CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204736Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA # **Supplement #**	NDA 204736
Applicant Name	Eisai, Inc
Date of Submission	9/27/2012
PDUFA Goal Date	3/27/2013
Proprietary Name / **Established (USAN) Name**	AcipHex® Sprinkle™ Rabeprazole
Dosage Forms / Strength	ACIPHEX® SPRINKLE™ (rabeprazole sodium) Delayed-Release Capsules
Proposed Indication(s)	Treatment of Gastroesophageal Reflux Disease (GERD) in Pediatric Patient Aged 1 to 11 Years • ACIPHEX® SPRINKLE™ is indicated for the healing and improvement of GERD symptoms [redacted (b) (4)] • ACIPHEX® SPRINKLE™ is indicated for the maintenance of healing of GERD [redacted (b) (4)]
Action/Recommended Action for NME:	*Approval,* Treatment of GERD in Pediatric Patients Aged 1 to 11 Years: For patients with bodyweight < 15 kg, 5 mg once daily with the option to increase to 10 mg; for patients with bodyweight ≥ 15 kg, 10 mg once daily

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Statistical Review	Freda Cooner, Ph.D. Michael Welch, PhD
Medical Officer Review	John Troiani, MD, PhD
DMA/OBP	Jun Park, Ph.D. Ruth Cordoba-Rodriguez, Ph.D
CMC	A Banerjee, PhD
PMHS	Amy Taylor, MD Jeanine Best, MD
ONDQA	Yichun Sun, PhD
Pharmacometrics	Nitin Merhotra, Ph.D. Jerry Yu, PhD
ONDQA Biopharm	Angela Dorantes

Clinical Pharmacology	Sue Chih Lee, PhD Insook Kim, PhD
Pharmacology Toxicology Review	Sushanta Chakder, Ph.D.
CDTL Review	Ruyi He, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

In this NDA supplement, the applicant proposes to expand the indications of AcipHex® Sprinkle™ to include healing, maintenance and treatment of gastroesophageal reflux disease (GERD) in children. The current submission presents new data from several clinical trials involving pharmackinetics, pharmacodynamics, efficacy and safety of AcipHex® Sprinkle™ in neonates, infants 1-11 months and children 1-11 years of age with GERD. This sNDA is submitted in response to the studies requested as part of the Written Request for AcipHex® Sprinkle™ for studies in infants and children with GERD. It includes the following studies:

1. Pharmacokinetic, Phamracodynamci and safety study in neonates and preterm infants with a corrected age less than 44 weeks
2. Efficacy and safety evaluation of pediatric patients 1-11 months of age
3. Pharmacokinetic, exposure/response and safety study in pediatric patients 1 to 11 years of age
4. Pharmacokinetic and safety study in pediatric patients 12-16 years of age.

Studies addressed in this supplement concern studies outlined as #1-3 but studies in adolescents have already been incorporated into the AcipHex® Sprinkle™ label. The primary end secondary endpoints, study population, study design and summary of results are delineated in Table 1 reproduced below from Dr. Troiani's review:

Table 1: Summary of Clinical Trials

Study	Study Population	Primary and Secondary Endpoints	Design	Summary of Results
RABGRD1005 (Study 1005)	0 to <1 month of age	PK/PD in neonates (0 to <1 month old)	Multicenter, open-label, short-term (5-28days) of once daily rabeprazole (n=69): Phase 1: 1mg Phase 2: 2, 3mg (random assignment)	AUC ~3-fold higher in neonates than in 1-11 month age group. PD: mean (pooled dose groups) % of time with gastric pH>4 on rabeprazole Day 5: 90% [range 80% to 100%] (63% pre-rabeprazole) Safety: 1 death in a medically complex premature infant with multisystem pathology, adjudicated as not related to rabeprazole. Rate of anemia TEAEs (11%-20%-24% in 1mg-2mg-3mg dose groups)
RABGRD3004 (Study 3004)	1 to 11 months of age with suspected GERD, symptomatic GERD, or endoscopically proven GERD	Co-Primary—changes from baseline in both: a) frequency of regurgitation from baseline ; AND b) weight-for-age Z-score Secondary—regurgitant volume, I-GERQ-DD score and subscores	Randomized, multicenter, open-label followed by double-blind (DB), placebo-controlled trial in 344 enrolled patients; 268 responders to 1-3 weeks of open-label rabeprazole were then randomized into a 5-week DB period (placebo vs rabeprazole). Interim futility stopping was added but ended up being as already planned at end of trial.	Efficacy was not demonstrated. Other PPIs were also not able to demonstrate efficacy in same population in 1-11 month age group, which was the subject of an AC convened in Nov-2010. Safety: No deaths. TEAEs (PBO v 5mg v 10mg): 47% v 43% v 50%. GERD, vomiting, fever, URI, elevated serum gastrin.
RABGRD3003	1 year to 11 years of	Primary—Histologic	Randomized,	Healing rates (low, high

Study	Study Population	Primary and Secondary Endpoints	Design	Summary of Results
Part 1 (Study 3003 Part 1)	age with "endoscopically proven" GERD[1]	or endoscopic esophageal mucosal healing[2] at 12 weeks Secondary—pooled and individual symptom scores[3]	multicenter, double-blinded (no placebo) trial (n=127) of 2 dose levels by bodyweight: ≤15kg: 5 or 10 mg >15kg: 10 or 20mg	dose): <15kg: 82%(14/17), 94%(15/16) ≥15kg: 76% (29/38), 78%(29/37) Safety: no deaths; no new AEs not already reported in adults and adolescents
RABGRD3003 Part 2 (Study 3003 Part 2)	1 year to 11 years of age who passed primary endpoint in Part 1	Primary—Histologic or endoscopic esophageal healing[2] after 24 additional weeks (total 36 weeks of rabeprazole including Part 1) Secondary—pooled and individual symptom scores[3]	Double-blinded continuation of Part 1 on same dose as in Part 1	Healing rates (low, high dose): ≤15kg: 100%(8/8), 100%(6/6) >15kg: 89% (16/18), 85%(17/20) Safety: no deaths; no new AEs not already reported in adults and adolescents

1. "Endoscopically proven" is Applicant's term that is defined as an [endoscopic] Hetzel-Dent (HD) score≥1 AND biopsy with Histologic Features of Reflux Esophagitis (HFRE) grade>0. All enrolled patients must have had a history of at least one GERD symptom in the last 3 months prior to screening.
2. Definition of "healing" is HD=0 or HFRE=0. This is also the definition of success on the primary endpoint on an individual subject basis.
3. Total GERD Symptom and Severity Score and derived subscores. This is a pooled symptom score that is not accepted or validated at the time of this review for purposes of FDA approval.

Rabeprazole is classified as a gastric proton pump inhibitor (PPI) and is currently marketed globally under the trade names AcipHex®, and Pariet®, as enteric-coated (EC) 10-mg or 20-mg rabeprazole tablets containing (b) (4) and (b) (4) mg rabeprazole free acid, respectively.

In the United States, rabeprazole is available as 20-mg AcipHex® tablets indicated for multiple diseases, including: short-term treatment in adults of erosive or ulcerative gastroesophageal reflux disease (GERD); symptomatic GERD; maintenance of healed erosive or ulcerative GERD; healing and symptomatic relief of duodenal ulcers; long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome; and eradication of *Helicobacter pylori* in combination with amoxicillin and clarithromycin. AcipHex® 20-mg tablets are also indicated for short-term treatment of symptomatic GERD in adolescents 12 years and above.

Gastroesophageal reflux is a common event occurring in children. GERD is characterized by increased exposure of the esophageal mucosa to the gastroduodenal contents, which are usually acidic and result in chronic symptoms, and may occur in children of all ages. In older children, the pathogenesis and clinical presentation of GERD resemble those in adults. Antacids, H_2-receptor blockers, and several PPIs, including rabeprazole, have been approved for the treatment of GERD in adolescents.

2. Background

Rabeprazole is classified as a gastric proton pump inhibitor (PPI) and is currently marketed globally under the trade names AcipHex®, and Pariet®, as enteric-coated (EC) 10-mg or 20-mg rabeprazole tablets containing (b) (4) and (b) (4) mg rabeprazole free acid, respectively.

In the United States, rabeprazole is available as 20-mg AcipHex® tablets, and is indicated for multiple conditions, including: short-term treatment in adults of erosive or ulcerative gastroesophageal reflux disease (GERD); symptomatic GERD and the maintenance of healed erosive or ulcerative GERD in adults. Other indications include healing and symptomatic relief of duodenal ulcers, long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome, and eradication of *Helicobacter pylori* in combination with amoxicillin and clarithromycin. AcipHex® 20-mg tablets are also indicated for short-term treatment of symptomatic GERD in adolescents 12 years and above.

Gastroesophageal reflux disease is a common gastrointestinal disorder characterized as symptomatic and erosive type, the latter that requires maintenance of healing, which can be accomplished by the use of multiple different proton pump inhibitors (PPIs). AcipHex® acts as an irreversible inhibitor of the (H+, K+)-ATPase (proton) pumps of parietal cells of the stomach. This action suppresses acid secretion, raises the pH of the stomach, and decreases damage to the esophageal mucosa during episodes of acid reflux. The Table below reproduced from Dr. Troiani's review delineates the currently available PPIs and the indications in children:

Children.

Table 2: Currently Available PPIs for proposed indications

Treatment	Indication in 1-11 year age group	Notes
NEXIUM® (esomeprazole) DR Capsules and Oral Suspension	**Section 1.1 Treatment of GERD** • *Healing of EE:* "…indicated for short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8 week course of NEXIUM may be considered." (dose: weight<20kg:10mg; weight≥20kg: 10mg or 20mg) • *sGERD*: "…indicated for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults and children 1 year or older." (dose: 10mg once daily)	In clinical trial in 1-11 year age group—multicenter parallel group with n=109 patients treated once daily for up to 8 weeks. "history of endoscopically-proven GERD" N=53 (49%) patients with EE at baseline. Patients were endoscopically characterized as to presence or absence of EE. "Although most of the patients who had follow up endoscopy at the end of 8 weeks of treatment healed, spontaneous healing cannot be ruled out because … the trial did not include a control group."
PRILOSEC® (omeprazole) DR tabs and DR Oral Suspension	**Section 1.3 Treatment of GERD (adults and pediatric patients)** • *Symptomatic GERD*: "… is indicated for treatment of heartburn and other symptoms associated with GERD in pediatric patients and adults (dose: weight "5 < 10kg": 5mg; weight "10 < 20 kg": 10mg; weight ≥20kg: 20mg). NOTE: treatment duration for pediatric sGERD is not specified in Highlights, Indications, or Dosage and Administration sections of label • *EE:* "…is indicated for the short-term treatment (4-8 weeks) of EE that has been diagnosed by endoscopy in pediatric patients and adults." (dose: weight "5 < 10kg": 5mg; weight "10 < 20 kg": 10mg; weight ≥20kg: 20mg) **Section 1.4 Maintenance of healing of EE (adults and pediatric patients)** "…is indicated to maintain healing of EE in	"effectiveness…for the treatment of nonerosive GERD in pediatric patients 1 to 16 years of age is based in part on data obtained from 125 pediatric patients in two uncontrolled Phase III studies." sGERD Study 1: n=12 pediatric patients 1 -2 years old "with history of clinically diagnosed GERD" treated for 8 weeks. 75% (9/12) had decreased vomiting/regurg episodes from baseline by at least 50%. sGERD Study 2: n=113 patients 2-16 years old "with a history of symptoms suggestive of nonerosive GERD" treated for 4 weeks. Successful response was defined as "no moderate or severe episodes of either pain-related symptoms or vomiting/regurgitation during the last 4 days of treatment." Response rates of 59% (58/98 in 20mg group) and 60% (9/15 in 10mg group).

Treatment	Indication in 1-11 year age group	Notes
	pediatric patients and adults." (dose: weight "5 < 10kg": 5mg; weight "10 < 20 kg": 10mg; weight ≥20kg: 20mg) NOTE: treatment duration for pediatric maintenance of healing of EE is not specified in Highlights, Indications ("Controlled studies do not extend beyond 12 months."), or Dosage and Administration sections of label.	Healing of EE: uncontrolled open-label dose-titration study in 1-16 year age group. EE healed in 90% (51/57) Maintenance of Healing of EE: uncontrolled open-label n=46. "54% of patients required half the healing dose" "41% had no relapse". 63% had "no overall symptoms"
PREVACID® (lansoprazole) DR Capsules, DR Oral Suspension, DR ODT	"**Pediatrics (8.4)**: (1-11 years of age) Short-term treatment of sGERD and short-term treatment of EE" (Highlights section, "Dosage and Administration"—none in Indications) **Section 1.7 GERD** • *Short-term Treatment of sGERD* "…is indicated for the treatment of heartburn and other symptoms associated with GERD. (dose: ≤30kg: 15mg; >30kg: 30mg--once daily for up to 12 weeks) • *Short-term Treatment of EE* "…is indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of EE. For patients who do not heal with PREVACID for 8 weeks (5-10%), it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of EE an additional 8-week course of PREVACID may be considered." (dose: ≤30kg: 15mg; >30kg: 30mg--once daily for up to 12 weeks)	Clinical trial in 1-11 year olds--uncontrolled open-label, n=66 patients "with GERD". After 8-12 weeks "50% reduction in frequency and severity of GERD symptoms". 21/27 with EE were healed at 8 weeks and 100% at 12 weeks by endoscopy.

Importantly no PPI is currently labeled for the maintenance treatment of erosive esophagitis secondary to GERD (eGERD) and labeling for all PPIs do not currently discriminate between treatment for symptomatic and erosive esophagitis (eGERD). This issue will be discussed below as this supplement addresses the pediatric indications for GERD related to the use of AcipHex® Sprinkle™ Delayed-Release capsules.

3. CMC

Dr. Yichun Sun is the CMC reviewer for this NDA and concluded in his review that this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

Dr. Houda Mahayni from ONDQA did review on the evaluation and acceptability of 1) the *in vitro* dissolution method and acceptance criteria, 2) the product stability with dosing vehicles, and 3) the waiver request for the lower dosage strengths (2.5 mg and 5 mg). Dr. Mahayni concluded that the proposed dissolution method conditions and acceptance criteria for each stage are acceptable.

From the ONDQA Biopharm review, the Applicant did not evaluate the alcohol dose dumping potential of their proposed modified release dosage form. In discussions with the Sponsor, on February 15, 2013, the Applicant made the post approval commitment to assess the effect of alcohol on the drug release of AcipHex® Sprinkle™ Delayed-Release Capsules and submit the study results no later than August 8, 2013.

4. Nonclinical Pharmacology/Toxicology

In the reviews of Drs. Ke Zhang and David Joseph, the changes to the label reflect the neonatal animal toxicity data. There was discussion of the placement of the nonclinical data appropriateness for section 13 or under the Pediatrics section of the label. There were concerns raised by this Signatory about the labeling implications of these data to support neonatal safety. Placement of the nonclinical data related to reversibility of the gastrin level, ECL hyperplasia and gastric mucosal thickness in a clinical section of the label would support neonatal safety by stating the reversibility of the adverse events and promote off-label use in this Signatory opinion.

As noted in Clinical below, there was significant evidence of achlorhydria in neonates exposed to AcipHex® Sprinkle™. The nonclinical data from neonatal animals reflects: "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.

"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."

Initially Dr. Joseph concluded: "The results of these toxicity studies in neonatal animals are consistent with the findings in the adult animals, and did not reveal any new toxicity. 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." Therefore, the nonclinical data are stated in section 13.2 of the AcipHex® Sprinkle™ label. The Signatory concurs with this decision.

5. Clinical Pharmacology/Biopharmaceutics

The reviewers, Nitin Mehrotra (Division of Pharmacometrics/OCP) and Insook Kim (Division of Clinical Pharmacology 3/OCP), reviewed clinical pharmacology data. Please refer to their reviews and that of the CDTL summary of Dr. He for detailed information summarizing these data. The Signatory agrees with Drs. Kim and Merhotra regarding their recommendation for approval of the supplement regarding labeling with doses outlined below in the 1-11 year old pediatric population. The justification for the dose identification is well supported and explained by Dr. Kim in her review. Briefly, Dr Kim states that there was no clear exposure-response relationship for the healing rate and there was no apparent relationship between rabeprazole systemic exposure, i.e. AUC and the probable healing of GERD. Distinction between the doses studied was not justifiable and concurred with the Clinical review. These data are reproduced and discussed below

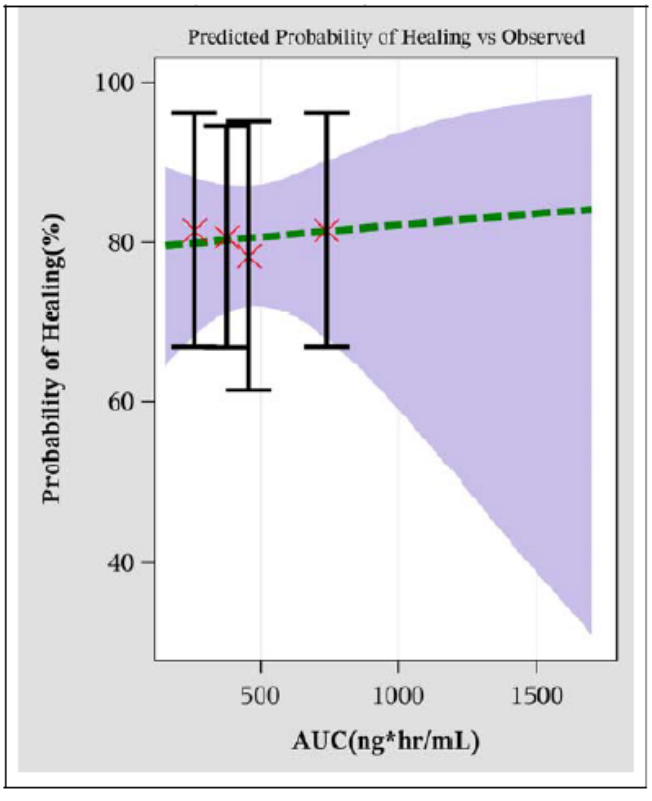


Figure 1: Probability of Healing versus AUC AcipHex(R) Sprinkle(TM)

Table 3: Endoscopic/Histologic Healing Rates During the 12 Week Double Blind Treatment Period

Body weight cohort	Patients < 15 kg		Patients ≥ 15 kg	
Dose	5mg	10 mg	10 mg	20 mg
Healing rate:% (n/N)	82 (14/17)	94 (15/16)	76 (29/38)	78 (29/37)

Reproduced from Dr. Kim, Clinical pharmacology review

In regards to the neonates, the mean apparent clearance in neonates < 1 month was predicted to be < 10% of that of infant's ages 1-11 months and 25% of children 1-11 years of age (review, Dr. Kim). The PK is so variable in neonates that its hard to identify a dose response but there is a trend towards exposure-response, there seems to be a trend of exposure response (see review, Pharmacometrics). What remains a concern is the prolonged exposure of AcipHex® Sprinkle™ in neonates suggested by delayed clearance and the physiological impact that it may exert. Many unknown questions remains including the effect of AcipHex® Sprinkle™ Delayed-release capsules on gastrin secretion since the study did not assess it, which leaves uncertainty. It is well established that the PPIs are associated with hypergastrinemia and this issue has been well investigated. The implications of neonatal hypergastrinemia remain unresolved but the evidence of achlorhydria is manifested and will be addressed in Labeling as discussed below in **Section 7** Safety.

5. Clinical Microbiology

Clinical microbiology considerations do not apply to this supplemental application because rabeprazole is not intended as an antimicrobial product.

6. Clinical/Statistical-Efficacy

The Clinical and Statistical reviewers recommend Approval of this application. I concur with this decision. The reader is referred to Dr. He's CDTL memorandum for further review and complete information of historical efficacy and safety data related to clinical trial and exposure data related to AcipHex® Sprinkle™. The indication approved for this sNDA includes the treatment of GERD in the 1-11 year old age group for short term treatment for up to 12 weeks at a dose of 5 mg (or 10 mg if inadequate response to 5 mg) for patients weighing less than 15 kg; and at a dose of 10 mg for patients weighing at least 15 kg. The Clinical reviewer and CDTL did not recommend approval of AcipHex® Sprinkle™ Delayed Release Capsules for the treatment of GERD in neonates less than 1 month or infants of 1 month to 11 months of age. These recommendations are consistent with similarly reported negative clinical trials of other PPIs in these age groups and presented earlier at the July 2010 GIDAC.

In addition, there is not an approved indication for the maintenance of healing of erosive esophagitis secondary to GERD in children 1-11 years of age. These issues are more fully discussed below.

The clinical trial design and development program for the 1-11 year old children recapitulated a classical approach using endoscopic grading using the Hetzel-Dent score and divided into two Part studies, one for healing and for "maintenance". In addition, there was report of histological healing after 12 and 36 weeks of treatment. The design was a dose ranging trial based on the acceptability of using extrapolation of efficacy in GERD management from adults, a concept acceptable to DGIEP. Data of interest include the apparent lack of dose response on efficacy as noted below in Dr. Troiani's summary reproduced below:

The primary endpoint for Parts 1 and 2 was endoscopic healing (HD=0) or histologic healing (HFRE=0) after 12 and 36 weeks of rabeprazole, respectively. There was no prespecified hypothesis testing. The 12-week (Part 1) healing rates were as follows:

- Low-weight cohort
  - Low-dose (5 mg): 82% (14/17)
  - High-dose (10mg): 94% (15/16)
- High-weight cohort
  - Low-dose (5 mg): 76% (29/38)
  - High-dose (10mg): 78% (29/37)

As noted below, the healing rates for endoscopic healing in Part 2 of the GERD study for an additional 24-week exposure period are not differentiated between the dose groups. The absence of a placebo comparator does not allow an interpretation of maintenance of healing of erosive esophagitis secondary to GERD. Despite the acceptable path of extrapolation of healing of EE in children from adult short-term trials, there is not acceptance of extrapolation for the indication of maintenance of healing. Boccia and colleagues, who question the role of PPI for maintenance of healing of EE in children, have recently reported their data on the maintenance treatment of erosive esophagitis, secondary to GERD in children using omeprazole[1]. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition/European Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN-ESPGHAN) guidance also questions the role of continued therapy with a PPI beyond an initial course of treatment except in certain age cohorts with particularly underlying conditions.

Furthermore, NASPGHAN states "trials of reduction of dose and withdrawal of PPI therapy should be performed after the patient has been asymptomatic for some time, that is, after 3 to 6 months on treatment. This approach will minimize the number of children that unnecessarily receive long-term treatment. PPIs should not be stopped abruptly, because rebound acid secretion may cause recurrence of symptoms."[2] In this development program, children after an initial

[1] Boccia et al. Maintenance therapy for erosive esophagitis in children after healing by omeprazole. Is it advisable? Am J Gastroenterol 2007;102:1291-1297.

[2] Pediatric GER Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 2009;49:498-547.

course of AcipHex® Sprinkle™ for healing of EE were not randomized to treatment or a placebo control. From the GIDAC held in November 2010, it has been accepted to extrapolate efficacy of GERD in children from adults but this does not apply to the maintenance indication. The trial design in the AcipHex® Sprinkle™ program does not satisfy the requirements for approval of a maintenance indication. Therefore, the sole indication for AcipHex® Sprinkle™ will be for the treatment of GERD in Children, Ages 1-11 years.

7. Safety

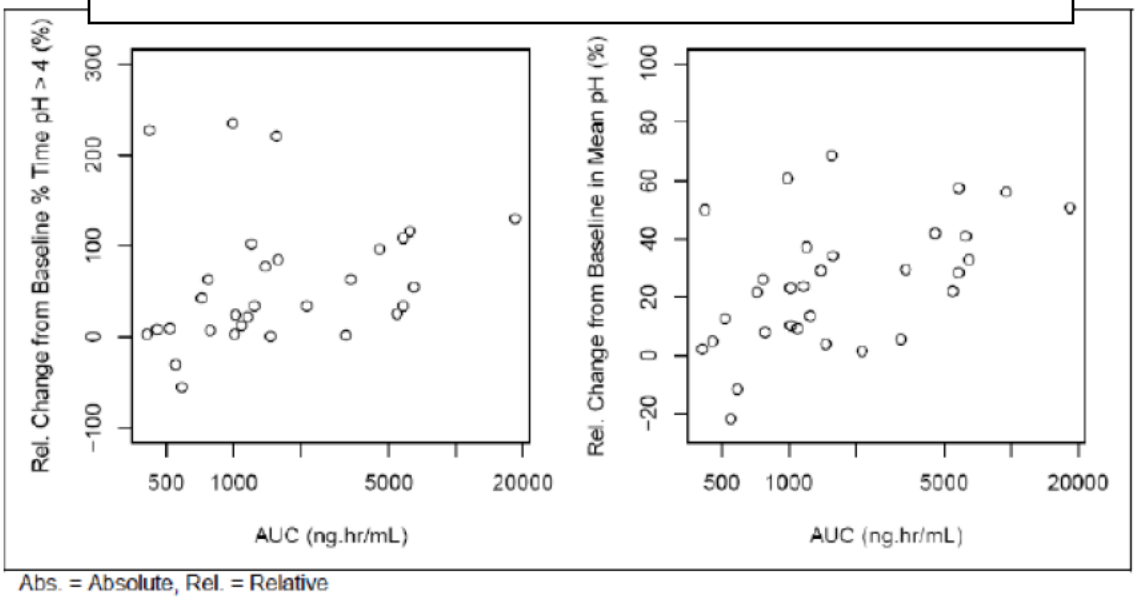
The reader is referred to reviews of Drs. Troiani and He for discussion of safety issues related to AcipHex® Sprinkle™ Delayed Release capsules. There are known serious adverse events related to the use of AcipHex® Sprinkle™ and one unique specific difference in pediatric safety than those reported in adults that deserves further discussion. The observation of neonatal achlorhydria as an adverse event is important to discuss. Dr Troiani specifically notes that neonates 0-<1 month of age in Study 1005 (PK/PD) after exposure to 1, 2 and 3 mg AcipHex® Sprinkle™ ™ developed profound acid suppression in a non dose-dependent manner. Specifically 1, 2 and 3 mg exposures were associated with 90%, 99%, and 81% with gastric pH>4. The specific data are reproduced below (Table 4 reproduced below, Dr. Insook Kim, review):

Table 4: Mean %Time intragastric pH>4 and intraesophageal pH<4

	Mean % time for intragastric pH > 4 (min, max)			Mean % time for intraesophageal pH < 4 (min, max)		
Dose	1 mg	2 mg	3 mg	1 mg	2 mg	3 mg
Day -1	67 (29, 98)	63 (33,98)	54 (28, 96)	4.2 (0, 17)	7.0 (0, 26)	18.2 (0, 62)
Day 1	88 (42, 100)	94 (80, 100)	78 (43, 99)	3.7 (0, 45)	1.0 (0, 2.7)	3.8 (0.01, 10)
Day 5	90 (45, 100)	99 (98, 100)	81 (30, 100)	2.5 (0, 17)	2.4 (0, 8.7)	2.1 (0.04, 20)

Pharmacometric reviewers also note below that there is high level of acid suppression with markedly delayed clearance in neonates. They note that the given the high variability of the

Figure 2: AUC versus %Time Intragastric pH>4 (Log Axis)



Abs. = Absolute, Rel. = Relative

Sources: Sponspor's Rabeprazole: A Population PK Model in Neonates, Infants and Adults, Page 92

pharmacodynamic effect, there appears that there is an increase in the relative change in time pH>4 with exposure to the drug in neonates but needs to be interpreted with caution--see Figure above. The evidence of high level of acid suppression, with markedly delayed clearance in neonates compared to infants and older children and values of acid suppression exceeding adult levels, suggests a more profound pharmacodynamic effect of AcipHex® Sprinkle™ in neonates-see Section, **Clinical Pharmacology.** The extent of profound acid suppression is in stark contrast to those data reported for another proton pump inhibitor, esomeprazole that reports less profound acid suppression in a similar age cohort[3]. Published reports have documented the potential relationship of acid reducing agents, which can cause prolonged acid suppression in neonates to the risk of development of necrotizing enterocolitis and infections, and studied specifically with the risk attribution to H_2 antagonist, ranitidine. Rantidine as all H_2 antagonists are recognized as less potent acid inhibitors than the members of the PPI class of drugs[4,5].

In terms of issues related to neonatal labeling specifically, the label requires further elaboration on the recommendation of not using AcipHex® Sprinkle™ in the neonate supported by safety concerns raised above. Importantly, the justification for this position is supported by Dr. Taylor of PMHS who notes that "when a pediatric indication is not supported by available data, the *Pediatric Use* subsection must contain a statement explaining that safety and effectiveness have not been established in the relevant pediatric population(s) (21 CFR 201.57(c)(9)(iv)(F). If a specific risk has been identified for pediatric patients, this risk information must be described in the *Pediatric Use* subsection and, if appropriate, placed in the CONTRAINDICATIONS section

[3] Omari T, Lundborg P, Sandstrom M et al. Pharmacodynamics and Systemic Exposure in preterm infants and term neonates with GERD. Journal of Pediatrics 2009;155:222-228.
[4] Terrin G, Passariello A, DeCurtis M et al. Ranitidine is Associated with Necrotizing Enterocolitis, Infections and Fatal Outcomes in Newborns. Pediatrics 2012;129:1-6.
[5] Ranitidine Label, drugs@fda.

or WARNINGS AND PRECAUTIONS section." Support for this comment is derived from the published Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling."[6] In addition, these issues are discussed below in **Section 11, Labeling.**

9. Advisory Committee Meeting

There was no Advisory Committee for this application. A previously conducted Gastrointestinal Drug Advisory Committee (GIDAC) on November 5, 2010 GIDAC addressing the issues of efficacy and safety of PPIs in the pediatric population concluded that the pathophysiology of symptomatic GERD in infants differs from adults. In contrast, EE is known to be acid-mediated, and therefore extrapolation from adult disease can be accepted and supported. In light of the ability to extrapolate efficacy in treatment of EE, the Committee supported reliance on pharmacokinetic/pharmacodynamic and safety studies in studies of PPIs for treatment of EE in infants. These recommendations did not apply to premature infants and neonates. Accordingly, in clinical practice, the use of PPI's in infants less than 1 year of age should be limited to management of acid related EE. In this application, only sGERD was studied and the label will not reflect doses recommended for the indication of GERD in infants 1-11 months.

10. Pediatrics

Since the original postmarketing requirements were mandated, in addition to the November 2010 GIDAC regarding pediatric GERD, significant other developments concerning the management of GERD in children have occurred. The role of PPIs for maintenance treatment of erosive esophagitis secondary to GERD in children has been recently studied by Boccia and colleagues, who question this role[7]. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition/European Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN-ESPGHAN) guidance also questions the role of continued therapy with a PPI beyond an initial course of treatment except in certain age cohorts with particular underlying conditions. Furthermore, NASPGHAN states "trials of reduction of dose and withdrawal of PPI therapy should be performed after the patient has been asymptomatic for some time, that is, after 3 to 6 months on treatment. This approach will minimize the number of children that unnecessarily receive long-term treatment. PPIs should not be stopped abruptly, because rebound acid secretion may cause recurrence of symptoms."[8] In this development program, the development program did not randomize children after initial course of AcipHex® Sprinkle™ for healing of EE and did not use a placebo control. From the GIDAC held in November 2010, it has been accepted to extrapolate efficacy of GERD in children from adults but this does not apply to the maintenance indication. The trial design in the AcipHex® Sprinkle™ program does not satisfy the requirements for approval of a maintenance indication.

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[6] Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, http://www fda.gov

[7] Boccia et al. Maintenance therapy for erosive esophagitis in children after healing by omeprazole. Is it advisable? Am J Gastroenterol 2007;102:1291-1297.

[8] Pediatric GER Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 2009;49:498-547.

11. Other Relevant Regulatory Issues

A. Financial Disclosures

All of the data from studies reviewed with this supplement were originally submitted for review with the original NDA. Therefore, there was new financial disclosure information submitted with this supplement. No clinical investigators involved in study T-EE05-135 had financial information to disclose.

B. DSI audits

According to Dr. Susan Leibenhaut from the Division of Good Clinical Practice Compliance, two clinical sites were inspected for this NDA and the final classification for both sites is NAI. The few issues raised during inspections are unlikely to have any effect on data integrity or efficacy outcome. The data generated by the sites appear acceptable in support of the indication targeted.

Two clinical sites were selected for inspection mainly due to high enrollment. All selected sites were inspected by the Division of Good Clinical Practice Compliance. Dr. Susan Leibenhaut from FDA DSI stated that the inspectional observations made at those clinical sites would not appear to have a substantive effect on safety and/or efficacy evaluations. The inspection of the sponsor indicated that its procedures for collecting, handling, and archiving the large amounts of data generated by these studies appear to be adequate. Other observations noted during the inspection of the sponsor would not appear to have a substantive effect on safety and/or efficacy evaluations.

Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the indication. See review by Dr. Susan Leibenhaut for detail.

The sponsor submitted financial certification and disclosures for Study 3003 and 3004. According to the sponsor, the clinical investigators who were filed to IND 33,985 and participated in support of this application, hold none of the disclosable financial arrangements with Johnson and Johnson Pharmaceutical Research & Development, L.L.C. as defined in 21CFR 54.2(a)(b)(c) and (f).

12. Labeling

This supplement included changes in labeling to the formulation for AcipHex® Sprinkle™, specifically noting that the proprietary name, 'AcipHex® Sprinkle™ and the dosage form 'Delayed-release capsules' is appropriate for this product. As Signatory, I concur.

The label has required further elaboration for not using AcipHex® Sprinkle™ in the neonate whose position is supported by concerns discussed above in **Section 8, Safety**. Briefly, the neonatal PK variability, difficulty in identifying dose response, trend of exposure response and concerns of safety were supportive reasons for labeling restriction in the neonate. The justification of a safety labeling for neonates is supported by Dr. Taylor of PMHS who notes that "when a pediatric indication is not supported by available data, the *Pediatric Use* subsection must contain a statement explaining that safety and effectiveness have not been established in the relevant pediatric population(s) (21 CFR 201.57(c)(9)(iv)(F). If a specific risk has been identified for pediatric patients, this risk information must be described in the *Pediatric Use* subsection and, if appropriate, placed in the CONTRAINDICATIONS section or WARNINGS

AND PRECAUTIONS section." Support for this comment is derived from the published Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling."[9]

Dr. He notes that the current proposed indication: "the healing and improvement of GERD symptoms and the maintenance of healing of GERD" is not appropriate. The indications of the healing and the maintenance of healing were granted in the past only to "erosive or ulcerative GERD". However, in the current NDA, study population included both non-erosive and erosive GERD. Therefore, Dr He recommends that the wording of indication change to "treatment of GERD in Pediatric Patients Aged 1 to 11 Years". I concur with this recommendation, but base this agreement on the historical precedent set in this Division. Moving forward, applications for pediatric GERD should be designed to address indications of sGERD and EE separately, rather than a generic indication for 'GERD' in the opinion of this Signatory.

There was significant and extensive discourse with the Sponsor regarding the maintenance treatment of GERD. This is the only Sponsor that has studied prolonged exposure to PPIs in children beyond short-term duration (i.e. 8 weeks). In deference to the requirement of reporting pediatric trials in Section 14 of the label, nominal information is cited. Safety data did not reveal any new safety concern with prolonged exposure and did not report any electrolyte disturbance or increased prevalence of bone fractures. However, the study did not implement a placebo control, and therefore was not powered for determination of efficacy. In addition, the issue of whether maintenance treatment is even required has been the subject of intense debate (see above). The indication of maintenance of GERD cannot be extrapolated further justifying the current exclusion of this indication for AcipHex® Sprinkle™.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action:
All of the review disciplines recommended the product for approval. This Signatory concurs with the approval recommendation.

13.2 Risk Benefit Assessment:
All of the review disciplines recommended the product for approval. This Signatory concurs with the approval recommendation. I concur with Drs. Troiani and He in their recommending approval of this supplement for AcipHex® Sprinkle™ Sprinkles for labeling for treatment of GERD in children 1-11 years of age. Dosing recommendations will be adapted to reflect the pharmacometric analyses performed by Clinical Pharmacology and summarized above. The product has a favorable risk/benefit profile and extends the indication to children 1- 11 years of age with GERD. Appropriate labeling of safety concerns in neonates and lack of efficacy in infants from 1-11 months of age will also be implemented.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:
There are no requirements for postmarketing evaluation.

[9] Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, http://www fda.gov

Recommendation for other Postmarketing Requirements and Commitments

The sponsor should assess the effect of alcohol on the drug release of AcipHex® Sprinkle™ Delayed Release Sprinkle Capsules. In the current NDA, the applicant did not evaluate the alcohol dose dumping potential of their proposed modified release dosage form. The timeline the sponsor submitted on February 15, 2013, states that the sponsor will conduct this study and submit the study results no later than August 8, 2013.

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

/s/

ANDREW E MULBERG
03/26/2013