is synonymous with Esomeprazole Delayed-Release Capsules Over-The-Counter (OTC) 20 mg. The latter name is used by the applicant throughout some of the submission. The name “Nexium 24HR” was reviewed and deemed acceptable by the Division of Medication Error Prevention and Risk Management (DMEPA).

## 1.2 Brief Discussion of Nonclinical Findings

Nonclinical studies were not submitted for NDA 204655 however the applicant cross-referenced NDA 21,153 which contains a detailed review of nonclinical studies for esomeprazole magnesium<sup>1</sup>. A general summary of Pharm/Tox information from NDA 21,153 is contained in the current review.

The nonclinical development of esomeprazole was conducted as a bridging program to information which supported the approval of omeprazole (Prilosec). This approach was taken because esomeprazole is an S-enantiomer of omeprazole which is a mixture of S- and R-enantiomers. The bridging program consisted of *in vitro* pharmacodynamic studies, single and repeat dose toxicology studies up to 3 month duration, a battery *in vitro* and *in vivo* genetic toxicology studies, and embryofetal toxicity studies in rats and rabbits. Carcinogenicity assessments were conducted with omeprazole and include a 2-year rat bioassay as well as a bioassay in p53 heterozygous mice.

Esomeprazole reduces gastric acid secretion through inhibition of the H<sup>+</sup>/K<sup>+</sup>-ATPase on the gastric parietal cells. Esomeprazole is protonated in the parietal cells to form the achiral sulphenamide that inhibits H<sup>+</sup>/K<sup>+</sup>-ATPase activity<sup>2</sup>. As stated above, esomeprazole is the S-enantiomer of omeprazole which contain both R- and S-

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<sup>1</sup> NDA 21-153, Nexium Delayed-Release Capsules. Pharmacology/Toxicology review (August 8, 2000) conducted by Ke Zhang, Ph.D., Pharmacologist

<sup>2</sup> Drug label for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

Accessed on DailyMed online resource at the following link:

<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f4853677-1622-4037-688b-fdf533a11d96#section-11>

enantiomers. The R-enantiomer is also protonated and converted to its active form in the parietal cells and inhibits gastric secretion.

The general toxicity of esomeprazole magnesium was characterized in rats and dogs<sup>1</sup>. The toxicity of esomeprazole in rats was characterized in repeat dose toxicity studies of 1-month (Wistar rats), 3-months (Wistar rats), and 13-weeks (Sprague-Dawley rats) duration. Each study also contained a group that was treated with omeprazole for comparison of toxicity. In all three rat toxicology studies, the stomach was a target organ of toxicity and was most evident in the high dose of each study. Histopathological changes in the stomach included eosinophilia in the 1 and 3-month rat studies, and additional findings of acanthosis and hyperkeratosis in the 13-week rat study. These findings occurred in individual males and females in the 1 month study, but included a majority of the animals in high dose groups in the 3-month and 13-week studies. Rats in the high dose groups of the 3-month and 13-week studies received 280 mg/kg/day esomeprazole which is approximately 136 times the human dose of 20 mg/day on the basis of body surface area (BSA). In the 3 and 13-month rat studies, the kidney was also a target organ of toxicity. Rats in the high dose group had basophilic cortical tubules and inflammatory cell infiltration. Similar findings were observed in the stomach and kidneys of rats that received omeprazole in this study. In dogs that were dosed with esomeprazole for 3 months, the mid-dose and high-dose groups had histopathological changes in the stomach including mucosal fibrosis, hyperplasia, chief cell atrophy and focal necrosis. Dogs in the mid- and high-dose groups received 5.5 mg/kg/day and 28 mg/kg/day which is 9 times and 45.4 times, respectively, of the human dose of 20 mg/day on the basis of BSA. Similar histopathological findings were observed in the stomachs of dogs that received omeprazole in this study.

The reproductive and developmental toxicity of esomeprazole magnesium was evaluated in pregnant female rats and rabbits. Pregnant rats received oral doses of 0, 14, 69, or 280 mg/kg esomeprazole during Gestational Days (GD) 6 through 16. Maternal body weight gain was reduced (20%) in the highest dose group. Treatment with esomeprazole did not impact the number of corpora lutea, implantations, number of dead and live fetuses, body weight of live fetuses, placental weight or sex ratio. No major malformations were observed in rats that were treated with esomeprazole and there were no changes in minor defects or variants that were related to treatment. Pregnant rabbits received oral doses of 0, 6.9, 28, or 86 mg/kg/day esomeprazole magnesium between GD 6 and 16. Maternal toxicity was evident by decrease body weight gain in the mid and high dose groups. The number of corpora lutea, implantations, number of dead and live fetuses, placental weight and sex ratio were not impacted in groups that received esomeprazole magnesium. Esomeprazole magnesium was not teratogenic in these studies.

Recently, the applicant updated the prescription Nexium drug label including (b) (4) Pregnancy Category C. The updated label includes information about a pre- and postnatal developmental toxicity study in rats which included evaluations of esomeprazole magnesium on bone development. Similar information regarding esomeprazole magnesium is found on the approved drug label for

esomeprazole strontium capsules<sup>3</sup>. Rats received oral doses of esomeprazole magnesium ranging from 14 to 280 mg/kg/day (6.8 to 136-times the human dose of 20 mg/day on the basis of BSA). Neonatal and postnatal survival were reduced at doses equal to and greater than 138 mg/kg/day, which is approximately 67 times the human dose of 20 mg/day. Body weight and weight gain were decreased and general developmental delays were observed post-weaning at a dose of 69 mg/kg/day (approximately 33 times the human dose of 20 mg/day). Offspring from rats that received 138 mg/kg/day (67 times the human dose) had physeal dysplasia of the femur. At a dose of 14 mg/kg/day, bone-related effects in offspring included decreased femur length, reduced width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild hypocellularity. These effects were observed at a dose which is approximately 6.8 times the human dose of 20 mg/day. Pregnant rats that received 138 mg/kg/day (67 times the human dose based on BSA) from GD 7 to postnatal day 21 had reduced (maternal) femur weight of up to 14% when compared with the group that was treated with vehicle.

Esomeprazole magnesium was negative for genotoxicity in the bacterial reverse mutation assay, *in vivo* chromosomal aberration assay in rat bone marrow cells, and the *in vivo* mouse micronucleus test. Esomeprazole was clastogenic in three *in vitro* chromosomal aberration assays in human peripheral blood cells. Omeprazole and another compound in this pharmacologic class were also positive in a chromosomal aberration assay in human peripheral blood cells<sup>2,4</sup>.

Carcinogenicity studies were not conducted with esomeprazole; however, a 2-year rat carcinogenicity study was conducted with oral doses of 1.7, 3.4, 13.8, and 140.8 mg/kg/day omeprazole. Gastric enterochromaffin (ECL) cell hyperplasia and carcinoids occurred in a dose-dependent manner in both male and female rats. The approved prescription drug label for Nexium capsules reports that the dose range of omeprazole in this study spans 0.7 to 57 times the human dose of 20 mg/day omeprazole. ECL carcinoids were also observed in rats receiving other proton pump inhibitors, as well as in rats receiving fundectomy or extended exposure to high-doses of H2 receptor antagonists<sup>2,4</sup>. Additional considerations on gastric toxicity can be found in the Integrated Summary and Safety Evaluation Section of this review.

## 1.3 Recommendations

### 1.3.1 Approvability

NDA 204655 is approvable from a Pharmacology/Toxicology perspective

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<sup>3</sup> Esomeprazole Strontium Capsules Drug Label. Accessed on DailyMed resource at the following link: <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=61a5a84e-0194-4f11-91f8-83d7ac404932#section-8>

<sup>4</sup> Lansoprazole Drug Label. Accessed on DailyMed resource at the following link: <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7BF9DDB1-D1B6-42EE-98BF-5A482118211E>

### 1.3.2 Additional Non Clinical Recommendations

None

### 1.3.3 Labeling

The applicant proposes the following text in the Drug Facts label:

**“If pregnant or breast-feeding, ask a health professional before use.”**

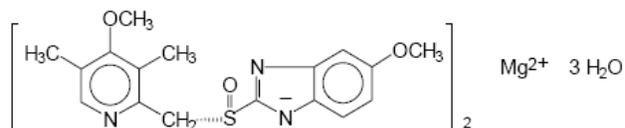
This text is identical to language on other nonprescription proton pump inhibitors and is acceptable from a Pharm/Tox perspective.

## 2 Drug Information

### 2.1 Drug

Generic Name	Esomeprazole magnesium trihydrate
Code Name	H 199/18
Chemical Name	bis(5-methoxy-2-((S)[(4-methoxy-3, 5-dimethyl-2-pyridinyl)methyl]sulfinyl)-1Hbenzimidazol-1-yl) magnesium trihydrate
Molecular Formula	C <sub>17</sub> H <sub>18</sub> MgN <sub>3</sub> O <sub>3</sub> S <sub>2</sub>
Molecular Weight	713. <sup>(b) (4)</sup> g/mol (Esomeprazole magnesium anhydrous) 767.2 g/mol (Esomeprazole magnesium trihydrate)

#### Structure



Pharmacologic Class                      Proton pump inhibitor (PPI)

### 2.2 Relevant INDs, NDAs, and DMFs

<sup>(b) (4)</sup> and <sup>(b) (4)</sup>: DMF <sup>(b) (4)</sup> DMF <sup>(b) (4)</sup> DMF <sup>(b) (4)</sup>

IND 53,733 – Nexium capsules (esomeprazole magnesium)

NDA 21-153 – Nexium capsules (esomeprazole magnesium)

NDA 21-689 – Nexium I.V. (esomeprazole sodium) injection

IND 111,185 – Development of Nexium capsules for use in OTC setting

### 2.3 Drug Formulation

Nexium 24HR is a purple gelatin capsule (14x5 mm) that has two yellow stripes and “NEXIUM 20 mg” printed in yellow around the shorter circumference (i.e. radial format) of the capsule. An additional yellow gelatin band is a tamper-indicator which joins the body and cap. The capsule contains white to slightly beige enteric coated esomeprazole pellets. Nexium 24HR capsule contains 22.3 mg esomeprazole magnesium trihydrate which equates to 20 mg esomeprazole. The ink on Nexium 24 HR [REDACTED] (b) (4) prescription Nexium drug product (NDA 21-153). The applicant estimates that [REDACTED] (u) (4) of ink is on each capsule. The following image of Nexium 24HR capsules was provided by the applicant.

Image of Nexium 24HR Delayed-Release Capsules



The approved prescription drug product (i.e. Nexium Delayed-Release capsule) is the [REDACTED] (b) (4) Nexium 24HR. The prescription capsules are further processed by the application of a yellow gelatin band which is a feature specific to Nexium 24HR. The composition of the gelatin band is listed in Table 1.

**Table 1. Composition of the Gelatin Band on Nexium 24HR Capsules\***

[REDACTED] (b) (4)

Regarding purity, Nexium 24 HR has a specification of NMT [REDACTED] (b) (4) % of [REDACTED] (b) (4), NMT [REDACTED] (b) (4) % Omeprazole sulphone (related compound A), NMT [REDACTED] (u) (4) % of any individual impurities, and NMT [REDACTED] (b) (4) % for total impurities. According to the drug specifications, Nexium 24 HR does not contain more than [REDACTED] (b) (4) % of the [REDACTED] (b) (4). Impurity specifications for Nexium 24HR are the same as specifications for Nexium Capsules (NDA 21-153).

Nexium 24HR capsules will be contained in a 45 mL high-density polyethylene (HDPE) square bottle with a (b) (4) closure. The bottle contains (b) (4) as a desiccant.

## 2.4 Comments on Novel Excipients

The proposed product does not contain novel excipients.

## 2.5 Comments on Impurities/Degradants of Concern

The impurity profile of Nexium 24HR is identical to Nexium Capsules which were approved under NDA 21-153. None of the specified impurities exceed the qualification threshold in ICH Q3B(R2) "Impurities in New Drug Products." Further comment is not warranted from a Pharm/Tox perspective.

## 2.6 Proposed Clinical Population and Dosing Regimen

Nexium 24HR is intended for adults ( $\geq 18$  years of age) with frequent heartburn that occurs two or more days a week. According to the dosing instructions, one 20 mg Nexium 24HR capsule should be taken daily for a duration of 14 days, with an option to repeat a 14-day course every 4 months. The consumer population and dosing regimen are the same as other proton-pump inhibitors in the OTC setting.

## 2.7 Regulatory Background

The applicant cross-references NDA 21-153 for Nexium Delayed-Release Capsules (esomeprazole magnesium) which was approved on February 20, 2001. Additionally, the applicant cross-references NDA 21-689 for Nexium I.V. which was approved on March 31, 2005. AstraZeneca is the applicant for both of these referenced NDAs. Phase 3 clinical trials for their current submission (NDA 204655) were conducted under IND 111,185 which was opened in 2011. The content of NDA 204655 was the subject of IND preliminary comments under IND 111,185 that were conveyed to the sponsor on January 15, 2013. In those preliminary responses, the sponsor was informed that relying on prior nonclinical development was an acceptable approach and that the sponsor should address whether there are any changes in the formulation for the proposed Nexium OTC product.

## 3 Studies Submitted

Nonclinical studies were not submitted to this application.

### 3.1 Studies Reviewed

None

### 3.2 Studies Not Reviewed

None

### 3.3 Previous Reviews Referenced

Information from the Pharmacology/Toxicology review of NDA 21-153 was cross-referenced and accessed during the review of NDA 204655.

## 11 Integrated Summary and Safety Evaluation

The applicant submitted NDA 204655 for Nexium 24HR Delayed-Release Capsules (20 mg) for the treatment of heartburn which occurs 2 or more days per week. This application is a partial Rx-to-OTC switch for consumers aged 18 years or older who experience heartburn. Nexium Delayed-release capsules will remain a prescription therapy for infants, children, and adolescents up to 17 years of age. The dosing instructions recommend one 20 mg Nexium 24HR capsule daily for 14 days every 4 months. Other PPIs in the OTC setting are indicated for the same consumer population and have an identical dosing regimen.

(b) (4)

Nexium 24HR also contains the same specifications for impurities as the prescription Nexium. Both the dosage form (i.e. 20 mg capsule containing esomeprazole magnesium) and impurity profile are acceptable from a Pharm/Tox perspective based on their prior approval, supportive nonclinical information, and clinical experience. Though they are similar in many respects, Nexium 24HR and the prescription product differ in their excipient profile. Nexium 24HR capsule contains an additional gelatin band around the body and cap which serves as a tamper-indicating feature. The excipients in this gelatin band are used in many FDA-approved products for oral delivery and do not require further qualification from a Pharmacology/Toxicology perspective.

Nonclinical studies were not conducted for the current submission; however the sponsor cross-references information from NDA 21-153 (Nexium Delayed-Release Capsules) for this application. Prior nonclinical development characterized the pharmacology and toxicology of esomeprazole magnesium as a proton-pump inhibitor that suppresses gastric acid secretion. General toxicology studies in rats and dogs indicate that the stomach is a target organ for esomeprazole magnesium. In rats, histopathologic changes to the stomach included eosinophilia after 1 and 3 months of treatment. After 13 weeks of treatment, acanthosis and hyperkeratosis were also observed. In dogs that received esomeprazole magnesium for 3 months, histopathological changes in the stomach included mucosal fibrosis, hyperplasia, chief cell atrophy and focal necrosis. The incidence and nature of the gastric findings was time- and dose-dependent. Sustained treatment with esomeprazole magnesium suppresses gastric acid secretion which can elicit changes in the microenvironment (i.e. hypergastrinemia, higher gastric pH, changes to flora). Such changes have also been observed in nonclinical and clinical studies when several other proton-pump inhibitors were used for extended periods. Studies with longer term treatment were not conducted with esomeprazole, however omeprazole was used for the assessment of carcinogenicity. Rats that were treated for 2 years with omeprazole had a dose-dependent increase in ECL hyperplasia and gastric carcinoids. Elevated gastrin levels resulting from extended exposure to proton pump inhibitors has been associated with ECL hyperplasia and ECL carcinoids

in rats<sup>2,5</sup>. The incidence of ECL hyperplasia also increased over time in humans that were treated with omeprazole in clinical trials<sup>2</sup>. Similarly, ECL hyperplasia increased in a time- and dose-dependent manner in patients that were treated with Nexium up to 6 to 12 months<sup>2</sup>. ECL carcinoids have not been observed in human clinical trials. The prolonged acid suppression appears to be a key element to the finding in rodents. Dosing in the rodent carcinogenicity studies takes place for a large proportion of their lifetime. The recommended dosing for 14 days every 4 months is an appropriate measure which may mitigate gastric effects from prolonged exposure to Nexium 24HR or other members of this class.

The dosing regimen (i.e. 14 days every 4 months) for Nexium 24HR is abbreviated when compared with the recommended dosing duration for most prescription Nexium indications. This distinction between dosing regimens for OTC versus prescription is typical among proton pump inhibitors. The Agency issued Drug Safety Communications for reduced magnesium levels and possible increased risk of fractures of the hip, wrist, and spine associated with prolonged use of proton pump inhibitors<sup>6,7</sup>. These safety communications were made for proton pump inhibitors as a class. The 14-day dosing regimen every 4-months for Nexium 24HR is identical to other OTC proton pump inhibitors. The dosing instructions for PPIs and safety signals for prolonged use of PPIs are generalized to the class, therefore the proposed dosing instructions for Nexium 24HR are acceptable.

Regarding reproductive and developmental toxicity, esomeprazole was not teratogenic in studies conducted in rats or rabbits. Information regarding bone effects in pre- and post-natal studies warranted a change in pregnancy category. Physeal dysplasia of the femur and reduced femur, cortical bone, and tibial growth plate measurements were observed. The narrowest exposure margin for these effects was approximately 6.8 times the human dose of 20 mg/day. The Drug Facts text “**If pregnant or breast-feeding, ask a health professional before use,**” is appropriate and similar to other nonprescription proton pump inhibitors.

In consideration of nonclinical information on esomeprazole magnesium, this application for Nexium 24HR is approvable from a Pharmacology/Toxicology perspective.

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<sup>5</sup> Larsson H, Håkanson R, Mattsson H, Ryberg B, Sundler F, Carlsson E. (1988) Omeprazole: its influence on gastric acid secretion, gastrin and ECL cells. *Toxicol Pathol.*16(2):267-72.

<sup>6</sup> FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs). Accessed at: <http://www.fda.gov/drugs/drugsafety/ucm245011.htm>

<sup>7</sup> FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. Accessed at: <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm213206.htm>

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/s/  
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ROBERT T DORSAM  
02/19/2014

PAUL C BROWN  
02/19/2014

I concur that this NDA can be approved from a pharmacology/toxicology perspective.

**PHARMACOLOGY/TOXICOLOGY  
NDA FILING CHECKLIST**

**NDA Number:** 204655

**Applicant:** AstraZeneca

**Stamp Date:** May 30, 2013

**Drug Name:** Nexium 24HR  
(esomeprazole magnesium)  
Delayed-Release Capsules  
OTC (20 mg)

**NDA Type:** 505 (b)(1)

**INTRODUCTION**

AstraZeneca submitted NDA 204655 as a partial Rx-to-OTC switch of Nexium 24HR (esomeprazole magnesium) Delayed Release Capsules (20 mg) for the treatment of frequent heartburn which occurs 2 or more days a week. The applicant cross-references nonclinical safety information from several INDs and NDAs which are listed below:

Application #	Established Name	Proprietary Name	Strength	Approval Date
NDA 19-810	Omeprazole	Prilosec Delayed-Release Capsules	20 and 40 mg	September 1989
IND 53,733	Esomeprazole Magnesium	Nexium Delayed-Release Capsules	10, 20, and 40 mg	August 1997
NDA 21-153	Esomeprazole Magnesium	Nexium Delayed-Release Capsules	20 and 40 mg	February 2001
IND 64,865	Esomeprazole Magnesium	Nexium IV for Injection	20 and 40 mg IV	June 2002
NDA 21-689	Esomeprazole Magnesium	Nexium IV for Injection	20 and 40 mg IV	March 2005
NDA 22-101	Esomeprazole Magnesium	Nexium For Delayed-Release Oral Suspension	10 mg suspension	September 2008
NDA 22-491	Esomeprazole (E)/Aspirin (ASA)	Axanum (esomeprazole magnesium)	E20mg/ASA 81 mg E20mg/ASA 325 mg E40mg/ASA 81 mg E40mg/ASA 325mg	Withdrawn 2011

The excipients and impurity profile of the proposed drug product are the same as Nexium Delayed-Release Capsules (20 mg), which was approved as a prescription product under NDA 21-153.

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND			Additional Pharm/Tox studies were not

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

**PHARMACOLOGY/TOXICOLOGY  
NDA FILING CHECKLIST**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
	studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		requested for this NDA application. The sponsor will rely upon the nonclinical safety information from several INDs and NDAs that are documented in, "1.4.4 - Cross Reference to Other Applications."
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	N/A		The sponsor relies upon nonclinical assessments that were reviewed in prior NDA applications (listed above). Additional GLP-compliant nonclinical studies were not required for this submission.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	N/A		Nonclinical studies were not requested during pre-submission discussions with the applicant.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?	N/A		The labeling for this product should adhere to 21 CFR 201.60 for the principle display panel and 21 CFR 201.66 for the Drug Facts label. Pharmacology/toxicology information such as human dose multiples is not necessary on an OTC label.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		The impurity profile is identical to the approved prescription Nexium delayed-release capsule (20 mg). There do not appear to be issues with the impurity profile from a Pharm/Tox perspective.

**PHARMACOLOGY/TOXICOLOGY  
NDA FILING CHECKLIST**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11	Has the applicant addressed any abuse potential issues in the submission?	N/A		There is no concern for abuse potential with this product.
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?	X		

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

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

Not applicable

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Robert T. Dorsam 7/2/13  
 \_\_\_\_\_  
 Reviewing Pharmacologist Date

\_\_\_\_\_  
 Team Leader/Supervisor Date

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/s/  
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ROBERT T DORSAM  
07/03/2013

PAUL C BROWN  
07/08/2013