

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204736Orig1s000**

**PHARMACOLOGY REVIEW(S)**

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

**FROM:** David B. Joseph  
Pharmacology Team Leader

**DATE:** March 23, 2013

**SUBJECT:** NDA 204,736 (SD # 1 dated September 27, 2012)

**Sponsor:** Eisai Inc.

**Drug Product:** Aciphex Sprinkle™ (rabeprazole sodium) Delayed-Release Capsules

**Comments:**

The Sponsor proposed the following for section 13.2 of the labeling:

**13.2 Animal Toxicology and/or Pharmacology**

“Studies in neonatal/juvenile and young adult rats and dogs were performed. In juvenile animal studies rabeprazole sodium was administered orally to rats for up to 5 weeks and to dogs for up to 13 weeks, each commencing on Day 7 post partum and followed by a 13-week recovery period. Rats were dosed at 5, 25 or 150 mg/kg/day and dogs were dosed at 3, 10 or 30 mg/kg/day. The data from these studies were comparable to those reported for young adult animals. Pharmacologically mediated changes, including increased serum gastrin levels and stomach changes, were observed at all dose levels in both rats and dogs. These observations were reversible over the 13-week recovery periods. Although body weights and/or crownrump lengths were minimally decreased during dosing, no effects on the development parameters were noted in either juvenile rats or dogs.”

In the Pharmacology/Toxicology review of this application by Dr. Ke Zhang, dated March 1, 2013, the following evaluation and recommendation was provided for the Sponsor’s proposed labeling section 13.2, for which I concurred:

“**Evaluation:** The results of these toxicity studies in neonatal animals are consistent with the findings in the adult animals, and did not reveal any new toxicities. Furthermore, the information described in this section does not appear to be necessary for safe and effective use of the drug in humans, which is the only justification for presenting animal data in section 13.2 (21 CFR 201.57). Therefore, section 13.2 should be removed from the labeling.”

The Sponsor responded to the Agency's proposed deletion of this section by transferring it to section 8.4 (Pediatric Use). In the ensuing discussion of this issue by the review team, the Maternal Health reviewer (Jeanine Best) stated that all juvenile animal studies that were conducted to support clinical studies in pediatric patients should be included in the label, either in section 8.4 or 13.2. The juvenile animal studies that are described in the Sponsor's labeling text were required to support clinical studies in pediatric patients less than one year of age. The review team determined that the most appropriate labeling section for this information was 13.2. Therefore, section 13.2 will contain the text that was initially proposed by the Sponsor.

**Recommendations:**

None.

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David B. Joseph, Ph.D.	Date
Pharmacology Team Leader	
Division of Gastroenterology and Inborn Errors Products	

cc:  
NDA 204,736  
DGIEP  
DGIEP/PM  
DGIEP/Dr. Joseph  
DGIEP/Dr. Zhang  
DGIEP/Dr. He  
DGIEP/Dr. Mulberg

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/s/  
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DAVID B JOSEPH  
03/23/2013

**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: 204,736  
Supporting document/s: 000  
Applicant's letter date: September 27, 2012  
CDER stamp date: September 27, 2012  
Product: Rabeprazole / Aciphex  
Indication: Gastroesophageal Reflux Disease (GERD)  
Applicant: Eisai Inc.  
Woodcliff Lake, NJ  
Review Division: Division of Gastroenterology and Inborn Errors  
Products (DGIEP)  
Reviewer: Ke Zhang, Ph.D.  
Supervisor/Team Leader: David Joseph, Ph.D.  
Division Director: Donna Griebel, M.D.  
Project Manager: Stacy Barley

*Template Version: September 1, 2010*

**Disclaimer**

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## **1. Executive Summary**

### **1.1 Introduction**

Rabeprazole was originally developed under IND 33,985 and approved under NDA 20,973 (Aciphex® (rabeprazole sodium) Delayed-Release Tablets) in 1999 for the treatment of duodenal ulcers, erosive or ulcerative gastroesophageal reflux disease (GERD), symptomatic GERD, maintenance of GERD healing, and pathological hypersecretory conditions, including Zollinger-Ellison Syndrome in adults. It is also approved for short-term treatment of GERD in adolescent patients 12 years of age and above. In the current NDA, the sponsor seeks approval of AcipHex® Delayed-Release Sprinkle Capsules for the healing, maintenance of healing, and symptom improvement of GERD in patients 1 to 11 years. In support of this NDA application, the sponsor conducted two neonatal toxicity studies in rats and dogs. These studies were submitted to NDA 20,973 Supplement 022 on December 28, 2007 and reviewed on May 30, 2008.

### **1.2 Brief Discussion of Nonclinical Findings**

In the 5-week oral toxicity study in the neonatal rats, E3810 was given by oral gavage to 7-day old rats at 0, 5, 25, and 150 mg/kg/day. Treatment increased the serum gastrin level and stomach weight. Histopathological examination revealed a dose-related increase in cytoplasmic eosinophilia of chief cells in the stomach. The gastric mucosal thickness was also increased in the high dose males and females. The mean density of ECL cells was increased in males at 5 mg/kg and higher and females at 25 mg/kg and higher. These changes were reversible. Treatment did not clearly affect the physical and behavioral development of the animals. Toxicokinetic analysis in this study included the unchanged drug (E3810), but not the thioether metabolite (PTBI), which is one of the primary metabolites in human plasma. Therefore, the Sponsor conducted a toxicokinetic bridging study in neonatal rats, using oral administration of 25 and 150 mg/kg/day E3810 on days 7 to 41 *post partum*. AUC values for PTBI exceeded that of E3810, with the exception of the low-dose group on *pp* day 7.

In the 90-day oral toxicity study in neonatal dogs, E3810 was given by oral gavage to 7-day old dogs at 0, 3, 10, and 30 mg/kg/day. Treatment increased the serum gastrin level, stomach weight and gastric mucosal thickness. Histopathological examination revealed degeneration/necrosis of parietal cells and mucosal hypertrophy/hyperplasia in the fundus of the stomach in a dose related manner. The changes were reversible. Treatment did not clearly affect the physical and behavioral development of the animals.

### **1.3 Recommendations**

#### **1.3.1 Approvability**

From a nonclinical standpoint, this NDA should be approved for the proposed indications.

#### **1.3.2 Additional Non Clinical Recommendations**

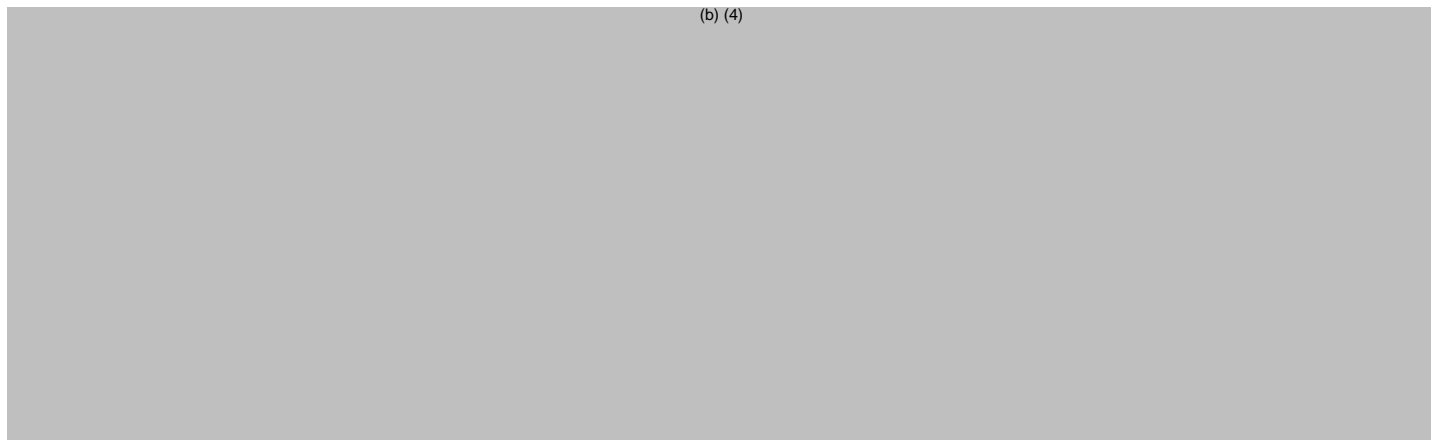
None

#### **1.3.3 Labeling**

##### **Sponsor's Version:**



##### **Sponsor's Version:**





(b) (4)

**Sponsor's Version:****13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40  $\mu\text{g}\cdot\text{hr}/\text{mL}$  which is 1.6 times the human exposure (plasma  $\text{AUC}_{0-\infty} = 0.88 \mu\text{g}\cdot\text{hr}/\text{mL}$ ) at the recommended dose for GERD (20 mg/day). In a 28-week carcinogenicity study in p53<sup>+/-</sup> transgenic mice, rabeprazole at oral doses of 20, 60, and 200 mg/kg/day did not cause an increase in the incidence rates of tumors but produced gastric mucosal hyperplasia at all doses. The systemic exposure to rabeprazole at 200 mg/kg/day is about 17-24 times the human exposure at the recommended dose for GERD. In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1  $\mu\text{g}\cdot\text{hr}/\text{mL}$  which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2  $\mu\text{g}\cdot\text{hr}/\text{mL}$  (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+/-) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8  $\mu\text{g}\cdot\text{hr}/\text{mL}$ , about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

**Evaluation:** This section is acceptable since it is identical to the approved label for Aciphex® (rabeprazole sodium) Delayed-Release Tablets. No new information with relevance to this section has been generated.

### **Sponsor's Version:**

#### **13.2 Animal Toxicology and/or Pharmacology**

Studies in neonatal/juvenile and young adult rats and dogs were performed. In juvenile animal studies rabeprazole sodium was administered orally to rats for up to 5 weeks and to dogs for up to 13 weeks, each commencing on Day 7 post partum and followed by a 13-week recovery period. Rats were dosed at 5, 25 or 150 mg/kg/day and dogs were dosed at 3, 10 or 30 mg/kg/day. The data from these studies were comparable to those reported for young adult animals. Pharmacologically mediated changes, including increased serum gastrin levels and stomach changes, were observed at all dose levels in both rats and dogs. These observations were reversible over the 13-week recovery periods. Although body weights and/or crownrump lengths were minimally decreased during dosing, no effects on the development parameters were noted in either juvenile rats or dogs.

**Evaluation:** The results of these toxicity studies in neonatal animals are consistent with the findings in the adult animals, and did not reveal any new toxicities. Furthermore, the information described in this section does not appear to be necessary for safe and effective use of the drug in humans, which is the only justification for presenting animal data in section 13.2 (21 CFR 201.57). Therefore, section 13.2 should be removed from the labeling.

## **2 Drug Information**

### **2.1 Drug**

Trade Name: Rabeprazole / Aciphex

Code Name: E3810

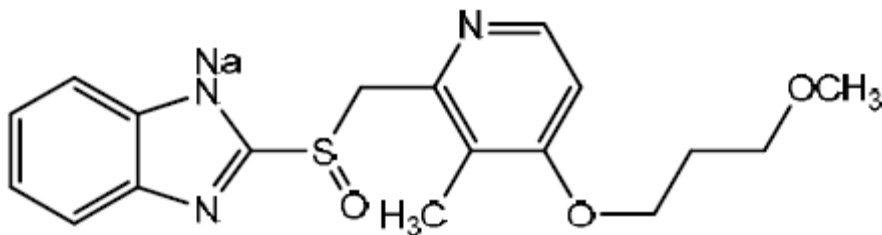
Chemical Name:

2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-benzimidazole sodium

Molecular Formula: C<sub>18</sub>H<sub>20</sub>N<sub>3</sub>NaO<sub>3</sub>S

MW: 381.42

Structure or Biochemical Description:



Pharmacologic Class: Gastric parietal cell H<sup>+</sup>/K<sup>+</sup>-ATPase (proton pump) inhibitor.

**2.2 Relevant INDs, NDAs, and DMFs:** IND 33,985, NDA 20,973

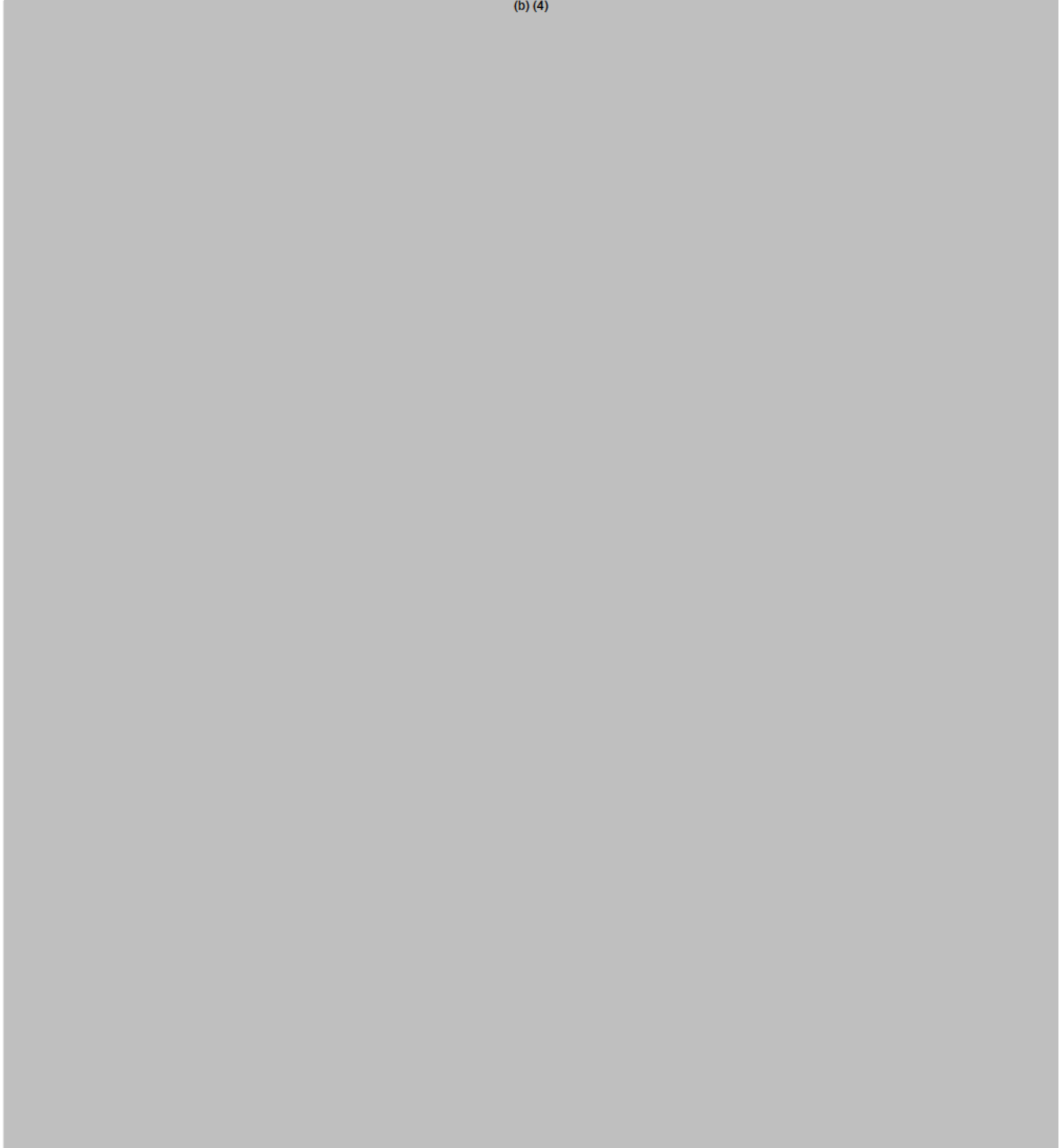
### 2.3 Drug Formulation

Delayed-Release Sprinkle Capsules

**Table 2.3.P.1-2 Components and Compositions of Rabeprazole Sodium Sprinkle Capsules, 2.5, 5 and 10 mg**

Component	Dosage Strength			Function	Reference to Quality Standard
	2.5 mg	5 mg	10 mg		
	Quantity per Unit Dose (mg)				

(b) (4)



**2.4 Comments on Novel Excipients: None**

**2.5 Comments on Impurities/Degradants of Concern:** See section 11 Integrated Summary and Safety Evaluation.

**2.6 Proposed Clinical Population and Dosing Regimen**

The proposed clinical population is pediatric patients 1 to 11 years with GERD. The proposed indications include healing, maintenance of healing, and improvement of symptoms in pediatric patients aged 1 to 11 years with GERD. The dosing regimens are shown in the table below.

Weight	Dosage	Healing and Improvement of Symptoms	Maintenance of Healing
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(b) (4)

**Regulatory Background**

Rabeprazole was originally developed under IND 33,985 and approved under NDA 20,973 (ACIPHEX® (rabeprazole sodium) Delayed-Release Tablets) in 1999 for the treatment of duodenal ulcers, erosive or ulcerative gastroesophageal reflux disease (GERD), symptomatic GERD, maintenance of GERD healing, and pathological hypersecretory conditions, including Zollinger-Ellison Syndrome in adults. It is also approved for short-term treatment of GERD in adolescent patients 12 years of age and above. In the current NDA, the sponsor seeks approval of AcipHex® Delayed-Release Sprinkle Capsules for the healing, maintenance of healing, and symptom improvement in GERD in patients 1 to 11 years.

**3 Studies Submitted**

1. Bridging TK study in juvenile rats
2. Protein binding studies for the thioether metabolite

### 3.1 Studies Reviewed

1. Bridging TK study in juvenile rats
2. Protein binding studies for the thioether metabolite

### 3.2 Studies Not Reviewed

None

### 3.3 Previous Reviews Referenced

The following pharmacology reviews under IND 33,985 and NDA 20,973 were referenced. Full reviews are included in this review verbatim:

1. Pharmacology Review (IND 33,985 SD# 683 dated April 6, 2009) by Ke Zhang, Ph.D. dated 2/25/2011
2. Pharmacology Review (NDA 20,973 Supplement 022 December 28, 2007) by Ke Zhang, Ph.D. dated 5/30/2008

## 4 Pharmacology

N/A

### 4.1 Primary Pharmacology

N/A

### 4.2 Secondary Pharmacology

N/A

### 4.3 Safety Pharmacology

N/A

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

#### **Protein Binding:**

Plasma protein binding of an E3810 metabolite (thioether-E3810, PTBI) was studied in rat plasma using equilibrium dialysis. The protein binding of thioether-E3810 was 98.76% at 100 ng/mL, and 98.75% at 1000 ng/mL.

## 5.2 Toxicokinetics

### Rabeprazole Sodium (E3810): Toxicokinetic Bridging Study by Oral Repeated-Doses in the Neonatal Rat (902423)

**Methods:** This was a bridging study to determine the toxicokinetic parameters of rabeprazole sodium (E3810) and its metabolite (thioether-E3810; PTBI) in neonatal rats. Rabeprazole (Lot Number: 11012101) was given by oral gavage to Sprague-Dawley CD (CrI:CD[SD]) rat pups (114 males and 114 female)s from Day 7 to 41 *post partum* (*pp*), at 25 or 150 mg/kg/day. The study design is presented in the following sponsor's table.

#### Experimental Design

Group Number	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Number of Animals			
			Males	Females	Males	Females
1/ E3810	25	10	36 <sup>a</sup>	36 <sup>a</sup>	21 <sup>b</sup> (3)	21 <sup>b</sup> (3)
2/ E3810	150	10	36 <sup>a</sup>	36 <sup>a</sup>	21 <sup>b</sup> (3)	21 <sup>b</sup> (3)

a Pups bled at Day 7 *pp*.

b Pups bled at Day 41 *pp*.

(N) Number of dosed spare pups

No control group was included in this study. The sponsor stated that the dose selection was based on the results of the 5-week study in neonatal rats (# 900948) in which rabeprazole sodium was given at 5, 25, and 150 mg/kg, starting on Day 7 *pp*. The doses of 150 and 25 mg/kg were the MTD and NOAEL, respectively, in the previous toxicity study in neonatal rats. Toxicokinetic analysis in that study included the unchanged drug (E3810), but not the thioether metabolite (PTBI), which is one of the primary metabolites in human plasma. Mortality, clinical signs of toxicity, body weights, and toxicokinetics were recorded in the present study.

#### Results:

**Clinical signs:** Thin fur cover, and skin scabs/lesions were noted in a few animals in all treated groups.

**Mortality:** One low dose female, and three high dose animals (one male, and two females) were either found dead or sacrificed between days 10 and 18 *pp*. Also, one spare low dose female, and three spare high dose animals (one male and two females) were also either found dead or sacrificed. The sponsor stated that "the cause of death could not be determined". The higher incidence of mortality in the high dose group as compared to the low dose group suggests that mortality may have been drug related.

**Body Weights:** The body weights in animals treated at 150 mg/kg were comparable to the animals treated at 25 mg/kg at the end of treatment period.

**Toxicokinetics:** The plasma levels of both E3810 and PTBI increased with increasing dose levels. AUC values for PTBI exceeded that of E3810, with the exception of the

low-dose group on *pp* day 7. The TK results are summarized in the following sponsor's table.

**Text Table 1 Toxicokinetic Summary of E3810**

Dose (mg/kg)	Day ( <i>pp</i> )	Male		Female	
		C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng·hr/mL)	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng·hr/mL)
25	7	4677	9250	3529	8605
	41	102.3	49.22	78.15	23.08
150	7	22260	38600	22810	37250
	41	774.3	400.9	861.2	351.7

**Text Table 2 Toxicokinetic Summary of PTBI**

Dose (mg/kg)	Day ( <i>pp</i> )	Male		Female	
		C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng·hr/mL)	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng·hr/mL)
25	7	992.3	4838	976.5	4533
	41	93.57	367.3	123.0	384.3
150	7	3781	47190	4121	55990
	41	325.7	1334	429.5	1563

## 6 General Toxicology

### 6.1 Single-Dose Toxicity

N/A

### 6.2 Repeat-Dose Toxicity

Rat:



5-week repeated oral toxicity study with E3810 in neonatal rats  
(900948)

Testing Laboratory:

(b) (4)

Study Start and Completion Dates: May 16, 2006 and April 19, 2007

GLP and QAU Compliance Statement: The sponsor included a statement of compliance with GLP regulations and a quality assurance statement.

Animals: Sprague-Dawley CD[Cr1:CD(SD) rats, 7 days old, 12-22 g.

Methods: To assess the repeated oral dose toxicity of E3810 in neonatal rats, E3810 was given by oral gavage to 7 days old rats (10/sex/group) at 0, 5, 25, and 150 mg/kg/day for 5 weeks. Mortality and clinical signs of toxicity were observed daily. Body weights were recorded twice weekly. The pups were

separated from their dams and housed individually on day 21 post partum. Food consumption was recorded. Ophthalmological examination was conducted at termination. Hematology, clinical chemistry, and urinalysis were performed at termination. Gross pathological examination was conducted and organ weights were determined. Histopathological examination was performed on all main study animals in all groups. In addition to the regular hematoxylin and eosin staining for examination by routine light microscopy, sections of the stomach taken from a consistent location from all main and recovery pups in all groups were stained with Grimelius stain and analyzed by histomorphometry to evaluate the enterochromaffin-like (ECL)-cells in the mucosa and fundic mucosal thickness. Plasma level of the test drug was determined on day 7 and 41 post partum. Physical and behavioral developments were also examined.

#### Results:

1. Clinical Signs of Toxicity: There were no treatment related changes.
2. Mortality: One control female and one high dose female were found dead without clinical signs of toxicity. The control female had head trauma and the cause of death for the high dose female was not known. Some TK animals died following blood collection.
3. Body Weight: The body weight gain was lower (~5-6%) in the high dose group as compared to the control during the treatment period.
4. Food Consumption: There were no treatment related changes.
5. Hematology: Red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were decreased (~5-10%) and reticulocyte count was increased (~16%) in the high dose males.

Serum phosphorus levels and total iron binding capacity were increased in the high dose group.

6. Clinical Chemistry: Increase in gastrin levels were noted in the high dose males and females at 4 and 24 hours after the last dose. The results were presented in Table 16 and this table is attached below.

**Table 16**                    **Group Mean Concentration of Gastrin (pg/mL)**Subgroup D - Toxicokinetic  
Day 41 Post Partum  
MalesGroup 2 - Rabeprazole 5 mg/kg  
Group 3 - Rabeprazole 25 mg/kg

Group 4 - Rabeprazole 150 mg/kg

Group	Summary Information	Final Results 4Hrs	Final Results 24Hrs
2	Mean	212.60	256.70
	SD	54.19	176.25
	N	3	3
3	Mean	258.45	103.85
	SD	29.63	53.53
	N	2	2
4	Mean	335.90	425.45
	SD	21.78	140.93
	N	2	2

**Table 16**                    **Group Mean Concentration of Gastrin (pg/mL)**Subgroup D - Toxicokinetic  
Day 41 Post Partum  
FemalesGroup 2 - Rabeprazole 5 mg/kg  
Group 3 - Rabeprazole 25 mg/kg

Group 4 - Rabeprazole 150 mg/kg

Group	Summary Information	Final Results 4Hrs	Final Results 24Hrs
2	Mean	195.25	161.83
	SD	107.98	101.65
	N	2	3
3	Mean	228.57	65.30
	SD	70.34	12.02
	N	3	2
4	Mean	463.40	192.23
	SD	167.84	70.72
	N	3	3

7. Urinalysis: There were no treatment related changes.

8. Ophthalmological examination: There were no treatment related changes.

9. Organ Weight: Stomach weights were increased in the males at doses of 25 mg/kg or higher and females at 150 mg/kg.

10. Gross Pathology: There were no treatment related changes.

11. Histopathology: Histopathological examination revealed a dose-related increase in cytoplasmic eosinophilia of chief cells

in the stomach. The gastric mucosal thickness was also increased in the high dose males and females. The mean density of enterochromaffin-like (ECL) cells was increased in males at 5 mg/kg or higher and females at 25 mg/kg or higher. The changes were reversible. The results were presented in Table 21 and this table is attached below.

**Table 21** Group Mean Histomorphometric Parameters  
Subgroup A - Main Study

Stomach Mucosa Male			
Group 1 - Vehicle Control		Group 3 - Rabeprazole 25 mg/kg	
Group 2 - Rabeprazole 5 mg/kg		Group 4 - Rabeprazole 150 mg/kg	
Group	Summary Information	Mucosal.Th μm	ECL-cells.Dn #/mm <sup>2</sup>
1	Mean	582.9	109
	S.D.	68.77	21.4
	N	10	10
2	Mean	587.1	143
	S.D.	75.12	48.5
	N	10	10
3	Mean	578.3	136
	S.D.	63.52	37.7
	N	10	10
4	Mean	629.0	156
	S.D.	41.59	43.4
	N	10	10

Significantly different from control group (group 1) value: A - P<= 0.05 B - P<= 0.01 C - P<= 0.001 (Dunnett )  
D - P<= 0.05 E - P<= 0.01 F - P<= 0.001 (Dunn )

**Table 21** Group Mean Histomorphometric Parameters  
Subgroup A - Main Study

Stomach Mucosa Female			
Group 1 - Vehicle Control		Group 3 - Rabeprazole 25 mg/kg	
Group 2 - Rabeprazole 5 mg/kg		Group 4 - Rabeprazole 150 mg/kg	
Group	Summary Information	Mucosal.Th μm	ECL-cells.Dn #/mm <sup>2</sup>
1	Mean	525.0	102
	S.D.	118.26	43.3
	N	10	10
2	Mean	507.6	105
	S.D.	38.39	23.8
	N	10	10
3	Mean	530.3	157
	S.D.	66.14	50.8
	N	10	10
4	Mean	596.5	191
	S.D.	57.11	77.1
	N	9	9

Significantly different from control group (group 1) value: A - P<= 0.05 B - P<= 0.01 C - P<= 0.001 (Dunnett )  
D - P<= 0.05 E - P<= 0.01 F - P<= 0.001 (Dunn )

12. Physical Development: There were no treatment related changes.

13. Behavioral assessment: Treatment did not change the behavioral development of the animals.

14. Plasma level of test drug: The maximum plasma level of the test drug was reached within 0.25-1 hour. The plasma levels of the test drug were similar in males and in females. The results were presented in the following table.

**Text Table 1 Toxicokinetic Summary**

Dose (mg/kg)	Day (pp)	Male		Female	
		C <sub>max</sub> (ng/mL)	AUC <sub>0-1</sub> (ng-hr/mL)	C <sub>max</sub> (ng/mL)	AUC <sub>0-1</sub> (ng-hr/mL)
5	7	741.6	2036	1345	1934
	41	7.531	3.144	13.50	3.959
25	7	5046	7167	5479	8699
	41	39.49	46.55	55.61	23.80
150	7	25800	54380	32527	57766
	41	197.6	145.9	240.8	207.7

The plasma levels of E3810 were dramatically lower on day 41 as compared to day 7. This could be result of maturation of the liver enzyme over time.

In summary, E3810 was given by oral gavage to 7 days old rats (10/sex/group) at 0, 5, 25, and 150 mg/kg/day for 5 weeks. Treatment increased the serum gastrin level and stomach weight. Histopathological examination revealed a dose-related increase in cytoplasmic eosinophilia of chief cells in the stomach. The gastric mucosal thickness was also increased in the high dose males and females. The mean density of ECL cells was increased in males at 5 mg/kg or higher and females at 25 mg/kg or higher. The changes were reversible. Treatment did not clearly affect the physical and behavioral development of the animals.

Dog:

13-week repeated oral toxicity study with E3810 in neonatal dogs  
(900949)

Testing Laboratory: [REDACTED] (b) (4)

Study Start and Completion Dates: June 21, 2006 and June 5, 2007

GLP and QAU Compliance Statement: The sponsor included a statement of compliance with GLP regulations and a quality assurance statement.

Animals: Beagle dogs, 7 days old,  
171-811 g.

Methods: To assess the repeated oral dose toxicity of E3810 in neonatal dogs, E3810 was given by oral gavage to 7 days old dogs (4/sex/group) at 0, 3, 10, and 30 mg/kg/day for 13 weeks. Mortality and clinical signs of toxicity were observed daily. Body weights were recorded twice weekly. Food consumption was recorded. Ophthalmological examination was conducted. Hematology, clinical chemistry, and urinalysis were performed at termination. Gross pathological examination was conducted and organ weights were determined. Histopathological examination was performed on all main study animals in all groups. In addition to the regular hematoxylin and eosin staining for examination by routine light microscopy, sections of the stomach taken from a consistent location from all main and recovery pups in all groups were stained with Grimelius stain and analyzed by histomorphometry to evaluate the ECL-cells in the mucosa and fundic mucosal thickness. Plasma level of the test drug was determined on day 7, 21, 42, 56, and 69 post partum. Physical and behavioral developments were also examined.

Results:

1. Clinical Signs of Toxicity: Following clinical signs of toxicity were noted in pups of the high dose group: salivation, vomiting, retching, soft, dry and/or liquid feces, swelling and redness of the anus with associated fur staining and/or wet ventral abdominal fur and hind limbs/tail.

Salivation, retching and soft and/or liquid feces were also noted in the mid dose group.

2. Mortality: One low dose female was sacrificed in moribund condition due to dosing error.
3. Body Weight: On Day 56 post partum, the body weights in the mid and high dose groups were approximately 89% to 94% of the controls, respectively. On day 94 post partum (end of the dosing period), the body weights in these groups were 79-84% and 89-94% of the controls, respectively.
4. Food Consumption: There were no treatment related changes.
5. Hematology: There were no treatment related changes.
6. Clinical Chemistry: Serum gastrin levels were increased (3 to 14 folds) at 4 and 24 hours after dosing in the treated animals during Week 6 as compared to the control. At Week 13, serum gastrin levels were increased (8 to 21 folds) in the treated animals as compared to the control. Slight increase in the total iron binding capacity and unsaturated iron binding capacity and slight decrease in serum iron were noted in all treatment groups during weeks 8 and 13.
7. Urinalysis: There were no treatment related changes.
8. Ophthalmological examination: There were no treatment related changes.
9. Organ Weight: Stomach weights were increased in the mid and high dose groups (8.4-8.7%) as compared to the control.
10. Gross Pathology: There were no treatment related changes.
11. Histopathology: Histopathological examination revealed degeneration/necrosis of parietal cells and mucosal hypertrophy/hyperplasia in the fundus of the stomach in a dose related manner. Increased mean gastric mucosal thickness was also noted. One high dose female had slight atrophy of chief cells.
12. Physical Development: There were no treatment related changes.
13. Behavioral assessment: Treatment did not change the behavioral development of the animals.

14. Plasma level of test drug: The maximum plasma level of the test drug was reached within 0.5 hours. The results were presented in the following table.

**Text Table 1 Toxicokinetic Summary**

Dose (mg/kg)	Day (pp)	Male		Female	
		C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng·hr/mL)	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng·hr/mL)
3	7	228	57	193	48
	21	556	302	99	66
	42	93	72	29	26
	56	270	206	321	219
	69	144	111	202	149
10	7	2115	3178	1912	2880
	21	670	550	738	511
	42	1400	991	1092	735
	56	254	210	286	225
	69	194	188	845	598
30	7	5443	8421	3263	5147
	21	5844	3599	3752	3074
	42	4023	2744	6312	4151
	56	2644	1912	4381	3612
	69	1411	1055	2454	1763

In summary, E3810 was given by oral gavage to 7 days old dogs at 0, 3, 10, and 30 mg/kg/day for 13 weeks. Treatment increased the serum gastrin level, stomach weight and gastric mucosal thickness. Histopathological examination revealed degeneration/necrosis of parietal cells and mucosal hypertrophy/hyperplasia in the fundus of the stomach in a dose related manner. The changes were reversible. Treatment did not clearly affect the physical and behavioral development of the animals.

## 7 Genetic Toxicology

N/A

### 7.4 Genetic Toxicity Studies with metabolites

N/A

## 8 Carcinogenicity

N/A



## **9 Reproductive and Developmental Toxicology**

### **9.1 Fertility and Early Embryonic Development**

N/A

### **9.2 Embryonic Fetal Development**

N/A

### **9.3 Prenatal and Postnatal Development**

N/A

## **10 Special Toxicology Studies**

N/A

## **11 Integrated Summary and Safety Evaluation**

Rabeprazole was originally developed under IND 33,985 and approved under NDA 20,973 (Aciphex® (rabeprazole sodium) Delayed-Release Tablets) in 1999 for the treatment of duodenal ulcers, erosive or ulcerative gastroesophageal reflux disease (GERD), symptomatic GERD, maintenance of GERD healing, and pathological hypersecretory conditions, including Zollinger-Ellison Syndrome in adults. It is also approved for short-term treatment of GERD in adolescent patients 12 years of age and above. In the current NDA, the sponsor seeks approval of AcipHex® Delayed-Release Sprinkle Capsules for the healing, maintenance of healing, and symptom improvement of GERD in patients age 1 to 11 years. In support of this NDA, the sponsor conducted two neonatal toxicity studies in rats and dogs. These studies were submitted to NDA 20,973 (supplement 022) on December 28, 2007 and reviewed on May 30, 2008.

In the 5-week oral toxicity study in neonatal rats, E3810 was given by oral gavage to 7 day-old rats at 0, 5, 25, and 150 mg/kg/day for 5 weeks. Treatment increased the serum gastrin level and stomach weight. Histopathological examination revealed a dose-related increase in cytoplasmic eosinophilia of chief cells in the stomach. The gastric mucosal thickness was also increased in the high dose males and females. The mean density of ECL cells was increased in males at 5 mg/kg and higher and in females at 25 mg/kg and higher. The changes were reversible. Treatment did not clearly affect the physical and behavioral development of the animals. Toxicokinetic analysis in this study included the unchanged drug (E3810), but not the thioether metabolite (PTBI), which is one of the primary metabolites in human plasma. Therefore, the Sponsor conducted a toxicokinetic bridging study in neonatal rats, using oral administration of 25 and 150 mg/kg/day E3810 on days 7 to 41 *post partum*. AUC values for PTBI exceeded that of E3810, with the exception of the low-dose group on *pp* day 7.

In the 90-day oral toxicity study in neonatal dogs, E3810 was given by oral gavage to 7-day old dogs at 0, 3, 10, and 30 mg/kg/day for 13 weeks. Treatment increased the serum gastrin level, stomach weight and gastric mucosal thickness.

Histopathological examination revealed degeneration/necrosis of parietal cells and mucosal hypertrophy/hyperplasia in the fundus of the stomach in a dose related manner. The changes were reversible. Treatment did not clearly affect the physical and behavioral development of the animals.

During the clinical studies in pediatric patients under IND 33,985, the sponsor discovered the presence of (b) (4) in the enteric coated granules contained in rabeprazole sodium sprinkle capsules. (b) (4) is the primary metabolite of (b) (4). (b) (4) is used as a (b) (4) in many approved drug products at amounts up to (b) (4) mg per dose (see FDA inactive ingredient database). The majority of (b) (4) is likely converted to (b) (4) in animals and humans, and thus it is reasonable to use the human exposure to (b) (4) to assess the safety of (b) (4). Based on our original assessment (see Appendix/Attachments for Pharmacology review of IND 33,985 dated February 25, 2011), the maximum exposure of (b) (4) from rabeprazole sodium sprinkle capsules will be (b) (4) µg/kg/day (b) (4) mg/day if a 60-kg body weight is assumed), which is within maximal daily level of (b) (4) ( (b) (4) mg (b) (4) /dose) in the FDA inactive ingredient database (b) (4) mg (b) (4) is equivalent to (b) (4) mg DEP). In the current NDA, the sponsor estimates that the potential maximum exposure to (b) (4) in the to-be-marketed formulation is (b) (4) µg/kg/day, which is less than the original estimation of (b) (4) µg/kg/day. Therefore, from a nonclinical standpoint, the exposure to (b) (4) via rabeprazole sodium sprinkle capsules is unlikely to be a safety risk in pediatric patients.

The sponsor seeks market approval of AcipHex® Delayed-Release Sprinkle Capsules for the healing, maintenance of healing, and symptom improvement of GERD in patients age 1 to 11 years. The results of the 5-week oral toxicity study in the neonatal rats and the 90-day oral toxicity in neonatal dogs did not reveal any new toxicities as compared to the adult animals. Therefore, from a nonclinical standpoint, we recommend that this application be approved for the proposed pediatric indications. The sponsor should be asked to revise the label as recommended.

## 12 Appendix/Attachments

1. Pharmacology review (SD# 683 dated April 6, 2009) dated 2/25/2011

PHARMACOLOGIST'S REVIEW OF IND 33,985  
(SD# 683 dated April 6, 2009)

Sponsor & Address: Eisai Medical Research Inc.  
Ridgefield, NJ

Reviewer: Ke Zhang, Ph.D.  
Pharmacologist

Date of HFD-180 Receipt: April 6, 2009

Date of Review: February 25, 2011

DRUG: Rabeprazole / Aciphex / E3810, Delayed release tablets

DRUG CLASS: Proton pump inhibitor / Antisecretory agent /  
Inhibitor of H<sup>+</sup>/K<sup>+</sup>-ATPase

Submission Contents: Correspondence

Background: The Sponsor discovered the presence of (b)(4) in the enteric coated granules contained in rabeprazole sodium sprinkle capsules, a formulation that is being tested in clinical studies of pediatric patients. To assess the safety risk of (b)(4) exposure in pediatric patients, the Sponsor obtained a consultation from an outside expert, Dr. (b)(4). Dr. (b)(4)'s consult report is included in the current submission. Based on his assessment, the Sponsor believes that the exposure to (b)(4) via rabeprazole sodium sprinkle capsules will not have adverse effects on the pediatric patients in the clinical trials.

**SUMMARY AND EVALUATION:**

(b)(4) is the primary metabolite of (b)(4). (b)(4) is used as a (b)(4) in many approved drug products at amounts up to (b)(4) mg per dose (see FDA inactive ingredient database). The majority of (b)(4) is likely converted to (b)(4) in animals and humans and thus it would be adequate to rely on the accepted exposure level for (b)(4) to assess the safety of (b)(4). The maximum exposure of (b)(4) from rabeprazole sodium sprinkle capsules is (b)(4) µg/kg/day or (b)(4) mg/day if a 60-kg body weight is assumed. This exposure is

within maximal daily level of (b) (4) ((b) (4) mg (b) (4) /dose) in the FDA inactive ingredient database. Therefore, from a nonclinical standpoint, the exposure to (b) (4) via rabeprazole sodium sprinkle capsules is unlikely to be a safety risk in pediatric patients. This issue was discussed in a team meeting on December 15, 2010. The team agreed with our assessment that the exposure to (b) (4) via rabeprazole sodium sprinkle capsules is unlikely to produce any adverse effects in pediatric patients, and that no further action is needed.

**RECOMMENDATION:** None.

\_\_\_\_\_  
Ke Zhang, Ph.D.      Date

\_\_\_\_\_  
David B. Joseph, Ph.D.      Date  
Pharmacology Team Leader, DGP

cc:  
NDA (b) (4)  
DGP  
DGP/PM  
DGP/Dr. Joseph  
DGP/Dr. Zhang

R/D Init.: 2/15/11  
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/s/  
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KE ZHANG  
02/25/2011

DAVID B JOSEPH  
03/01/2011  
I concur.

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/s/  
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KE ZHANG  
03/01/2013

DAVID B JOSEPH  
03/01/2013  
I concur.

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number:** 204,736

**Applicant:** Eisai Inc.

**Stamp Date:** September 27,  
2012

**Drug Name:** Aciphex  
(rabeprazole sodium)

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

On **initial** overview of the NDA 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 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		
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?	x		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		

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

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

**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.

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

Ke Zhang, Ph.D.

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Reviewing Pharmacologist Date

David Joseph, Ph.D.

---

Team Leader/Supervisor Date

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



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KE ZHANG  
10/31/2012

DAVID B JOSEPH  
10/31/2012