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FROM: Hugo E. Gallo-Torres, M.D., Ph.D.
Medical Team Leader
Division of Gastrointestinal and Coagulation Drug Products

TO: Pediatric Advisory Subcommittee Members

SUBJECT: Briefing Document for June 11, 2002 Advisory Committee Meeting
on the Proton-Pump Inhibitor (PPI) Template. Justification for
Studies in Pediatric Patients

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I. BACKGROUND

Gastroesophageal reflux (GER) is a physiological event and occurs in almost all individuals to some degree. **Gastroesophageal reflux disease (GERD)** is characterized by an increased exposure of the esophageal mucosa to gastro-duodenal contents (usually **acidic**, but on occasions it could be alkaline or (even neutral). The esophageal body is a major component of the antireflux mechanism. Disruption of esophageal peristalsis affects both volume clearance and delivery of swallowed saliva to the distal esophageal body. But some patients with GERD, particularly those with severe esophagitis, exhibit impaired esophageal response to reflux¹.

“It is likely that this impairment prolongs acid clearance and may also influence the proximal extent of the refluxate within the esophageal body.” Gastric acid production constitutes a critical element in the pathogenesis of GERD, and **acid suppression** comprises the principal mechanism for therapy². However, the optimal timing and degree of acid suppression differ significantly in GERD patients. Indeed, the most commonly used approach employs the neutralization or suppression of intragastric acidity whereby, despite the continued reflux of gastric contents into the esophagus, the refluxate is rendered nonirritating to the esophageal mucosa. This widespread medical approach not only provides symptomatic relief, but also treats and prevents mucosal injury³.

For older pediatric patients, the presentation of GERD (and thereby its treatment) resembles GERD in adults. However, for younger pediatric patients (especially those under one year of age), the presentation of GERD appeared to be dissimilar to the condition in adults. Therefore, to obtain input on pediatric gastroesophageal reflux disease, FDA employees attended workshops, reviewed new literature publications, consulted intramural and extramural experts and received additional useful information. Based on this input, the Agency now requires **efficacy data** regarding proton-pump inhibitors (PPIs) in pediatric patients less than one year of age, including neonates and preterm infants. The reasons justifying the Agency’s request of efficacy studies in this and other groups of pediatric patients are the subject of the present document.

The appraisal starts with information on GERD pulmonary symptoms (Section II). Adult patients are addressed first. This is followed by considerations of GERD in infants, including neonates/prematures. The required studies in the formal Written Request (WR) of the PPI template are summarized in Section III. In Section IV, specific justification for requesting studies 1 and 2 in the PPI template is given. Included in this Section are considerations on proof of concept, usage, apnea as an endpoint of efficacy assessment, other possible etiological factors for GER, usefulness of esophageal pH monitoring in neonates/prematures, dosing requirements, formulations, and basic designs of studies

¹ R.H. Holloway et al. *Esophageal Body Motor Responses to Responses to Reflux Events: Secondary Peristalsis*. Amer. J. Med. 108 (4A): 20S-26 S (2000).

² This can be achieved with the administration of antacids, histamine H₂-receptor antagonists (cimetidine, ranitidine, famotidine or nizatidine) or proton pumps inhibitors (PPIs= omeprazole, lansoprazole, rabeprazole, pantoprazole or esomeprazole)

³ M.M. Wolfe and G. Sachs. *Acid Suppression: Optimizing Therapy for Gastrointestinal Healing, Gastroesophageal Reflux Disease, and Stress-Related erosive Syndrome*. Gastroenterology 118: 59-S31 (2000)

needed. The present document ends with a list of key literature publications on the subject matter. These are provided as part of the briefing package.

II. GERD and Pulmonary Systems

A. GERD in Adults

Reflux esophagitis (RE), a chemical irritation resulting from the repeated or prolonged exposure of the esophageal squamous epithelium to gastric acid contents or intraduodenal contents including biliary secretions, is indicative of incompetence of the lower esophageal sphincter (LES), often associated with a sliding hiatal hernia.

In adults, the symptoms and presentations of GERD are numerous and include more than just esophageal symptoms (heartburn, regurgitation, dysphagia and odynophagia). Many patients with GER complain of associated symptoms of bloating, early satiety, belching and nausea⁴. Some patients with GER complain of “water brash” (hypersalivation), or “globus” (feeling of a lump in the throat, a symptom that differs from dysphagia in that the latter is specific for periods of swallowing solids or liquids). Indeed, GERD has now been associated with the below listed pulmonary, otolaryngologic, as well as other extraesophageal signs and symptoms:

⁴ There is no evidence that the GER itself can cause these symptoms, but their presence in patients with GER is certainly common.

PULMONARY/EENT MANIFESTATIONS OF GERD^{a,b}

• <u>Pulmonary</u>	<u>EENT</u>
Aspiration	
Asthma	Dysphonia
Pulmonary Fibrosis	Cough
Pneumonia	Hoarseness
Chronic Bronchitis	Laryngitis
Sleep Apnea	Sinusitis
	Globus
	Cancer
	Subglottic Stenosis
	Pharyngitis

a) M.B. Fennerty. Extraesophageal GERD: Presentations and Approach to Treatment.

AGA Postgraduate Course, May 15-16 (1999).

b) The pathophysiology of extraesophageal GERD symptoms includes

- Gastropharyngeal reflux with or without microaspiration
- Stimulation of an esophagopulmonary reflex

In adults, pulmonary symptoms of GER include **aspiration** and **asthma**. Patients with severe GER are at increased risk of pulmonary aspiration of gastric contents. Such patients may present with various symptoms, including nighttime cough, recurrent pneumonia, or unexplained fever. Although these complications are likely to occur in patients with more typical and severe reflux symptoms, occasionally that is not the case.⁵

In some (**adult**) patients with GER, attention of the patient and the physician is first given to **asthma**. Typically, the patient has the same wheezing as do other patients with asthma, but several clinical features may suggest the possibility of GER being the cause of asthma. The patient whose symptoms are principally nocturnal should be suspected as having GER. Likewise, the patient whose asthma begins in middle age and whose history is negative for allergy may be considered a possible GER patient.⁶

⁵ A patient with unexplained chronic cough, chronic bronchitis, pulmonary fibrosis, or recurrent pneumonia should raise the suspicion of GER as a possible cause. This association of pulmonary symptoms and GER is probably more important in the patient with esophageal motor dysfunction. Thus, a patient with **systemic sclerosis** may have pulmonary disease to a large extent on the basis of severe esophageal dysfunction and superimposed gastroesophageal reflux with pulmonary aspiration.

⁶ Although some authors have suggested that the asthma is secondary to **reflex bronchial constriction** related to stimulation of vagal afferent fibers in the esophagus, it is possible that actual pulmonary

In adults, the response to anti-reflux therapy in this group of patients with extraesophageal symptoms also appears to be dissimilar to patients presenting with classical GERD. One approach to treatment consists of a) a twice daily PPI (OME 40 to 80 mg or lansoprazole 60 to 120 mg per day) for 3 months plus b) an H₂-receptor antagonist in the evening to prevent the **recently** demonstrated “**nocturnal acid breakthrough**”. It is worth noting however, that the therapeutic response is less, takes longer to obtain, and may be more difficult to maintain in this patient population.⁷

In patients with obstructive airway disease, GER is common. This may result from therapy for the chest condition or, indeed, from repeated coughing. But there are some adult patients, particularly those with nocturnal symptoms, in whom **GER is suspected as a trigger for asthma**. Prolonged pH monitoring may be helpful in deciding whether respiratory symptoms **provoke or are provoked by GER** but mere demonstration of abnormal reflux does not in itself indicate that GER is responsible for the respiratory illness. Careful correlation of the timing of reflux events with symptoms, recorded accurately using a diary or by means of an event marker or in a data log, must be carried out to conclude whether **GER is a cause or an effect**.⁸

As summarized below, many of the constraints encountered when attempting to associate GER with respiratory symptoms in adults, are also identified when considering GER in infants less than one year of age, including neonates and preterm infants.

B. GERD IN INFANTS, INCLUDING NEONATES AND PRETERM INFANTS

Many aspects of the apparent association between GERD and respiratory signs/symptoms, in the 0 to 1 month age group, remain to be clarified. During the last **20** years, many reports on GER in infants have been published. In its broadest application, the term is often extended to include the infant who “spits up” frequently after feedings.⁹ According to Sutphen,¹⁰

aspiration is responsible for some reflux-induced asthma. Under the clinical circumstances cited, **evaluations for reflux** should be undertaken. Those patients in whom an association can be shown may respond to antireflux measures, including fundoplication.

⁷ The optimal means of managing these patients is yet to be determined.

⁸ J.S. de Caestecker and R.C. Heading. Esophageal pH Monitoring. *Gastroenterology Clinics of North America*. 19:645-669 (1990).

⁹ This definition clearly includes a substantial number of normal infants who are a source of parental stress but do not necessarily deserve diagnostic studies or drug intervention. The “art” involved in caring for infants with GER lies in the appropriate exclusion of normal infants from therapy of diagnostic studies. The “spitty” infant with colic and stressed parents will almost certainly improve spontaneously. Committing such a child to diagnostic tests and therapy should be avoided when possible. Beyond the second year of life, new cases of GER are most often associated with chronic lung disease, chronic neurologic dysfunction, or underlying gastrointestinal disease. It is relatively uncommon to see an otherwise normal older child present with newly diagnosed primary GER.

¹⁰ J.L. Sutphen. Pediatric Gastroesophageal Reflux Disease. *Gastroenterology Clinics of North America*. 19:617-643 (1990)

“It is likely that our modern practices of infant feeding and care are to a great extent responsible for the development of infantile GER. Studies of breast-feeding practices of primitive tribes reveal that infants are fed approximately every 13 minutes. The average duration of the feed is 2 minutes. Between feedings the infant is often kept upright in a sling. In contrast, modern feeding practices are designed to increase the bolus size of the feeding so that adequate satiety can be produced to allow an average interfeeding interval of 4 hours. Moreover, the infant is often recumbent in a crib between feedings. An infant is unable to assume a sitting posture spontaneously until 7 to 8 months and sometimes as late as 11 months of age. In addition, solid foods are not offered until 6 months of age. The combination of large fluid boluses, recumbent posture, and inability to sit up when a reflux episode is initiated makes the infant a prime candidate for GER. Add to this a diaper change, generally performed after a meal, and involving elevation of the legs above the stomach, and it is a miracle that all infants do not have chronic GER.”

K. Geboes et al.¹¹ reported that there is a maturational effect of lower esophageal sphincter (LES) competence manifest by an increase in resting sphincter pressure during the first 6 months of life. Morphologically, there is a short intra-abdominal segment of the esophagus during infancy, which has led some investigators¹² to suspect relative incompetence. These considerations may be contributory; however, older, mentally retarded, but presumably physiologically mature children who are fed fluid diets and kept in a recumbent position develop GER **in spite of adequate sphincter function**. Therefore, feeding practices are probably the dominant factor in infantile GER. According to several authors, including S.R. Orenstein,¹³ pivotal physiologic changes occur between different pediatric age groups, such as the aforementioned maintenance of upright posture and independent ambulation after infancy, and full growth and maturation by (adolescence) adulthood. The most fundamental changes in GERD occur between infancy and childhood; the changes between childhood and adulthood are quantitative rather than qualitative. In other words, most of the above mentioned pulmonary/EENT manifestations of GERD in adults (**Section II. A.**) occur in neonates/infants. These are patients that cannot express what they are experiencing.

Aside from GERD in neonates/preterm infants the natural history of infantile GERD includes the following: a) it becomes symptomatic a month or so after birth, b) it peaks by 4-5 months of age, and c) it goes into remission by 12-24 months. This is in contrast to GERD in older children and adults, whose reflux disease, once present, waxes and wanes but does not resolve in at least half of individuals.¹⁴

¹¹ Virchow's Arch. A 401: 45 (1983)

¹² Such as Goldman and Antonioli, Human Pathol. 13: 423 (1982)

¹³ S.R. Orenstein. GERD in Children and Adolescents: Diagnosis and Management. AGA Postgraduate Course, May 15-16 (1999).

¹⁴ Whether infantile GERD predisposes to the complications of GERD in older children and adults is currently undocumented.

The symptomatic presentations include regurgitation (ejection of refluxate from the mouth), crying¹⁵ and irritability which may be the nonverbal infant's equivalent of the adult complaint of heartburn, upper respiratory symptoms¹⁶ (stridor, obstructive apnea) and lower respiratory symptoms¹⁷ (bronchospasm, pneumonia).

Another interesting consideration is that the contribution of **pepsin** has been relatively ignored. An experimental study suggested that hydrochloric acid without pepsin produces comparatively few changes, at least in the rabbit epithelium [J. Salo et al. *Dig. Dis. Sci.* 28:440-448 (1983)]. Much of the damaging effect of increased gastric acid exposure is probably due to the accompanying increased gastric peptic activity, which promotes cell shedding. **Pepsinogen** is secreted by newborns, but not by very premature infants.¹⁸

With the above succinct background in mind, an important turning point which significantly influenced the types of studies that should be required of sponsors of PPIs for proper use of these drugs in neonates/prematures infants, was the December 6-8, 2000 Pediatric Symposium (Washington, D.C.), organized by Drs. Carlo DiLorenzo and Harland Winter [Treatment of Gastroesophageal Reflux Disease. "*Children are Different*". Current Knowledge and Future Research].¹⁹ The following is quoted from page 1 of the transcript on the Section: "**What Are the Right Research Question to Ask?**"

JEFFREY BLUMER: "Listening to all this, I'm struck by the fact that we're talking on so many different planes. I was struck by Harland Winter's question about what is

¹⁵ W. Treem, et al. *Gastroesophageal reflux in the older child: Presentation, response to treatment and long-term follow-up.* *Clin. Pediatr.* 30: 435-440 (1991)

Distinguishing crying due to esophagitis from crying due to "colic" is particularly challenging, because the pathophysiology of the latter is completely unknown, and there is no gold standard for its diagnosis. Psychosociologic interactions between the child and stressed parents may lead to vicious cycles of increased crying, and may further confuse the issue. There may be clues in the relationship of crying to meals and to regurgitation, but these aspects have not been completely clarified. A positive diagnostic evaluation for esophagitis may suggest the diagnosis of GERD, and a response of the crying to therapy for GERD may be similarly helpful.

¹⁶ The infant's proximal airway is relatively small, soft, and hampered by immature reflexes, all of which make upper airway obstruction a more frequent sequel of GERD in infants than in adults. A fairly common diagnostic dilemma in infants is the single cyanotic episode witnessed only by anxious parents and resolving spontaneously or with minimal intervention. **Half of all apneic episodes thoroughly evaluated in a huge series from Belgium were determined to be due to GERD.** The reflux-mediated apnea is usually obstructive (respiratory efforts continue during laryngeal closure), postprandial, and occurs while the infant is supine or seated. Whether these episodes mandate diagnostic evaluation or aggressive antireflux therapy or both is difficult to answer.

¹⁷ These are somewhat more prominent during expiration than inspiration, are less commonly a result of reflux in infants than in older children and adults. This age-relationship is attributable to changes in the relative cross-sectional areas of the upper and lower airways, in the relative stiffness of the structures, and in the increasing predominance of reflex bronchospasm over reflex laryngospasm.

¹⁸ B. Weisselberg et al. *Basal and meal-stimulated pepsinogen secretion in preterm infants: a longitudinal study.* *J. Pediatr. Gastroenterol. Nutr.* 15:58-62 (1992)

¹⁹ This course was sponsored by the Children's Digestive Health and Nutrition Foundation in cooperation with the North American Society for Pediatric Gastroenterology and Nutrition.

going to incentivize industry to do these studies, and I'm sitting here surrounded by industry representatives. The PPRU network has been inundated with study proposals, some of which we couldn't do, some of which we succeeded in accomplishing, some of which are ongoing. I'm struck by the contrast between Laura James' presentation and what we heard this morning, which is a very different approach to questions about drugs. I'm afraid that we pharmacologists are really not asking the same questions as the gastroenterologists. We aren't."

"Then I'm struck by Dr. Gallo-Torres' question, which he keeps coming back to **what are we treating?** And if we look at the acid-suppression data in neonates that Dr. James presented, I get back to Dr. Gallo-Torres' question, what are we treating here?"

"And finally, what we do with the pharmacokinetic studies? I can tell you, based on the pharmacokinetic data, exactly what dose to give a child of any size and age to suppress their acid production. Now can I tell you that's going to control their reflux? No. And we need to somehow work this out...."

III. FDA's formal WR (PPI Template):

Required Studies

The template for Written Requests for proton-pump inhibitors used in the treatment of GERD covers the pediatric age range from birth through 16 years of age. As summarized below, the types of studies that are requested differ for each of four age groups encompassed by the Written Request. In the material that follows, only the inclusion criteria and the main aspects of the design are given, as applied to each Pediatric age group. This is followed by a comment on the specified study. Other sections of the WR, including Objectives and rationale, Study Evaluations and Endpoints, Other Clinical Outcomes and Endpoints, Drug Information, Statistical Information Needed, Labeling That May Result from the studies, Format of Report to be Submitted, Timeframe for Submitting Reports of the Studies, and Response to Written Requests, can be found in the sample of a *Written request for Proton-Pump Inhibitors Used to Treat Gastroesophageal Reflux Disease (GERD)*. (Found elsewhere in this package).

INDICATION TO BE STUDIED: Treatment of gastroesophageal reflux disease (GERD)

A. STUDIES REQUESTED IN NEONATES AND PRETERM INFANTS

The Written Request asks for two types of studies in the neonate and preterm infant with a corrected age of less than 44 weeks age group: a) a pharmacokinetic, pharmacodynamic, and safety study (Study 1), and b) an efficacy and safety study (see Study 2). In pediatric patients adult efficacy data can not be extrapolated to this age

group. Therefore, in addition to pharmacokinetic, pharmacodynamic, and safety information, the Written Request asks for an efficacy study of a randomized withdrawal design. A randomized withdrawal design can minimize prolonged exposure to placebo in situations where it is felt that inclusion of a placebo arm is undesirable or unfeasible. In addition, the Written Request has provisions for prompt discontinuation from randomized study therapy when discontinuation is felt to be clinically appropriate (see Study 2 for details).

Study 1: Pharmacokinetic (Pk), Pharmacodynamic (Pd), and Safety Study in Neonates and in Preterm Infants With a Corrected Age Less Than 44 Weeks

Inclusion criteria: To be included in this study, infants will (a) be monitored patients admitted to a newborn intensive care unit (NICU) or special care nursery, (b) have evidence of obstructive apnea by pneumographic monitoring, (c) be considered candidates for acid suppressive therapy to treat a presumptive diagnosis of GERD, (d) either be term or post-term infants within the neonatal period, or be preterm infants with a corrected age of less than 44 weeks, and (e) have a body weight of at least 800 grams. Patients of both sexes will be enrolled in the study.

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of [INSERT DRUG NAME]. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 24 patients (i.e., at least 12 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated-dose PK, PD, and safety study of [INSERT DRUG NAME]. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal proportions. At least 12 patients per treatment group will complete this part of the study if a standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed in at least six of these (or other) patients who require tube placement or pH monitoring for clinical management not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

Study 2: Efficacy and Safety Study in Neonates and in Preterm Infants With a Corrected Age of Less Than 44 Weeks

Inclusion criteria: To be included in this study, patients must meet the same inclusion criteria specified above for Study 1.

Design: This will be a multicenter, treatment-withdrawal study of the efficacy and safety of [*INSERT DRUG NAME*] in which treatment withdrawal is randomized, double-blind, and placebo-controlled. The dosage(s) of [*INSERT DRUG NAME*] used in this study will be selected as dosages likely to be therapeutically effective and safe based on data obtained from Study 1 and as suggested by the results of other studies (e.g., literature studies of pediatric patients). Patients will be stratified by whether or not they are receiving methylxanthine (e.g., theophylline, caffeine) for treatment of central apnea and by corrected age. Protocol design will also consider whether or not patients receive concomitant prokinetic agents (e.g., metoclopramide, erythromycin). The number of patients per treatment group required to complete the study is described in the Statistical Information section. Independent data review committees (e.g., for safety, efficacy, or both) may be established to review accumulating data to detect early evidence of great benefit or harm of treatment.

Run-in phase: All patients will receive [*INSERT DRUG NAME*] in this phase. Treatment in this phase will be of sufficient duration to ensure that gastric acid suppression by [*INSERT DRUG NAME*] is at steady state. An open-label design is acceptable. The reasons for any patient discontinuations during this part of the study (e.g., lack of therapeutic response, adverse event) will be captured in detail.

Withdrawal phase: At the conclusion of the run-in phase, patients will be randomly assigned (in approximately equal proportions) in a double-blind fashion to continue receiving their current dosage of [*INSERT DRUG NAME*] or to receive matching placebo. Following randomization, patients will be monitored closely to allow for prompt discontinuation from randomized study treatment if clinically appropriate. The protocol will define discontinuation criteria for patients who have adverse events or fail therapy during the withdrawal phase. Patients who are removed from randomized study treatment will be given appropriate alternative medical therapies.

Therapy for central apnea will be tracked. Individuals such as caregivers, who will be making observational assessments of apnea or bradycardia, will be trained appropriately in apnea/bradycardia monitoring procedures. Additionally, cardiorespiratory monitors used to assess apnea and bradycardia will be capable of recording and storing each patient's data for the duration of the study.

B. STUDIES REQUESTED IN PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE

The Written Request asks for two types of studies in pediatric patients 1 to 11 months of age, inclusive a) a pharmacokinetic, pharmacodynamic, and safety study (**Study 3**), and b) an efficacy and safety study (**Study 4**). In this age group, the course of pathological GERD is sufficiently similar to the course of GERD in adults to permit extrapolation of adult efficacy data to this pediatric age group. For example, manifestations of GERD in this age group often involve the respiratory tract or are supraesophageal, whereas in adults patients manifestations of GERD typically involve the gastrointestinal tract. In addition, the effects of the proton pump inhibitor, both beneficial and adverse, may also differ in patients in this age group and in adults.

Therefore, in addition to pharmacokinetic, pharmacodynamic, and safety data, the Written Request asks for an efficacy study of a randomized withdrawal design. A randomized withdrawal design can minimize prolonged exposure to placebo in situations, where is felt that such an approach (use of placebo) is undesirable or unfeasible. In addition, the Written Request has provisions for prompt discontinuation from randomized study therapy when discontinuation is felt to be clinically appropriate.

Study 3: Pharmacokinetic, Pharmacodynamic and Safety Study in Pediatric Patients 1 to 11 Months of Age

Inclusion criteria: To be included in this study, infants will (a) be hospitalized patients considered to be candidates for acid suppressive therapy because of a presumptive diagnosis of GERD, and (b) either be a term or post-term infant beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected age of at least 44 weeks but less than 12 months. Patients of both sexes will be enrolled in the study.

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of *[INSERT DRUG NAME]*. Adequate justification for dose selection will be provided. Patients will be allocated to treatment groups in approximately equal proportions. At least 20 patients (i.e., at least 10 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated dose PK, PD, and safety study of *[INSERT DRUG NAME]* in pediatric patients. The study will be designed to characterize the change in gastric and/or esophageal pH after repeated doses of *[INSERT DRUG NAME]*. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal proportions. At least 12 patients per treatment group will complete pharmacokinetic

assessments if a standard PK approach is used. Alternatively, a population PK approach may be used. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed in at least six of these (or other) patients who require tube placement or pH monitoring for clinical management not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

Study 4: Efficacy and Safety Study in Pediatric Patients 1 To 11 Months of Age

Inclusion criteria: To be included in this study, infants will (a) be patients with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD, and (b) either be a term or post-term infant beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected age of at least 44 weeks but less than 12 months. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

The method by which the clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD is made will be recorded and summarized for each patient. These summaries will include the clinical history and results of laboratory tests used to establish the diagnosis (e.g., pH probe, gastroesophageal endoscopy, radionuclide milk study). Results from such laboratory tests will be provided regardless of whether they supported the final clinical diagnosis or not.

Design: This will be a multicenter, treatment-withdrawal study of the efficacy and safety of [*INSERT DRUG NAME*] in which treatment withdrawal is randomized, double-blind, and placebo controlled. The dosage(s) of [*INSERT DRUG NAME*] used in this study will be selected as dosages likely to be therapeutically effective and safe based on data obtained from Study 3, and as suggested by the results of other studies (e.g., literature studies of pediatric patients). The number of patients per treatment group required to complete the study is described in the Statistical Information section. Independent data review committees (e.g., for safety, efficacy, or both) may be established to review accumulating data to detect early evidence of great benefit or harm of treatment.

Run-in phase: All patients will receive [*INSERT DRUG NAME*] in this phase. Treatment in this phase will be of sufficient duration to ensure that gastric acid suppression by [*INSERT DRUG NAME*] is at steady state. An open-label design is acceptable. The reasons for any patient discontinuations during this part of the study (e.g., lack of therapeutic response, adverse event) will be captured in detail.

Withdrawal phase: At the conclusion of the run-in phase, patients will be randomly assigned (in approximately equal proportions) in a double-blind fashion to continue receiving their current dosage of [*INSERT DRUG NAME*] or to receive matching placebo. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example,

telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes.

Following randomization, patients will be followed closely to allow for prompt discontinuation from randomized study treatment if clinically appropriate. The protocol will define discontinuation criteria for patients who have adverse events or fail therapy during the withdrawal phase. Patients who are removed from randomized study treatment will be given appropriate alternative medical therapies.

C. STUDY REQUESTED IN PEDIATRIC PATIENTS 1 TO 11 YEARS OF AGE

The Written Request asks for a pharmacokinetic, exposure/response, and safety study in Pediatric patients 1 to 11 years of age, inclusive (Study 5). As in pediatric patients 12 to 16 years of age (see below), approval for pediatric use in this age group can be based on adequate and well-controlled studies in adults, with additional information supporting pediatric use. In this age group, however, the additional information supporting pediatric use includes not only pharmacokinetic and safety information, but also an exposure/response study. The exposure/response study is intended to provide some information on the effects of different doses of the proton pump inhibitor on clinical outcomes.

Study 5: Pharmacokinetic, Exposure/Response, and Safety Study in Pediatric Patients 1 to 11 Years of Age

Inclusion criteria: To be included in this study, patients will (a) be 1 to 11 years of age inclusive, (b) have endoscopically proven GERD, and (c) have had endoscopic examination as part of their diagnostic evaluation. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

Pharmacokinetic Component:

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of [INSERT DRUG NAME]. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated-dose pharmacokinetic and safety study of at least two dose-levels of [INSERT DRUG NAME]. Patients will be randomly allocated to treatment groups in approximately equal proportions. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of

the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Exposure/Response Component:

This will be a randomized, double blind, dose-ranging study of *[INSERT DRUG NAME]*. The dosages *[INSERT DRUG NAME]* of used in this study will be selected as dosages likely to be therapeutically effective and safe, based on data from the pharmacokinetic component of this study as well as from other studies in pediatric patients and adults. Eligible patients will be randomized in approximately equal proportions to one of at least three dose levels of *[INSERT DRUG NAME]*. After randomization, the overall duration of the trial will be at least eight weeks. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes. At least 40 patients 1 to 5 years of age and 40 patients 6 to 11 years of age will complete at least 8 weeks treatment.

D. STUDY REQUESTED IN PEDIATRIC PATIENTS 12 TO 16 YEARS OF AGE

The Written Request asks for a pharmacokinetic and safety study in Pediatric patients 12 to 16y of age, inclusive (Study 6). The course of GERD in this age group is similar to the course of GERD in adults. Moreover, the effects of the proton pump inhibitor, both beneficial and adverse, are expected to be similar in this pediatric age group and adults. Therefore, approval for pediatric use in this age group can be based on adequate and well-controlled studies in adults, with additional information supporting pediatric use (i.e., the pharmacokinetic and safety information requested in Study 6).

Study 6: Pharmacokinetic and Safety Study in Pediatric Patients 12 to 16 Years of Age

Inclusion criteria: To be included in this study, patients will (a) be 12 to 16 years of age inclusive, and (b) have a clinical diagnosis of suspected GERD, symptomatic GERD or endoscopically proven GERD. Endoscopy is not required for study entry or participation. Patients of both sexes will be enrolled in the single- and repeated-dose components of the study as well as in the eight-week safety component.

Pharmacokinetic Component:

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of *[INSERT DRUG NAME]*. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated-dose pharmacokinetic and safety study of at least two dose-levels of *[INSERT DRUG NAME]*. Patients will be randomly allocated to treatment groups in approximately equal proportions. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Eight-week Safety Component:

This will be a multicenter safety study of *[INSERT DRUG NAME]*. An open-label, non-randomized design is acceptable. Dosages of *[INSERT DRUG NAME]* used in this study will be selected as dosages likely to be therapeutically effective and safe based on data from the pharmacokinetic component of this study as well as from other studies in pediatric patients and adults. Patients will be treated for at least eight weeks. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes. At least 100 patients will complete at least eight weeks of treatment.

IV. Further Considerations on Studies 1 and 2 in the WR (PPI Template)

After the above-mentioned December 2000 Pediatric Symposium, representatives from FDA's Division of Gastrointestinal and Coagulation Drug Products met with representatives from the Division of Pulmonary Drug Products²⁰ to discuss design issues surrounding the use of PPIs in pediatric subjects. In short, it was strongly felt by the participants that, based on **widespread off-label usage** for reflux-related symptoms, there is a solid basis to request studies in neonates/premature infants [as well as infants/children below age 12 and adolescent ages 12 to 17].

With regard to the specific 0 to 1 month of age population, the clinical points made fell under the categories briefly summarized below.

Proof of concept

At some point during the development of the present Written Request (PPI template) a pilot study before embarking on an efficacy trial was considered. This Medical Team Leader (MTL) carefully considered this possibility and believes that the proof of concept has been done a) by the discussions and conclusions at the December 2000 Pediatric Symposium; b) the Agency's Pediatric Exclusivity Implementation Team agreeing that these studies should be requested; and c) by label the H₂-receptor antagonists for that age range: acid suppression down to pediatric patients 0 to 1 months of age.

²⁰ Present at this meeting, held on February 2001, were Drs. D. Birenbaum, E.P. Stark, C. Lee, M. Avigan, K. Robie-Suh, L. Talarico and Hugo E. Gallo-Torres.

Usages

- There is unquestionably, widespread usage of omeprazole and other PPIs to suppress gastric acid secretion in the treatment of episodes of apnea detected in neonatal nurseries.

Apnea as an endpoint of efficacy assessment

It is worth mentioning that often the apneic episodes are **multifactorial** in etiology.

- Apnea can be a) central; b) mixed; or c) obstructive. Apnea can manifest different grades of severity:
 - apnea alone (without other manifestations), present for short periods
 - apnea associated with cyanosis, a drop in O₂ saturation and/or bradycardia.
- A central apnea component is often related to gestational prematurity and is often treated with either **caffeine or theophylline**, drugs which may interfere with the metabolism of some PPIs, such as omeprazole.
- Although episodes of obstructive apnea may be a manifestation of GER, they may also be related to head/torso positioning.
- Obstructive apnea can be distinguished by a "**pneumogram**" that detects chest muscle contraction in conjunction with mouth/nasal airflow.

Other possible etiological factors for GERD

The pathophysiological mechanism of GER in neonates/prematures may be related to **reduced populsive gastric motility**. This, together with an exaggerated loss of gastroesophageal sphincter tone, may facilitate reflux of gastric contents with the esophagus first and the upper respiratory tract next. If this mechanism predominates, the most effective treatment may be a combination of a PPI with a prokinetic agent.²¹ This empirical approach is sometimes tried, at some institutions.

²¹ Indeed, the effects of a motility agent may be as or even more relevant than a PPI. Drug class linked comparative therapeutic effects need to be studied (single and combination agents vs placebo).

Usefulness of esophageal pH monitoring in neonates/prematures

A number of suggested indications for pH monitoring in infants and young children have emerged. These include recurrent respiratory infection, apnea, "near miss" **sudden infant death**, and failure to thrive, associated with recurrent vomiting or regurgitation.²² There are however, a number of problems associated with the recognition of abnormal GER in infants, including a rapidly changing normal pattern of reflux in the first 16 months of life.²³ Therefore, esophageal pH monitoring in neonates may have limited utility in the detection of pathological reflux since there is a background of reflux which is normal in this age group. On the other hand, this medical team leader believes that establishing the presence of reflux may be useful in classifying patients (any age) into the following 4 categories with regards to the **respiratory symptom(s)**:

- symptoms with reflux
- reflux with no symptoms
- symptoms with no reflux
- no reflux and no symptoms

This information may be useful because depending upon the group categorization, different therapeutic modalities, including use/not use of a PPI either (alone) or in combination with a prokinetic, may be considered.

Dosing Requirements

The PPI template requests the testing of at least two dose levels of the drug under consideration. The reason behind this request is that dosing requirements in neonates/prematures are not fully known. The required doses are most likely impacted by Cytochrome P₄₅₀ enzyme developmental immaturity. But **route of administration** (there is now an intravenous form of a PPI, pantoprazole, available for those patients unable to continue taking the oral formulation), and **concomitantly administered medications** may also play a significant role in determining the required dose.

²² [Editorial. *Gastro-esophageal reflux and apparent life threatening events in infancy*. Lancet 2:261 (1988)]

²³ A.R. Euler and W.J. Byrne. *Twenty-four hour esophageal pH probe testing. A comparative analysis*. Gastroenterology 80:957 (1981)]

Formulations

For obvious reasons, homogenous liquid formulations or those for parenteral (i.e. intravenous) use are preferred for neonates/prematures.

Basic Study Design

As mentioned above, in conjunction with the mentioned consultants who are specialists in broncopulmonary diseases, the Division concluded that both efficacy (studies appropriately powered) and safety data in infants less than one year of age, including neonates or preterm infants, must be required in the WRs for PPIs.

V. Selected Literature Publications

Selected references are provided at the end of this briefing package.

Hugo E. Gallo-Torres, M.D., Ph.D.
Medical Team Leader
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