Clinical Pharmacology Study Protocol

Drug Substance	Esomeprazole magnesium
Study Code	D9614C00007
Date	[redacted]

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	**Date of Amendment**

Administrative Change No.	**Date of Administrative Change**

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ASTRAZENECA PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

In the case of a medical emergency you may contact the Study Delivery Operations Specialist. If the Study Delivery Operations Specialist is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Role in the study	Name	Address and Telephone number
Study Delivery Operations Specialist	[redacted]	[redacted]
Study Delivery Leader	[redacted]	[redacted]
Study Team Physician	[redacted]	[redacted]
Covance Central Laboratories Project Manager	[redacted]	[redacted]

- For further clarifications regarding:
- Procedures in case of medical emergency see Section 8.2
- Procedures in case of overdose see Section 8.3.
- Procedures in case of pregnancy see Section 8.4

PROTOCOL SYNOPSIS

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

Investigators

Up to 5 research centers in the United States will be selected to perform this study.

Study center(s), type and number of subjects planned

Approximately 40 male and female patients from 1 to 11 years age inclusive with endoscopically-proven GERD will be enrolled in order to obtain at least 24 evaluable patients.

Study period		Phase of development
Estimated date of first subject enrolled	[redacted]	Phase I
Estimated date of last subject completed	[redacted]	

Objectives

Primary Objective:

To determine the area under the plasma concentration-time curve (AUC) of esomeprazole after single oral doses of 5 mg, 10 mg or 20 mg esomeprazole in pediatric patients 1 to 11 years-old inclusive with endoscopically-proven GERD.

The Secondary Objectives of the study are:

1. To determine the $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2\lambda z}$, apparent oral clearance (CL/F) and apparent volume of distribution during terminal phase ($V_{\lambda z}/F$) of esomeprazole after single oral doses of 5 mg, 10 mg and 20 mg esomeprazole in pediatric patients 1 to 11 years-old inclusive with endoscopically-proven GERD.

2. To determine AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2\lambda z}$ of the 5-hydroxy and sulphone metabolites of esomeprazole after a single oral dose of 5 mg, 10 mg, and 20 mg esomeprazole in pediatric patients 1 to 11 years-old inclusive with endoscopically-proven GERD.

3. To assess the safety and tolerability of esomeprazole in pediatric patients 1 to 11 years-old inclusive with endoscopically-proven GERD.

Study design

This is a randomized, open-label study to be conducted at approximately 5 research centers to evaluate the pharmacokinetics, safety and tolerability of esomeprazole 5 mg, 10 mg and 20 mg when given as a single oral dose to pediatric patients, 1 to 11 years-old inclusive with endoscopically-proven GERD.

Approximately 40 male and female patients from 1 to 11 years of age inclusive with endoscopically-proven GERD will be enrolled in order to obtain at least 24 evaluable patients. Patients will be randomized into the study based on weight.

Investigational product, dosage and mode of administration

Esomeprazole magnesium blue clinical image capsules formulated as 5 mg, 10 mg and 20 mg will be used for oral administration as either an intact capsule with water or as an opened capsule mixed with a small amount of applesauce followed by water.

The study drug will be administered orally as an intact capsule with a minimum of 30 mL of water to a maximum of 180 mL of water or as an opened capsule mixed with a small amount of applesauce (up to 1 tablespoon) followed by a minimum of 30 mL of water to a maximum of 180 mL of water. AstraZeneca will supply the applesauce.

Duration of treatment

Each patient will receive a single oral dose of esomeprazole (5 mg, 10 mg or 20 mg) based on the randomization schedule.

Variables

- Pharmacokinetic

Blood samples will be analyzed to determine the pharmacokinetics of esomeprazole (AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2\lambda z}$, CL/F,$V_{\lambda z}/F$ and the pharmcokinetics of its 5-hydroxy and sulphone metabolites (AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2\lambda z}$) in the specified population.

- **Safety**

Safety and tolerability will be assessed by means of incidence and severity of all adverse events, laboratory parameters, vital signs and physical examination.

- **Statistical methods**

The aim of this study is to determine the area under the plasma concentration–time curve (AUC) of esomeprazole after a single oral dose of 5 mg, 10 mg or 20 mg esomeprazole. Plasma concentration data, pharmacokinetic data, safety information obtained from laboratory assessments, and adverse events will be summarized using descriptive statistics by weight group and dose.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Asparatate aminotransferase
AUC	Area under plasma concentration-time curve from zero to infinity [amount x time/volume]
$AUC_{(0-t)}$	Area under plasma concentration-time curve from zero to time t [amount x time/volume]
AZDD	AstraZeneca Drug Dictionary
BMI	Body mass index
BUN	Blood urea nitrogen
ºC	Degrees Celsius
CL	Total body clearance of drug from plasma [volume/time] or [volume/time/body surface area] or [volume/time/body surface area/1.73] or volume/time/body weight]
CL/F	Apparent oral clearance
cm	Centimeter
C_{max}	Maximum plasma (peak) drug concentration
C_{last}	Last quantifiable plasma concentration after a single dose or last administration
CRC	Clinical Research Center
CRF	Case report form
DQF	Data query form
GCP	Good Clinical Practice
GER	Gastroesophageal Reflux
GERD	Gastroesophageal Reflux Disease
HDPE	High-Density Polyethylene
ICH	International Conference on Harmonization
IRB	Institutional Review Board
kg	Kilogram

Abbreviation or special term	Explanation
λ_z	The slope of the terminal phase of the log-linear concentration-time curve
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 4.7.1.1)
OTC	Over the counter
PI	Principal Investigator is a person responsible for the conduct of a clinical study at a study site. Every study center has a Principal Investigator.
PK	Pharmacokinetics
PPI	Proton Pump Inhibitor
RBC	Red blood cells
RFC	Relative Centrifugal Force
SAE	Serious adverse event
SSRI	Selective Serotonin Re-Uptake Inhibitor
t_{max}	Time to reach peak or maximum concentration following drug administration [time]
$t_{1/2\lambda z}$	The terminal half-life, calculated by ln2/λz
Variable	A characteristic or property of a subject that may vary eg, from time to time or between patients.
$V_{\lambda z}/F$	Apparent volume of distribution during terminal phase
WHO	World Health Organization

1. INTRODUCTION

1.1 Background

Gastroesophageal reflux (GER) is defined as the retrograde passage of gastric contents into the esophagus or supraesophageal regions. It is presumed to be caused by a transient relaxation of the lower esophageal sphincter and is commonly reported in healthy infants and children as a physiologic event (Vandenplas and Sacre-Smits 1987, Vandenplas et al 1991, Gustafsson and Ribbling 1988, Nelson et al 2000). Simple physiologic reflux evolves into pathologic GER or gastroesophageal reflux disease (GERD) when the reflux produces an adverse symptomatology in patients. The acidic nature of the refluxate, and more importantly the presence of activated pepsin, is considered to be the principal irritant causing mucosal inflammation, resulting symptomatology, and other potential long-term outcomes associated with GERD. The transition from physiologic GER to pathological GER or GERD involves a combination of events that include recurrent transient lower esophageal sphincter relaxation (tLSER) and mucosal inflammation with eventual ineffective esophageal body peristalsis. GERD may also be complicated by delayed gastric emptying and gastric distension (Orenstein 1991, Werlin 1980).

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have published guidelines (Rudolph et al 2001, Vandeplas et al 1993) for the diagnosis and treatment of GERD in children and adolescents. Common clinical manifestations of GERD in children include vomiting, poor weight gain, dysphagia, abdominal or substernal pain, esophagitis and respiratory disorders. Studies on the prevalence of GERD in the pediatric population are limited. A practice based study on the frequency of symptoms associated with GERD (heartburn, epigastric pain and regurgitation) showed that parents of 3 to 17 year old children reported that their children experienced the symptoms 1.8% to 8.2% of the time. Furthermore, the occurrence of abdominal pain was reported by 23.9% and 14.7% of the parents of 3 to 9 year old children and 10 to 17 year old children, respectively, and by 27.9% of the 10 to 17 year old children themselves (Nelson et al 2000). In this study, the prevalence of at least weekly heartburn was lower in children compared to adults[(17.8%) Locke et al 1997], while acid regurgitation was comparable at 6% (Nelson et al 2000, Locke et al 1997). When looking at abdominal pain in general, the frequency ranged from 14.7% to 27.9% of the time (Nelson et al 2000). Chronic GERD results in both esophageal and extraesophageal symptom complexes that tend to be more unique for children under the age of 1 year. For the age group we are addressing in this protocol, the clinical presentation (signs and symptoms) progressively simulates that of adults as described in the literature (Richter 1997, DeMeester et all 1999, Euler and Ament 1977, Herbst et al 1978, Rudolph et al 2001 and Youseff, N and Orenstein 2001).

Pharmacologic treatment for GERD is aimed at reducing the amount of gastric acid exposure to the esophageal and supraesophageal mucosa. Successful treatment leads to symptom relief and helps to prevent complications of chronic reflux. Gastric acid secretion is controlled by negative feedback mechanism under normal physiologic conditions. The proton-transporting

enzymes involved in the production of hydrochloric acid in the stomach are known as gastric parietal cell H^+/K^+-ATPase, or "proton pump". Compounds that inhibit these enzymes are known as Proton Pump Inhibitors, or PPIs. PPIs bind covalently to the proton pump on the apical surface of the gastric parietal cells, irreversibly inhibiting the inward transport of H^+ ions by gastric parietal cell H^+/K^+-ATPase. Esomeprazole, the S-isomer of omeprazole, has the capacity to selectively inhibit this enzyme thereby inhibiting gastric acid production.

1.2 Rationale

From literature reviews, standard of medical practice, and information gathered from AstraZeneca's safety and efficacy databases, the consensus is that for patients older than 1 year of age, GERD's clinical presentation and course is similar to that of the adult population. Therefore efficacy of esomeprazole in this population can be extrapolated from adult data. However, additional studies are required in the area of pharmacokinetics and safety in order to provide adequate dosing guidelines and to further ensure the safety of esomeprazole in this pediatric population.

Clinical studies have demonstrated PPIs to be the most effective pharmacologic agents available for the treatment of GERD in adults. A meta-analysis by Chiba and colleagues showed PPIs were significantly more effective than Histamine Receptor Anatagonists (H_2RAs)for complete symptom relief (77.4% vs. 47.6%) (Chiba et al 1997). Drug utilization data suggest that PPI use in children will continue to dramatically increase as physicians gain increased confidence in the efficacy, safety and convenience of these agents. However, there remains limited clinical efficacy and safety data for PPI use in children. (Gunasekaran et al 2002, Gremese et al 2002, Tolia et al 2002). Studies on omeprazole have shown it to be effective in treating GERD-related esophagitis in infants and children (Hassall et al 2000). Currently, only omeprazole and lansoprazole have approved indications for use in children.

NASPGHAN's and ESPGHAN's clinical guidelines for the diagnosis of GERD (Rudolph et al 2001, Vandenplas et al 1993) in the various pediatric age groups are based on the presenting degree of severity. First and foremost, most cases of uncomplicated pediatric GERD are diagnosed based on history and physical exam. The rationale for including endoscoped patients is to allow for full characterization of the extent of GERD involvement. Although most pediatric patients with GERD do not have visible erosive esophagitis on endoscopy, there is still a percentage that will demonstrate histological evidence of esophageal inflammation.

This study will contribute to and broaden the pharmacokinetic knowledge of esomeprazole help to further characterize the disease process in the 1-11 year old age group while following the GERD diagnostic and management guidelines of NASPGHAN and ESPGHAN (Rudolph et al 2001, Vandenplas et al 1993).

2. STUDY OBJECTIVES

2.1 Primary objective

To determine the area under the plasma concentration-time curve (AUC) of esomeprazole after single oral doses of 5 mg, 10 mg and 20 mg esomeprazole in pediatric patients 1 to 11 years old inclusive with endoscopically-proven GERD.

2.2 Secondary objective(s)

The secondary objectives of the study are:

1. To determine the $AUC_{(0\text{-}t)}$, C_{max}, t_{max}, $t_{1/2\lambda z}$, apparent oral clearance (CL/F) and apparent volume of distribution during terminal phase ($V_{\lambda z}/F$) of esomeprazole after single oral doses of 5 mg, 10 mg and 20 mg esomeprazole in pediatric patients 1 to 11 years-old inclusive with endoscopically-proven GERD.

2. To determine AUC, $AUC_{(0\text{-}t)}$, C_{max}, t_{max}, $t_{1/2\lambda z}$ of the 5-hydroxy and sulphone metabolites of esomeprazole after a single oral dose of 5 mg, 10 mg, and 20 mg esomeprazole in pediatric patients 1 to 11 years-old inclusive with endoscopically-proven GERD.

3. To assess the safety and tolerability after a single oral dose of esomeprazole in pediatric patients 1 to 11 years old inclusive with endoscopically- proven GERD.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca standard procedures.

This is a randomized, open-label study to be conducted in approximately 5 research centers to evaluate the pharmacokinetics, safety and tolerability of esomeprazole 5 mg, 10 mg and 20 mg when given as a single oral dose to pediatric patients, 1 to 11 years old-inclusive with endoscopically-proven GERD.

Approximately 40 male and female patients from 1 to 11 years of age inclusive with endoscopically-proven GERD will be enrolled in order to obtain at least 24 evaluable patients.

Patients will be randomized into the study based on weight. Once the necessary number of patients for each group has been met, recruitment will be stopped for that group but will continue for the other groups until the total number of patients has expected to be randomized has been reached.

Patients who weigh 8 kg to <20 kg will be randomized into 1 of 2 dosing groups (Group A or Group B). Patients randomized to Group A will receive a single, 5 mg oral dose of

esomeprazole. Patients randomized to Group B will receive a single, 10 mg oral dose of esomeprazole.

Patients who weigh ≥20 kg will be randomized into 1 of 2 dosing groups (Group C or Group D). Patients randomized to Group C will receive a single, 10 mg oral dose of esomeprazole. Patients randomized to Group D will receive a single, 20 mg oral dose of esomeprazole.

3.1.1 Screening Period (Visit 1)

In order to establish eligibility to participate in this study, patients will undergo all screening procedures and assessments within 21 days prior to Day 1. Patients who have had a prior endoscopy can be included in the study if the endoscopy has been performed within 14 days of enrollment (Visit 1). Patients and/or their parent/guardian will have the study design fully explained to them. Each patients' parent/guardian will provide written informed consent with assent from the patient (if appropriate) prior to any study related procedures or assessments. If a patient is taking prescribed PPI therapy and/or H_2RAs he/she must be able to stop taking these therapies 7 days prior to randomization on Day 1 for PPIs and 3 days prior to randomization on Day 1 for H_2RA.

Please refer to Figure 1 and Table 1 for the timing and detailed descriptions of the assessments and procedures to be performed during the screening period and the trial.

3.1.2 Day –1

Patients aged 1-5 years will begin a 4-hour fast prior to study drug administration on Day 1 and will remain fasting until approximately 1 hour after the administration of the study drug. All fluids will be allowed until 4 hours prior to the administration of study drug. However, only water will be allowed up to 1 hour prior to the administration of the study drug.

Patients aged 6-11 years will begin an overnight fast on Day-1 and will remain fasting until approximately 2 hours after the administration of the study drug. All fluids will be allowed until 4 hours prior to the administration of study drug and only water will be allowed up to 1 hour prior to the administration of study drug.

3.1.3 Day 1 (Visit 2)

Patients will arrive at the CRC either the evening before or in the morning of Day 1 as directed by CRC staff. At this time patients will be reassessed with regard to the study eligibility criteria and begin Day 1 study procedures as outlined in Table 1. Patients who still meet the eligibility criteria will be randomized at this time.

All study drug will be administered by CRC personnel. Esomeprazole as either 5 mg or 10 mg capsules (for patients who weigh 8 to <20 kg) or as either 10 mg or 20 mg capsules (for patients who weigh ≥20 kg) will be dosed according to the randomization schedule. The dose will be administered 1 hour prior to breakfast (for patients who are aged 1-5 years) or 2 hours prior to breakfast (for patients who are aged 6-11 years).

Patients will be discharged from the CRC after the 6-hour post dose PK sample collection if they have been able to tolerate at least one meal after the fast and after being assessed by study personnel and found to be stable.

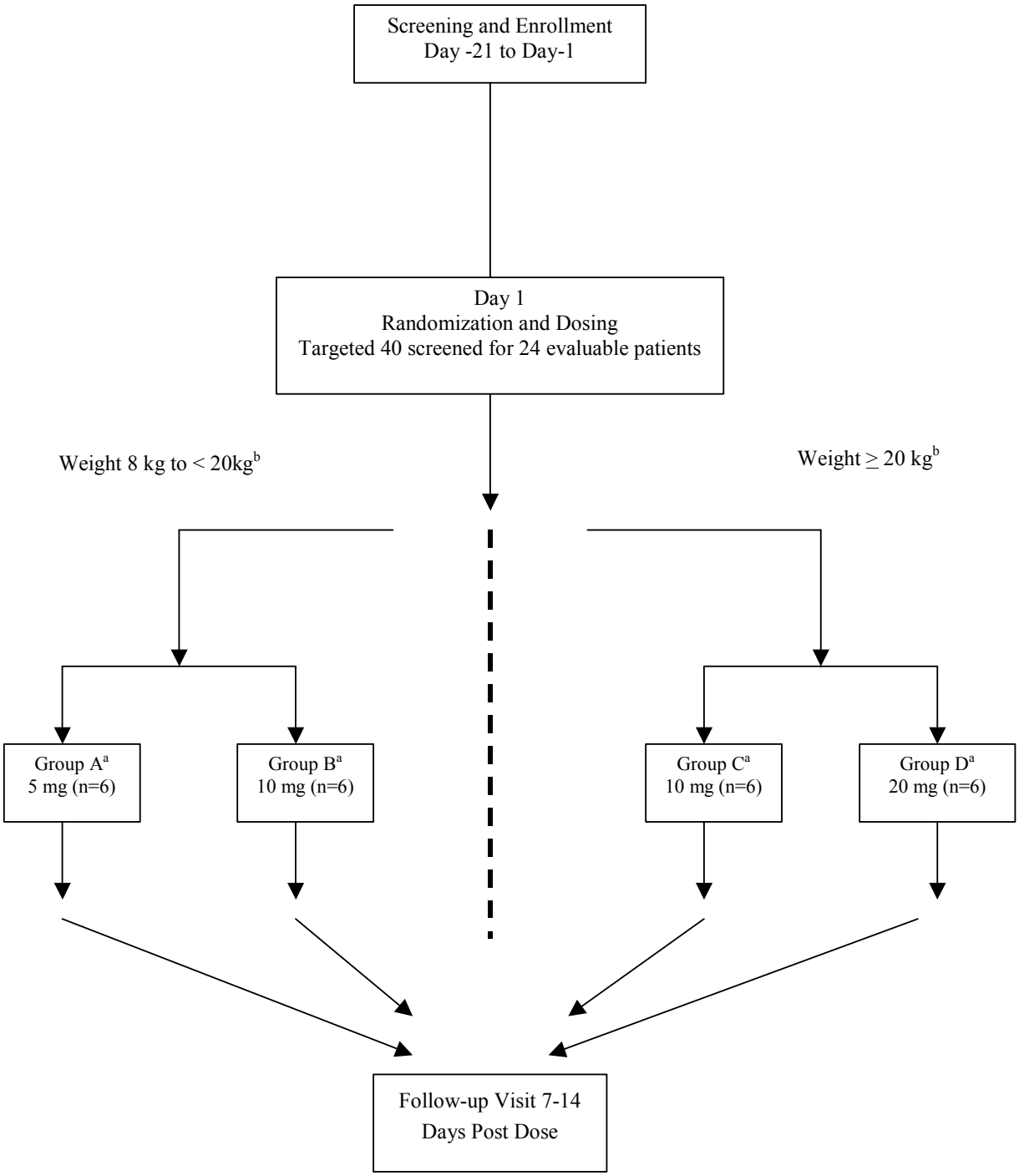
Please refer to the Table 1 and Table 5 for the timing and detailed descriptions of the assessments and procedures to be performed on Day 1.

3.1.4 Follow-up (Visit 3)

Patients will return to the CRC for a follow-up visit preferably at 7 days after study drug administration. If necessary this visit may be scheduled up to 14 days after study drug administration.

Please refer to Table 1 for a detailed description of the assessments and procedures to be performed during the follow-up visit.

Figure 1 Study flow chart



a A minimum of 6 evaluable patients per dosing group will be required. Refer to Table 4.
b Please refer to Table 2

Table 1 Study plan

Assessment/Procedure	Screening Period (Within 21 days prior to randomization (Visit 1)	Day 1 (Dosing and PK Day) (Visit 2)	Follow-Up Visit (7-14 days after Day 1) (Visit 3)
Informed consent/assent	X		
Demographics	X		
Review inclusion/exclusion	X	X	
Full Medical History including surgical history	X		
Complete physical exam	X		X
Vital signs [a]	X	X	X
Concomitant medications	X	X	X
Clinical chemistry, hematology, urinalysis	X		X
Urine pregnancy test [b]		X	
Endoscopic examination [c]	X		
Randomization		X	
Study drug administration [d]		X	
Blood samples for esomeprazole concentration [e]		X	
Meals [f]		X	
Adverse Events		X	X
Serious Adverse Events	X	X	X

a. Blood pressure and pulse will be evaluated in the seated position. Vital signs will also include respiratory rate and either oral, rectal or tympanic temperature evaluations. On Study Day 1 vital signs evaluations will occur prior to dosing.
b. A urine pregnancy test will be required for all post-menarchal females on Day 1 prior to study drug administration.
c. Endoscopy will be performed during the screening period unless the patient has had a prior endoscopy within 14 days prior to enrollment (Visit 1) into the study.
d. Study drug will be administered by CRC personnel.
e. Blood samples (0.8 mL-1mL each) will be collected as follows: pre-dose, 0.5, 1.0. 1.5, 2.0, 3.0, 4.0 and 6 hours post dose.
f. A light low-fat breakfast will be served 1-hour post dose (for patients 1-5) and 2 hours post dose (for patients 6-11) following study drug administration. Lunch will be provided following the 4-hour post dose PK sample collection.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

Physicians have limited options when considering treatment to alleviate GERD symptoms in pediatric patients aged 1-11 years old. Presently, there are only 2 approved PPIs available to treat Pediatric GERD, omeprazole (2-16 years) and lansoprazole (1-17 years). Adult studies have demonstrated a greater acid-suppressive capacity for esomeprazole against all other available PPIs but pharmacokinetic and safety data in the younger age groups is still needed.

In this study, the patient population will be comprised of 24 evaluable male and female patients aged 1 to 11 years old inclusive who have endoscopically-proven GERD (ie reflux esophagitis, erosive or non-erosive). Randomization will be stratified by weight as explained in Figure 1. At least 6 patients will be randomized into each of the 4 dosing categories see Figure 1. When at least 6 evaluable patients have been randomized per group, recruitment of patients for that group will be stopped. The sample size was selected based on the need to provide data sufficient to describe the PK profile for esomeprazole in this population.

Esomeprazole doses for this pediatric population were selected based on extensive work done with available omeprazole and esomeprazole data using appropriate modeling techniques and a thorough review of pediatric pharmacokinetic and pharmacodynamic literature (AstraZeneca Clinical Pharmacology Report, J. Li 2003). The esomeprazole exposure (AUC) and the response (efficacy and safety) relationship in a pediatric population were established via comprehensive pharmacokinetic and population PK modeling analysis of the omeprazole data in pediatric and adult patients and the esomeprazole data in adult patients. Extrapolating the esomeprazole doses from adults to children was consistent with the FDA Guidance for Industry: Exposure-response relationships-study design, data analysis, and regulatory applications (April 2003). With the established exposure-response relationship and an assumption of 8 kg to 60 kg of body weight range for children in this age group (1 to 11 years of age inclusive), it is estimated that the dosing range of 5mg to 20mg will have a reasonable chance to show efficacy and limit unnecessary high exposure. The pediatric dosing rationale can be applied to the different age groups based on approximate weight as estimated in the standard growth curves. Ultimately, randomization is stratified by weight but the chosen dosing schedule can still be reconciled in most cases with the corresponding age groups.

Table 2 provides minimum and maximum dosages based on weight:

Table 2 Dosing grid

Age	Weight	Total Doses	Approximate dose in mg/kg
1 –11 years	≥ 8 kg and <20 kg	5 mg or 10 mg	(*0.25 mg/kg - 0.6 mg/kg*) or (*0.5 mg/kg - 1.25mg/kg*)
	≥20 kg	10 mg or 20 mg	(*0.5 mg/kg -1.0 mg/kg*) for lowest weight patient

AUC was chosen as the primary variable since it has been well established that the inhibition of acid secretion by esomeprazole is well correlated with the AUC of esomeprazole (Andersson, et al 2001).

3.2.2 Risk/benefit and ethical assessment

The findings from completed studies D9614C00099 and D9614C00094 did not show any major safety and/or tolerability issues with single daily doses of esomeprazole in the pediatric population in children aged 1-17 years of age inclusive with symptoms of GERD. During these studies there were few adverse events, no discontinuations due to adverse events, no deaths and 1 serious adverse event that was not considered to be treatment related. In addition, study D9614C00098 was designed to gain safety and tolerability information of single daily oral doses of esomeprazole over an 8-week period. The results of this study demonstrated that esomeprazole was safe and well tolerated in the study population of pediatric GERD patients aged 12-17 years inclusive. There were no deaths, no serious adverse events, and few discontinuations due to adverse events during this study.

Information provided from these 3 studies demonstrated that esomeprazole addresses the medical need to provide treatment of GERD in pediatric patients. The safety of esomeprazole for the short-term treatment of GERD symptoms has been established in the population studied. In addition, a significant reduction in the severity of GERD symptoms and improvements in the patients' quality of life were observed in study D9614C00098 (a double-blind non-placebo controlled trial).

The purpose of the current study is to gain additional pharmacokinetic data in patients aged 1 to 11 years inclusive who have endoscopic evidence of GERD and to assess the safety and tolerability in this age group.

This is a low risk study. All endoscopic procedures pertaining to this study population are part of the standard of care and none will be done solely for research purposes. There is an minimal risk with phlebotomy being performed during this study. The study drug has a strong safety profile. The study will not provide any direct benefit to the patients. However, at the end of the study, families of patients will receive vouchers that will allow for covering the cost of medical treatment for 8 weeks at the discretion of the investigator. Information concerning the disease state in the patient will be determined and this can aid in future treatment options.

3.3 Selection of study population

Approximately 40 male and female patients from 1 to 11 years of age inclusive with endoscopically-proven GERD will be enrolled to obtain at least 24 evaluable patients.

Patients will be randomized into the study based on weight. Once the necessary number of evaluable patients for each group has been met, recruitment will be stopped for that group but will continue for the other groups until the total number of patients expected to be randomized has been reached.

Patients will be enrolled in this study based upon a clinical diagnosis of endoscopically proven GERD. Criteria for endoscopy will depend on clinical presentation and investigator assessment. No endoscopic procedures will be done solely for research purposes. Investigators may establish and document the clinical diagnosis of GERD according to the Pediatric GE Reflux Clinical Guidelines (2001) formulated by NASPGHAN.

Endoscopy enables both visualization and biopsy of the esophageal mucosa, and characterization of macroscopic and microscopic esophagitis as well as erosive or non-erosive lesions. Endoscopy and biopsy can determine the presence and severity of esophagitis as well as rule out other disorders such as eosinophilic esophagitis/gastroenteritis and *H. pylori.* Endoscopic visualization of esophageal erosions or ulcerations correlates to some degree with histopathological esophagitis, but the severity of endoscopic and histopathological changes may not correlate since lesions can be patchy and a biopsy samples only a small portion of the mucosal surface. Endoscopic grading systems for the severity of erosive esophagitis such as the Los Angeles (LA) Classification (Lundell et al 1999), have not yet been validated in children but may provide more uniform definitions of severity, if applied. In addition to the LA Classification used for the characterization of erosive esophagitis, other endoscopic findings may also be indicative of non-erosive esophagitis. The other pediatric endoscopic GERD descriptors reported in the literature (ie hyperemia, ulcers, nodularity, vertical lines) will be assessed with the appropriate histological confirmation when indicated as such (Gupta et al, 1997). Due to poor correlation between endoscopic appearance and histopathology, esophageal biopsy is recommended when diagnostic endoscopy is performed.

Valid pediatric indicators of histologic (microscopic) reflux esophagitis in children include intraepithelial eosinophils or neutrophils as well as morphometric measure of basal cell layer thickness and papillary height. (Liacouras et al 1998, Ruchelli et al 1999).

All degrees of esophageal inflammation will be noted so that a full characterization of esophageal inflammation is available at study entry. Patients who have macroscopic (visible) changes of esophagitis during Visit 1 can be included. If erosions are visible, biopsies will not be required for inclusion into the study but can be performed at the discretion of the investigator for medical reasons or as standard of care.

3.3.1 Study selection record

Investigator(s) must keep a record of all patients (on the screening/enrollment log) who were considered to be eligible for this study and whose parent/guardian signed the informed consent/assent. This information is necessary to establish that the subject population was selected without bias. Patients who do not successfully complete screening must not be re-screened without prior approval from AstraZeneca.

3.3.2 Inclusion criteria

For inclusion in the study patients must fulfill all of the following criteria:

1. Provision of signed, written informed consent from patient's parent/guardian with assent from the patient if appropriate.

2. Patients between the ages of 1 and 11 inclusive and must be able to take solid or bland food (eg, applesauce).

3. Patients must weigh at least 8 kg and at the investigator's discretion be able to undergo extraction of an adequate volume of blood.

4. The patient's weight for height percentile should be less than the 90^{th} percentile and/or the BMI must be between the 5^{th} and 85^{th} percentile for age.

5. Patients may be diagnosed with endoscopically-proven GERD by the investigator during the screening period (Visit 1). In addition patients with a previous (within 14 days of Visit 1) endoscopic diagnosis of GERD induced esophagitis will not be required to have another endoscopy to be enrolled into this study. The diagnosis of esophagitis can be made by the Principal Investigator or may be referred from other endoscopy specialists or centers. Endoscopic evidence will be accepted if there is adequate documentation (ie, complete endoscopic reports, pathology reports or photo documentation). Patients with extra-esophageal and/or atypical symptoms (ie failure to thrive, reactive airway disease, etc.) who are candidates for endoscopy will qualify for inclusion provided they have endoscopic signs of GERD.

6. Patients should not take any prescription or over the counter PPIs for 7 days and or/H_2RA therapy for 3 days prior to the dose of the study drug through completion of study procedures on Day 1. Resumption of treatment with PPIs and H_2RAswill be at the discretion of the investigator.

7. Patients/parents/guardians must be willing to communicate with the investigator and comply with all study procedures.

8. Post-menarchal females must have a negative urine pregnancy test at the time of randomization on Day 1.

3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Use of any other investigational compound or participation in another clinical trial within 28 days prior to the screening visit.

2. History or presence of gastrointestinal, hepatic or renal disease or other conditions that could interfere with absorption, distribution, metabolism or excretion of esomeprazole.

3. Unstable diabetes mellitus or history of seizure disorder.

4. Any acute or chronic illness or a medical history, which in the opinion of the investigator and/or sponsor, could compromise the patient's safety or successful participation in the study.

5. Patients with the following diseases/conditions: active gastrointestinal bleed, active peptic ulcer disease, eosinophilic gastroenteritis, allergic gastroenteropathies, inflammatory bowel disease, bleeding disorders, seizure disorders, acute pancreatitis, metabolic diseases or meningitis. Patients with a past history (prior to study enrollment) of Erosive Esophagitis (EE), Duodenal Ulcers (DU), Gastric Ulcers (GU) and/or *H. pylori* infection are eligible for this study if they satisfy other inclusion/exclusion criteria. Patients with active *H .pylori* infection maybe enrolled into the study provided anti-*Helicobacter* antibiotic therapy is withheld until after the study is completed. This decision will be made at the investigator's discretion and with agreement from the patient's parent/guardian.

6. Female patients who are taking hormonal contraceptives for medical reasons.

7. Patients who must remain on any of the following concomitant medications during the course of the study: bismuth-containing products, barbiturates, anti-convulsants, anti-coagulants, narcotics, anti-neoplastic agents, H_2RAs, sucralfate, ant-emetics, systemic steroids (oral and intravenous, pro-motility drugs (eg, cisapride, metoclopramide, domperidone or macrolide antibiotics such as erythromycin. Use of topical erythromycin is permissible. Occasional doses of NSAIDs or salicylates ($\leq$ 3days) to treat acute conditions are permissible.

8. The patient's endoscopic findings must have no evidence of advanced esophageal lesions due to GERD or other severe upper GI tract pathology (eg, Barrett's, stricture, neoplasm).

9. Patients with a history or a current need for resectional or reconstructive surgery of the GI tract (eg, esophagus, stomach, duodenum, jejunum or colon).

10. History of multiple drug allergies unless otherwise agreed by AstraZeneca and the investigator.

11. Hypersensitivity, allergy or intolerance to esomeprazole, any ingredient in its formulation or any drug with a similar chemical structure to esomeprazole.

12. Current use of anti-epileptic medications phenytoin, mephenytoin, antineoplastic agents, pro-motility drugs (prokinetics), sucralfate or warfarin.

13. Use of any drug known to affect the pharmacokinetic parameters of esomeprazole within 14 days prior to administration of study drug on Day 1. These drugs include, but are not limited to, enzyme inducers such as phenobarbital, carbamazepine, rifampin and St. John's Wort, or enzyme inhibitors such as clarithromycin,

erythromycin, SSRIs, cimetidine, itraconazole, protease inhibitors and ketaconazole.

14. Clinically significant abnormal values at screening from laboratory measurements, vital signs or other physical examination findings which, in the opinion of the investigator, may either put the patient at risk when participating in the study, other than those directly related to some concurrent and stable disease or if the values from laboratory measurements are both unexplained and clinically significant.

3.3.4 Restrictions

1. Patients aged 1-5 years inclusive must fast for 4 hours prior to study drug administration until approximately 1 hour following study drug administration on the morning of the Day1 (Visit 2). All fluids will be allowed until 4 hours before study drug administration and only water will be allowed until 1 hour before study drug administration.

2. Patients aged 6-11 years inclusive must fast overnight until approximately 2 hours following the administration of study administration on Day 1 (Visit 2). All fluids will be allowed until 4 hours before study drug administration and only water up to 1 hour before study drug administration.

3. Patients should not take any prescription or over the counter PPIs from 7 days prior to randomization through completion of study procedures on Day 1. Resumption of treatment with PPIs will be at the discretion of the investigator.

4. Patients should not take any prescription or over-the counter H_2-RAs from 3 days prior to randomization through completion of study procedures on Day 1. Resumption of treatment with H_2RAs will be at the discretion of the investigator.

5. Patients should not take antacids from 24 hours prior to randomization through completion of study procedures on Day 1. Resumption of treatment with antacids will be at the discretion of the investigator.

3.3.5 Discontinuation of subjects from treatment or assessment

3.3.5.1 Criteria for discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the patient, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca
- Occurrence of a Serious Adverse Event.

- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca.
- Incorrect enrollment ie, the patient does not to meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up

3.3.5.2 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up until resolution or until the investigator decides that no further follow-up is necessary.

If a patient is being withdrawn due to a suspected infection in WHO risk categories 2, 3, and 4, no biological samples from this subject are allowed to be sent to the laboratory. Samples will be destroyed according to normal routines at the study site.

If possible, patients who discontinue early should return for the follow-up visit at 7-14days after the administration of study drug. See Table 1 for procedures for follow-up visit.

3.3.5.3 Procedures for handling incorrect enrolled patients

Patients not meeting the inclusion criteria or who meet any of the exclusion criteria for the study should, under no circumstances, be enrolled into the study. There can be no exceptions to this rule. Where patients not meeting the study eligibility criteria are enrolled in error, incorrectly randomized, or where patients subsequently fail to meet the criteria for the study post enrollment, procedures to be followed for the discontinuation of such subjects can be found in 3.3.5.2.

3.4 Treatment(s)

The investigator or institution has the responsibility of establishing a system for handling trial treatments, including investigational medicinal products, so to ensure that:

- Deliveries of such products from AstraZeneca's Investigational Products Section are correctly received by the investigator or his/her designee.
- Such deliveries are recorded on a drug log.
- Trial treatments are only dispensed to trial patients in accordance with the protocol.
- Trial treatments are handled and stored safely and properly.
- Any unused investigational products are accounted for and returned to a designated facility or to AstraZeneca for destruction.

At the end of the trial, it must be possible to reconcile delivery records with records of usage and returned stock. Any discrepancies must be accounted for. Certificates of delivery and return must be signed by the investigator or his/her designee.

3.4.1 Investigational product(s)

3.4.1.1 Identity of investigational product

AstraZeneca will provide the investigator with open-label clinical trial material packaged into tamper-evident high-density polyethylene (HDPE) bottles. The bottles of 10 mg or 20 mg esomeprazole capsules will contain 1 capsule per bottle. The bottles containing the 5 mg esomeprazole capsules will contain 3 capsules per bottle; however, only 1 capsule from the bottle containing 5 mg should be administered per patient. The remainder of the bottle will be returned to AstraZeneca for destruction at the end of the trial.

The 5 mg, 10 mg and 20 mg esomeprazole capsules are opaque, light blue, size #2 hard gelatin capsules.

Bottle labels will be color coded to distinguish the strength of the capsules and dose.

Table 3 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch number
Esomeprazole	5 mg	AstraZeneca	H 1504-01-01	***
Esomeprazole	10 mg	AstraZeneca	H 1221-02-01	***
Esomeprazole	20 mg	AstraZeneca	H 1189-04-01	***

*** Batch number will be recorded in the study master file and identified in the clinical study report.

3.4.1.2 Labeling

All clinical trial material will be packaged and labeled by AstraZeneca. The treatment packs will be clearly marked according to national requirements regarding the use for clinical trial investigation only and will also be labeled with the drug name, dose, study reference number and storage conditions. It is the responsibility of the investigator to ensure that accurate accountability records are maintained throughout the study. The label will be a 2 panel label. The tear off panel should be placed on the appropriate CRF page.

3.4.1.3 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational product label and Investigator Brochure. All study drug will be stored in their original containers in a lockable storage facility until dispensed to the patients.

3.4.1.4 Accountability

It is the investigator and/or institution's responsibility to establish a system for handling study treatments, including investigational medicinal products to ensure that:

- Deliveries of products from AstraZeneca are correctly received by the Investigator or his/her designee.
- Such deliveries are recorded on a drug log.

The investigator must maintain accurate record accounting for the receipt of the investigational materials and for the disposition of the material. This record keeping will consist of a dispensing record including the identification of the patient to whom drug is dispensed, the quantity and the date of dispensing. The record is in addition to any drug accountability information recorded on the CRFs. At the completion of this study, it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the Investigator or a designated responsible person. The responsible person must ensure:

- Study treatments are handled and stored safely and properly.
- Study treatments are only dispensed to study subjects in accordance with this protocol.

The investigational materials are to be administered by the Investigator, Sub-investigator or his/her designee. Under no circumstances will the Investigator allow the investigational product to be used other than directed by the protocol without prior AstraZeneca approval.

The Investigator will retain all remaining study medication along with any study treatments not dispensed. At the termination of the study or at the request of AstraZeneca or its designee, the Investigator must return unused supplies to AstraZeneca or its designee. This return will be documented by using an Investigational Product Return Invoice (or an equivalent form) supplied by AstraZeneca.

It is essential that all medication be accounted for by the investigator or institution, and that any discrepancies are explained and documented.

3.4.2 Doses and treatment regimens

On Day 1 patients weighing 8 kg to <20 kg will be randomized to either Group A or Group B. On Day 1 patients weighing ≥20 kg will be randomized to either Group C or Group D. The randomization scheme will be computer generated by AstraZeneca and provided to the site. The dose of study drug will be administered as follows:

- Patients randomized to Group A will receive a single 5 mg oral dose of esomeprazole after a 4-hour fast.

- Patients randomized to Group B will receive a single 10 mg oral dose of esomeprazole after a 4-hour fast.

- Patients randomized to Group C will receive a single 10 mg oral dose of esomeprazole after an overnight fast.

- Patients randomized to Group D will receive a single 20 mg oral dose of esomeprazole after an overnight fast.

The study drug will be administered orally as an intact capsule with a minimum of 30 mL of water to a maximum of 180 mL of water or as an opened capsule mixed with a small amount of applesauce (up to 1 tablespoon) followed by a minimum of 30 mL of water to a maximum 180 mL of water. AstraZeneca will supply the applesauce.

The capsules or contents of the opened capsules should not be chewed, crushed or divided. The date and the time of the study drug administration will be recorded on the CRF.

3.4.3 Method of assigning subjects to treatment groups

Written informed consent/assent will be obtained at enrollment and the patients will then be assigned an enrollment number starting with E0001001 for patients enrolled at site 1, E0002001 for patients enrolled at site 2 and E0003001 for patients enrolling at site 3 and continuing sequentially for each additional site enrolling patients for this trial.

- On Day 1 prior to dosing, patients randomized to Group A and Group B will be assigned a 4 digit randomization where the first digit corresponds to the site number and the last 3 digits (beginning with 101) correspond to the randomization number (eg, 1101 would correspond to the first patient randomized at Site 1 and 2101 would correspond to the first patient randomized at Site 2). Numbers will continue sequentially as each patient is randomized.

- On Day 1 prior to dosing, patients randomized to Group C and Group D will be assigned a 4 digit randomization number where the first digit corresponds to the site number and the last 3 digits (beginning with 201) corresponds to the randomization number (eg, 1201 would correspond to the first patient randomized at Site 1 and 2201 would correspond to the first patient randomized at Site 2). Numbers will continue sequentially as each patient is randomized.

If a patient discontinues from the study the randomization number will not be re-used and the patient will not be allowed to re-enter the study.

Table 4 Treatment group assignments

Patients Weighing 8 kg to <20 kg		Patients Weighing ≥20 kg	
Group A N=6	Group B N=6	Group C N=6	Group D N=6
Esomeprazole 5 mg	Esomeprazole 10 mg	Esomeprazole 10 mg	Esomeprazole 20 mg

3.4.4 Blinding and procedures for unblinding the study (Not applicable)

3.4.5 Concomitant medication

Concurrent therapies with PPIs are not permitted within 7 days prior to Day 1 through completion of all study procedures on Study Day 1.

Concurrent therapies with H_2RAs are not permitted within 3 days prior to Day 1 and through completion of study procedures on Study Day 1.

Concurrent therapies with over the counter (OTC) antacids are not permitted within 24 hours prior to Day 1 until completion of study procedures on Day 1.

Any medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the case report form (CRF).

Concomitant use of the following medications during the study is prohibited:

- Bismuth-containing antacids
- Barbiturates
- Warfarin-anticoagulants
- Narcotics
- Antineoplastic agents
- H_2RAs
- Sucralfate
- Anti-emetics
- Systemic steroids (oral or intravenous)

- Pro-motility drugs (ie, cisapride, metoclopramide)
- Macrolide antibiotics (ie, erythromycin)
- Prostaglandin analogs

3.4.6 Treatment compliance

Compliance will be assured by the supervised administration of the study drug by site personnel.

4. MEASUREMENT OF STUDY VARIABLES

The timing of these measurements is detailed in the Study Plan Table 1

Note: PK sampling must be performed at (or as close as possible to) the precise scheduled elapsed time in relation to dose.

4.1 Medical examination and demographic measurements

4.1.1 Enrollment medical examination and demographic measurements

Each patient's signed and dated informed consent/assent must be obtained before conducting any procedure specifically for the study. See Table 1 for procedures to be completed during the screening visit. Demographics (date of birth, sex, race, height, weight and date of informed consent/assent) for each patient will be obtained and recorded on the appropriate CRF, whether the patient is randomized or not to study drug.

4.1.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria must be assessed and reviewed with each patient/parent/guardian at the screening visit and on Day 1 in order to establish and confirm the patient's eligibility to participate or continue in the study. Information regarding whether the patient has met the eligibility criteria and has been randomized or not randomized into the study will be recorded on the appropriate CRF.

4.1.3 Medical/Surgical History

A detailed medical history including, surgical and medication history will be recorded for each patient during the screening visit. Significant medical conditions and surgical events are to be recorded on the appropriate CRF.

The medication history must identify any known drug allergies, and use of chronic medications. All medications and over the counter products including vitamins and herbal supplements used within 2 weeks prior to the screening visit are to be recorded on the CRF. See Table 1 for the timing of this procedure.

4.1.4 Height and Weight

Height will be measured in centimeters (cm) and weight will be measured in kilograms (Kg). Measurements should be taken without shoes and in light clothing. See Table 1 for the timing of this procedure. Height and weight will be recorded on the appropriate CRF.

4.1.5 Endoscopic evaluations

4.1.5.1 Methods of assessment

An upper GI endoscopic examination (ie, esophagus, stomach, duodenum) will be performed in each patient during the screening period. The endoscopy will not be required if the diagnosis of GERD is already established per Inclusion Criteria 5. The endoscopic examination including mucosal biopsies should be done according to routine standards of pediatric medical practice (guidelines for the performance of Pediatric Endoscopy published by NASPGHAN) (Squires and Colletti, 1996). The main purpose is to document the extent of esophagitis and determine to rule out exclusionary conditions (ie, ulcers, bleeding lesions, etc).

Patients found to have macroscopic changes of esophagitis on the endoscopy are eligible to be enrolled. Endoscopic findings may be classified as erosive esophagitis but can also include other pediatric endoscopic GERD descriptors reported in the literature (ie, hyperemia, ulcers, nodularity) with the appropriate histological confirmation when indicated (Gilger et al 2004). In the absence of these alternate visible findings, or in the presence of only erythema or non-specific inflammation, the biopsy confirmation (see Section 3.3) of GERD esophagitis is required for study inclusion. Only patients with endoscopic and/or histological documentation of GERD-related esophagitis obtained endoscopically are eligible for inclusion.

Any subject with advanced esophageal lesions (ie, strictures, Barrett's) will be excluded from the study. Gastric and duodenal ulcer findings will also be exclusionary. Hiatal hernia will not be an exclusion unless considered by the Principal Investigator to be severe enough to warrant surgical intervention.

Los Angeles classification

Grade A One (or more) mucosal break no longer than 5 mm that does not extend between the tops of 2 mucosal folds.

Grade B One (or more) mucosal break more than 5 mm that do not extend between the tops of 2 mucosal folds.

Grade C One (or more) mucosal break that is continuous between the tops of 2 or more mucosal folds but which involves less than 75% of the circumference.

Grade D One (or more) mucosal break that involves at least 75% of the circumference.

4.1.5.2 Photo documentation

Photo documentation, preferably as color printouts, (videotapes are also acceptable), will be used as source documentation and must be available in duplicate. The Z-line and cardia should be visible on the photos, when possible, and the investigator should aim to visualize the whole circumference of the lower esophagus in order to document absence or presence of esophagitis as noted in the previous section.

A label (provided by AstraZeneca) will be attached to the back of the printouts (other forms of photo documentation are labeled correspondingly). The label will contain the enrollment number; visit number and date of endoscopy.

One copy of the photo documentation should be stored in the investigator's study file and the other will be collected and submitted to AstraZeneca. The copy submitted to AstraZeneca should not have any patient's identifiers (ie, name or birthdate). The copy of the photo will be collected during the monitoring visit and stored at AstraZeneca.

Exploratory analyses of random samples of photos will be performed during the study, in order to ensure photo quality and consistency in applying LA-Classification between the various study centers. The purpose of this procedure is not interfere with the investigator's judgment, which will be the basis for analyses and results presented in the study report, but to gain valuable information for the planning of future studies in this age group. The copy of t

Lack of photo documentation due to equipment malfunction or patient related complications should be reported to AstraZeneca and will not necessarily constitute grounds for patient exclusion.

4.1.6 Histology

4.1.6.1 Methods of Assessment

Whenever there are no clear-cut visible lesions of erosive esophagitis, biopsies for histological confirmation of GERD-esophagitis will be taken. The investigational center will use its standard age-appropriate equipment for biopsy sampling.

If needed, biopsies should be taken from the distal esophagus, approximately 0.5 cm above the Z-line (squamo-columnar junction) based on the investigator's assessment of landmarks and from an area with an abnormal appearance suspicious for non-erosive esophagitis.

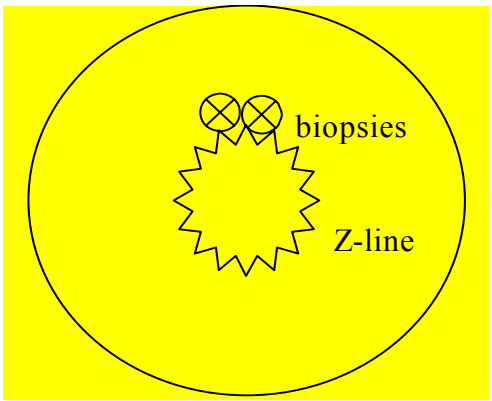
If erosions are visible, biopsies are not needed for the purpose of this protocol and should be taken only at the discretion of the investigator for medical reasons.

The specimens from the distal esophagus should be placed in a single specimen container with 4% buffered parformaldehyde.

The biopsy samples will be processed and analyzed at the site's local laboratory.

Figure 2 Location of biopsies from esophagus

2 biopsies should be taken approximately 0.5 cm above the Z-line based on the investigator's assessment of landmarks



The PI may at his/her discretion, obtain gastric and duodenal biopsies per the standard of care to rule out exclusionary conditions (eg, eosinophilic gastroenteritis, allergic gastropathy, etc). However, a biopsy will not be required for this protocol.

Histological changes in the squamous epithelium in the distal esophagus, such as intercellular space dilatations, basal cell hyperplasia and length of papillae, will be graded according to (Ismail-Beigi et al 1970, 1974 and Solcia et al 2000). Intraepithelial cells will be characterized and counted (intraepithelial lymphocytes, neutrophilic and eosinophilic granulocytes).

4.1.7 Follow-up Medical Examination

Patients will return to the CRC for a follow-up visit preferably at 7 days after study drug administration. If necessary this visit may be scheduled up to 14 days after study drug administration.

Please refer to the Table 1 for procedures to be completed during the follow-up visit..

4.2 Pharmacokinetic measurements

For timing of individual samples refer to the study plan Table 1 and Table 5.

4.2.1 Determination of drug concentration in biological samples

Venous blood samples for PK analysis will be collected on Day 1 at the times listed in Table 1 and Table 5. Blood samples will be collected, labeled, processed and shipped as detailed in Sections 4.2.2 and 4.2.3 and 4.2.4. The date and actual time of collection will be recorded on the appropriate page of the CRF.

Table 5 Investigational plan for study day 1

Time (Hours/minutes)	Blood samples for pharmacokinetics	Activity
Pre-Dose	1	Within 30 minutes of dose
0:00		Randomization and Study Drug Administration
0:30	2	
1:00	3	Breakfast; patients **1-5 years**
1:30	4	
2:00	5	Breakfast; patients **6-11 years**
3:00	6	
4:00	7	Lunch
6:00	8	

Determination of esomeprazole and its 5-hydroxy and sulphone metabolites in plasma will be made using liquid-liquid extraction, reversed-phase liquid chromatography and mass-spectrometric detection. The lower limit of quantification (LLOQ) for all analytes is set to 5.00 nmol/L. Samples for determination of esomeprazole and its metabolites in plasma will be analyzed by DMPK & Bioanalytical Chemistry, AstraZeneca R&D Mölndal, Sweden.

4.2.2 Collection of biological samples

Venous blood samples (1 mL) for the determination of plasma concentrations of esomeprazole and its 5-hydroxy and sulphone metabolites will be collected at the times presented in Table 5. Blood samples will be collected, labeled and shipped as detailed below. The labels for the PK cryovials and sample list will be provided by AstraZeneca R&D, Mölndal, Sweden. In order to ensure that the writing on the label does not smear or run, it is suggested that a piece of clear plastic tape be placed over the label. The date and time of collection will be recorded on the appropriate CRF.

After applying a tourniquet, venous blood will be taken. Blood samples (1mL) will be collected into a 2 mL blood collection tube containing lithium heparin. Disposable needles and disposable tubes shall be used. Individual draws for each time point maybe performed or an indwelling catheter may be used. If an indwelling catheter is used, an additional 1 mL sample must first be drawn for each time point and discarded. To ensure that the line remains patent, the indwelling catheter can be flushed with either saline or heparin. A numbing agent (such as Emla® cream, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware) may be

used prior to taking blood or inserting an indwelling catheter. AstraZeneca shall be notified of the topical numbing agent and its use will be recorded on the appropriate page of the CRF.

All plasma samples will be gently inverted 3 times to mix the blood with the heparin. All samples should be kept at room temperature prior to centrifugation. Centrifugation should occur within 60 minutes or less after collection of the sample. The blood samples will be centrifuged for 10 minutes at room temperature or lower (range 4-25°C) and at a relative centrifugal force (RFC) of approximately 1500xg.

The plasma will be transferred to an appropriately labeled 4 mL Cryovial™ (T130 series, Simport Plastics, Ltd., Quebec, Canada) and will be immediately frozen upright in racks. Samples should be frozen at -20ºC or below and kept frozen at this temperature before, during and after transport to the designated laboratory.

Samples will be disposed of after the clinical study report has been finalized.

4.2.3 Labeling of plasma samples

Pre-printed bar-coded labels will be provided by AstraZeneca. These labels will include the following information:

Study Number: D9614C00007
Randomization #
Sample Number: #s1-8
Scheduled Time
LIMS Identification Number

The labels will be covered with a piece of clear plastic tape to prevent the ink from smearing or running. The label must only be used for the intended sample and the pre-printed information must not be changed.

Two identical labels will be provided for each time point. One label must be used for the sample tube and the identical one will be attached to the Sample Log.

In order for the bar code to be read, the labels must be attached with the bar code **lengthwise** on the tube. One of each label must be attached to the Sample Log following the numbered order of the pre-numbered fields. Labels for samples planned, but not collected, must also be placed on the Sample Log and then crossed out. The Sample Log must accompany the samples when shipped. A copy of the Sample log will be placed in the Investigator's Study File.

In case a pre-printed label is not available for a certain sample, blank labels, delivered together with the pre-printed ones, should be used and completed with all the information needed for identification of the sample (ie, randomization/subject number, sample number and sample time).

4.2.4 Shipping of plasma samples

All plasma samples will be shipped (by World Courier) to the address below. The samples must be sorted by individual and scheduled time in boxes with individual sample partitions and packed securely to avoid breakage during transit, should be double-bagged to contain leaks and should be packed with a sufficient quantity of dry ice to ensure they remain frozen for 72 hours. All applicable shipping regulations must be followed. Documentation sufficient to identify each sample must be included in the shipment. The primary contact at AstraZeneca and the designated laboratory must be notified **before** samples are shipped.

Samples should only be shipped on Monday through Wednesday. Do not ship samples on or before a US or Swedish legal holiday.

All batches of plasma samples, accompanied with the corresponding Sample Log, shall be addressed to:

[redacted]

Prior to shipping, a fax message with shipping/tracking number and time of expected arrival must be sent to [redacted].

4.3 Pharmacodynamic measurements (Not applicable)

4.4 Safety measurements

For timing of individual measurement refer to Study Plan Table 1

4.4.1 Laboratory safety measurements

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis parameters will be taken at the times given in the Study Plan Table 1. The date and time of collection will be recorded on the appropriate CRF.

The following laboratory variables will be measured:

Chemistry assessments will include: Sodium, potassium, chloride, glucose, creatinine, BUN, alkaline phosphatase, ALT, AST, calcium, total bilirubin and albumin.

Hematology assessments will include: WBC, RBC, hemoglobin, hematocrit, platelet count and WBC differential.

Urinalysis assessments will include: Specific gravity, pH, protein, glucose, blood, ketones, nitrates, and a microscopic evaluation.

4.4.2 Urine pregnancy test

For all post menarchal female patients a urine pregnancy test will be obtained prior to study drug administration on Day 1.

4.4.3 Vital signs

4.4.3.1 Blood pressure and heart rate

For timing of individual measurements, refer to Study Plan Table 1

On each study day, blood pressure and pulse will be measured using a standard blood pressure recording device with an appropriate cuff size after the patient has been resting for at least 5 minutes if possible.. It is best to use the same arm if possible for all blood pressure evaluations.

4.4.3.2 Temperature

For timing of individual measurements, refer to Table 1

Either oral, rectal or tympanic temperature will be recorded in ºC. Abnormal oral temperatures should be confirmed by either of the other 2 routes. It is preferable to use the same method of assessing temperature at each evaluation per patient.

4.4.3.3 Respiratory rate

For timing of individual measurements refer to Table 1.

Respiratory rate will consist of a 1-minute count of respirations and should be assessed preferably after the patient has rested for 5 minutes.

4.4.4 Additional Vital Signs

Vital signs assessments in addition to those discussed above can be made at the discretion of the investigator in order to follow the patient's condition. These assessments should be entered as unscheduled assessments in the appropriate section of the CRF.

4.4.5 Complete Physical Examination

For timing of individual measurements, refer to the Study Plan Table 1

The complete physical examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears, and throat), lymph nodes, thyroid, musculoskeletal/extremities, (including spine), cardiovascular, lungs, abdomen and neurological systems.

4.5 Genetic measurements and co-variables (Not applicable)

4.6 Volume of blood sampling

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 6 Volume of blood to be drawn from each subject

Assessment		**Sample volume (mL)**	**n of samples**	**Total volume (mL)**
Blood samples for PK assessment		1.0 mL (2.0 mL if using an indwelling catheter)	8	8.0 mL (16 mL if using an indwelling catheter)
Blood samples for safety assessments	Clinical chemistry	2.5 mL	2	5.0mL
	Hematology	2.0 mL	2	4.0 mL
Total				**17 mL (25** if samples are collected from a indwelling catheter)

4.7 Adverse Events

The methods for collecting adverse events are described below.

4.7.1 Adverse Events

4.7.1.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The Principal Investigator is responsible for ensuring this.

Adverse event

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question, "do you consider that there is a reasonable possibility that the event may have been caused by any of the following: study medication, other medication?" For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Pharmacology Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes."

Other Significant Adverse Events (OAE)

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, will be classified as OAEs. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

4.7.1.2 Recording of adverse events

Adverse events will be collected from the first dose of the investigational product until the follow-up visit. However, SAEs will be reported from the time when the informed consent is obtained through the follow-up visit. All SAEs will be recorded and immediately reported to the sponsor. The date of the final follow-up visit will be the last date when the investigator actively will ask for the AEs occurring during the study.

The following variables will be recorded for each AE in the CRF: verbatim, date when the AE started and stopped, action taken with regard to the investigational product, maximum intensity, outcome, causality and whether the AE constitutes and SAE or not.

Causality of non-serious adverse events will be assessed in the same way for SAEs. See Appendix B for further guidance.

Intensity will be assessed according to the following scale:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.7.1.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

All adverse events spontaneously reported by the volunteer and/or in response to the question "have you had any health problems since the previous visit?" or revealed by observation will be collected and recorded in the CRF. When collecting adverse events, the recording of the diagnosis (when possible) is preferred over recording a list of signs or symptoms (eg, upper gastrointestinal hemorrhage should be used rather than hematemesis, melena and anemia). However if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom should be recorded separately.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 8.4.

Adverse events will be coded by AstraZeneca staff at AstraZeneca R&D, Wilmington, Delaware, using the Medical Dictionary for Regulatory Activities (MedDRA).

Laboratory and vital sign abnormalities will not be recorded as an AE unless any criterion for an SAE is fulfilled, the patient discontinues the study due to the result(s), or the investigator considers it of such clinical importance as to merit recording it as an AE. If a laboratory value or a vital sign is associated with clinical signs and symptoms, the signs and symptoms should be reported as an AE and the associated laboratory or vital signs should be considered additional information. Any sign or symptom that fulfills the SAE definition (Appendix B) or is the reason for discontinuation of treatment of investigational products should be reported accordingly.

Any AEs/SAEs that are unresolved at the last AE assessment in the study are to be followed up by the investigator as long as medically indicated, but without further recording in the CRF. It is the responsibility of the investigator to ensure that this occurs. AstraZeneca retains the right to request additional information for any volunteer with an ongoing AE/SAE at the end of the study, if judged necessary.

4.7.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (ie, immediately but no later than the end of the next business day) of when he or she becomes aware of it.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day one for all fatal and life-threatening cases and by day five for all other SAEs.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. . For a non-serious AE that become serious but which is not fatal or life threatening a report should be received within 5 days.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the CRF. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

You must report any serious adverse event, including death due to any cause immediately. Complete the AstraZeneca Serious Adverse Event Report Form and contact one of the team members listed in the AstraZeneca emergency contact (see Procedures in case of medical emergency 8.2 of this protocol).

You must follow all patients with a serious adverse event, including discontinued patient, until resolution of the adverse event.

5. STUDY MANAGEMENT

5.1 Monitoring

5.1.1 Study monitoring

The monitoring of this study will be performed in accordance with the principles of Good Clinical Practice (GCP) as laid out in the International Conference on Harmonization (ICH) document “Good Clinical Practice: Consolidated Guideline”.

Before first patient into the study, a representative of AstraZeneca will visit the investigational study site to:

- determine the adequacy of the facilities
- discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the investigational site, including visits to:

- provide information and support to the investigator(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case CRFs, and that investigational product accountability checks are being performed
- perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient (eg, clinic charts).

The monitor or another AstraZeneca representative will always be available between visits if the investigator(s) or other staff at the center needs information and advice.

5.1.2 Data verification

It is a prerequisite of this study that the study monitor has direct access to source data for data verification. This will be done by comparing data from the CRFs with those in the patient's medical notes (permission from the subject will be sought as part of the consent process). Such verification is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

Case report forms will not be used as source documents.

Monitoring including source data verification should routinely be performed prior to the transfer of data to AstraZeneca Data Management.

5.2 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, an IRB may visit the center to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-

related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her center.

5.3 Training of staff

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

5.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol must be notified to or approved by each IRB before implementation.

If an administrative change is required, each IRB must be notified and/approved if necessary.

If a protocol amendment requires a change to a particular center's Informed Consent Form, then AstraZeneca and the center's IRB must be notified. Approval of the revised Master Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each Principal Investigator(s) who in turn is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

5.5 Study agreements

The Principal Investigator at each center must comply with all the terms, conditions, and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this protocol shall prevail.

5.6 Study timetable and end of study

The study is expected to start in June 2006 and to be completed by January 2007.

5.7 Data management

5.7.1 Case report forms

Paper CRF (pCRFS) will be used to record all data from all patients including screen failures and all randomized patients. The pCRFS will be in triplicate on carbonless paper. Data should

be recorded directly and legibly from source documents onto the pCRFs in blue or black ballpoint pen. Corrections to the pCRFs should be made legibly, and initialed, and dated. Correction fluid or covering labels must not be used. The top and middle sheets will be collected and forwarded to data management personnel. The bottom sheet will be retained in the Investigator Study File.

The AstraZeneca Monitor or company representing AstraZeneca will check data at the monitoring visits to the study site. Source data verification (SDV) will be done by checking printouts of entered data against source data (ie, laboratory results and other health records at the study site). The Investigator, together with the AstraZeneca monitor, will ensure that the data in the pCRFs are accurate, complete and legible.

Data from the completed pCRFs will be entered into AstraZeneca's clinical study database (AMOS) and validated under the direction of the Data Manager in accordance with the Data Entry Instructions. After data entry the data will be verified and cleaned with electronic data checks comprised of validated computer programs such as SPOLA and manual data review. Any data requiring coding will be classified using both MedDRA and AZDD. Later questions and corrections will be noted and verified by the investigator. Any missing, impossible or inconsistent recordings in the pCRFs will be referred back to the Investigator using a data query form (DQF) and be documented for each individual subject before clean file status is declared. Responses should be received by Data Management and updated within an agreed number of days upon generating the data queries. (These timelines will be reduced nearing Clean File). Clean File will be declared when all of the following have been completed; all data discrepancies are resolved or accepted; all coding is complete and has been medically reviewed and approved; data checks has been run and discrepancies resolved, and quality control of the database against the CRF, any scheduled and relevant data sources has been completed.

After clean file, updates to the database will only be allowed in exceptional cases and with the required documentation.

6. PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY, GENETIC AND STATISTICAL METHODOLOGY

6.1 Pharmacokinetic/pharmacodynamic evaluation

6.1.1 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic analysis will be done using non-compartmental methods. The actual sampling times, if different from protocol times, will be used in the pharmacokinetic calculations. Plasma concentrations below LLOQ will be excluded except for the pre-dose samples where they will be taken as zero. Furthermore, if there is more than 1 plasma concentration below LLOQ prior to C_{max} then the last one before the first actual plasma concentrations will be calculated as LLOQ/2.

The following pharmacokinetic parameters will be calculated for each subject if possible:

$AUC_{(0-t)}$ the area under the plasma concentration versus time curve from time zero to the last quantifiable concentration (C_{last}) calculated by the log/linear trapezoidal method

AUC $AUC_0 + C_{last}/\lambda z$ when λ is the terminal rate constant estimated from individual linear least squares regression on the terminal part of the log concentration versus time curve.

C_{max} the observed maximum plasma concentration

t_{max} the time to reach C_{max}

$t_{½\lambda z}$ the terminal half-life, calculated by IN2/λz

CL/F the apparent oral clearance calculated as dose/AUC

$V_{\lambda z}/F$ the apparent volume of distribution during terminal phase calculated as (Dose/(AUC* λz))

6.2 Safety evaluation

6.2.1 Calculation or derivation of safety variables

Safety and tolerability will be assessed by means of incidence and severity of the following:

- Adverse events
- Laboratory parameters
- Vital signs
- Physical examination

6.3 Genetics as a co-variate (Not applicable)

6.4 Statistical methods and determination of sample size

6.4.1 Statistical evaluation

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized before, database lock.

6.4.2 Description of variables in relation to hypotheses

The pharmacokinetic characteristics of esomeprazole will be assessed by plasma concentration, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{½\lambda z}$,CL/F and $V_{\lambda z}/F$. The pharmacokinetic characteristics of the metabolites, 5-hydroxy and sulphone, will be assessed by plasma concentration, AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, and $t_{½\lambda z}$.

Safety and tolerability will be assessed in terms of adverse events, vital signs including blood pressure and pulse rate, respiratory rate and laboratory variables including clinical chemistry, haematology, and urinalysis.

6.4.3 Description of analysis sets

6.4.3.1 Safety analysis set

The safety analysis set will include all patients who receive 1 dose of study medication.

6.4.3.2 Pharmacokinetics analysis set

The pharmacokinetics analysis set will include all patients with adequate data and with no protocol deviations that would have an impact on the pharmacokinetics of esomeprazole.

6.4.4 Methods of statistical analyses

For analysis purposes, a treatment group will be defined in terms of actual dose administered. All analyses will be performed using SAS Version 8. (SAS Institute, Inc. Cary, NC) statistical software system.

No formal statistical hypothesis testing of the pharmacokinetic or safety data will be done.

The plasma concentration of esomeprazole and esomeprazole metabolites will be summarized and reported as descriptive statistics. In addition, the following PK parameters will be summarized: (AUC, $AUC_{(0\text{-}t)}$, C_{max}, t_{max}, $t_{½\lambda z}$,CL/F and $V_{\lambda z}/F$) for esomeprazole and (AUC, $AUC_{(0\text{-}t)}$, C_{max}, t_{max}, $t_{½\lambda z}$) for the 5-hydroxy-sulphone metabolites of esomeprazole.

Descriptive statistics will be used to evaluate vital signs and clinical laboratory assessments. Clinical chemistry, hematology and urinalysis values outside the normal reference range will be flagged.

6.4.5 Determination of sample size

This sample size was selected based on the need to provide data sufficient to describe the pharmacokinetic profile for esomeprazole in this population, while at the same time minimizing the number of patients that need to be enrolled. Twelve patients in the 8 kg to <20 kg weight group (6 evaluable patients at each dose) and 12 patients in the ≥20 kg weight group (6 evaluable patients at each dose) will provide adequate information to support further development. The sample size is not based on any power calculations.

6.5 Interim analyses (Not applicable)

6.6 Data presentation (Not applicable)

6.7 Data monitoring committee

There will not be a Data Monitoring board; however, a Data and Safety Monitoring Plan will be available for this study. The Clinical Study Physician will monitor SAEs on a continuous basis. A Drug Safety Physician will review all serious unexpected reports that are assessed by

the investigator and are considered to be causally related to the study drug. This review will take place within 15 days from AZ notification of the event. In addition, a safety sub-team, consisting of the AZ Drug Safety Physician, the Study Physician, Study Delivery Operations Specialist and other Study Team members will meet on a regular basis to review non-serious AE's, discontinuations due to AE's and clinically significant laboratory data and vital signs. This safety sub-team will also review any safety issues that arise from other Nexium pediatric studies. Ad hoc safety meetings will be held anytime a potential safety issue is identified. Any potential safety signals identified which may impact upon the benefit-risk of the product or protocol or lead to a change in the way the product is administered during future trials or the post-marketing setting will be communicated in a timely manner to investigators and regulatory authorities.

7. ETHICS

7.1 Ethics review

The final study protocol and the final version of the Master Informed Consent and Assent Form must be approved in writing by the IRB as appropriate. The investigator(s) must submit the written IRB approval to AstraZeneca before he or she can enroll any patient into the study.

The Principal Investigator(s) is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

Under no circumstances will the investigation be extended beyond the limitations defined in this protocol or any subsequent amendments.

7.2 Ethical conduct of the study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

7.3 Informed Consent

The Principal Investigator at each center will ensure that the patient/parent/guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Parents/guardians must also be notified that they are free to discontinue their child from the study at any time. The patient/parent/guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The patients's signed and dated assent (if appropriate) and the patient's parent/guardian's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The Principal Investigator must store the original, signed Pediatric Study Subject Information and Consent Form and Pediatric Assent Form. A copy of these forms must be given to the patient/parent/guardian.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

7.4 Subject data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by randomization code/study code/initials.

The Master Informed Consent Form will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, and the IRB may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

8. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

8.1 AstraZeneca emergency contact procedure

In the case of a medical emergency, contact AstraZeneca personnel shown below.

- [redacted] Phone: [redacted] /Fax: [redacted]
- [redacted] Phone: [redacted]

8.2 Procedures in case of medical emergency

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.3.**

8.3 Procedures in case of overdose

A single oral 510-mg/kg dose of esomeprazole (about 103 times the human dose on a body surface area basis) was lethal to rats. The major signs of toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia and intermittent convulsions.

There have been some reports of overdose with esomeprazole. Reports have been received of over dosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache and dry mouth.

No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein-bound, it is not expected to be removed by dialysis. In the event of over dosage, treatment should be symptomatic and supportive.

As with management of any overdose, the possibility of multiple drug ingestion should be considered. For current information or any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians Desk Reference (PDR) or local telephone book.

- Use of study medication in doses in excess of that specified in the protocol should not be recorded in the CRF as an AE of 'Overdose' unless there are associated symptoms or signs.

- An Overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRF.

- An Overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRF. In addition, the Overdose should be reported on the separate AZ "Clinical Study Overdose Report Form."

- An Overdose without associated symptoms should not be recorded as an AE in the CRF. The Overdose should be reported on the separate AZ "Clinical Study Overdose Report Form".

8.4 Procedures in case of pregnancy

Pregnancy testing will be performed prior to randomization on Day 1 only in post-pubertal females if applicable.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

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Clinical Pharmacology Study Protocol Appendix A	
Drug Substance	Esomeprazole magnesium
Study Code	D9614C00007
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

[redacted]

[redacted]
Date
(Day Month Year)

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

ASTRAZENECA SIGNATURE(S)

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

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[redacted]

Date
(Day Month Year)

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SIGNATURE OF PRINCIPAL INVESTIGATOR

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

This Clinical Study Protocol and all Amendments to the CSP has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Centre No.: 001

Signature:

[redacted]

Date
(Day Month Year)

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

SIGNATURE OF PRINCIPAL INVESTIGATOR

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

This Clinical Study Protocol and all Amendments to the CSP has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Centre No.:

Signature:

_____ _____

Date
(Day Month Year)

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Clinical Pharmacology Study Protocol Appendix B	
Drug Substance	Esomeprazole magnesium
Study Code	D9614C00007
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by acetaminophen overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Pharmacology Study Protocol Appendix C

Drug Substance	Esomeprazole magnesium
Study Code	D9614C00007
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix C
WHO Risk Categories

Risk group	Shipping Requirement	Pathogen	Risk to individuals	Risk to the community	Examples of Pathogens and their Risk groups
1	Standard Diagnostic (IATA PI650)	A micro-organism that is unlikely to cause human disease.	NONE OR VERY LOW	NONE OR VERY LOW	Most bacteria, fungi and viruses
2	Standard Diagnostic (IATA PI650)	A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited.	MODERATE	LOW	Legionella pneumophila E. Coli 0157
3	Standard Diagnostic (IATA PI650)	A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.	HIGH	LOW	HIV Hepatitis B Hepatitis C
4	High risk(IATA PI602)	A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.	HIGH	HIGH	Lassa Fever Ebola Virus

If a subject is being withdrawn due to a suspected infection in WHO risk categories 2, 3 and 4 no biological samples from this subject are allowed to be sent to the laboratory. Samples will be destroyed according to normal routines at the study site.

Clinical Pharmacology Study Protocol Appendix: D	
Drug Substance	Esomeprazole magnesium
Study Code	D9614C00007
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix D
Nexium Package Insert

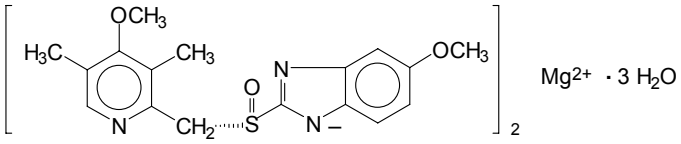
NEXIUM®

(esomeprazole magnesium)
DELAYED-RELEASE CAPSULES

Rx only

DESCRIPTION

The active ingredient in NEXIUM® (esomeprazole magnesium) Delayed-Release Capsules is bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-yl) magnesium trihydrate, a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Its empirical formula is $(C_{17}H_{18}N_3O_3S)_2Mg \times 3\ H_2O$ with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis. The structural formula is:



The magnesium salt is a white to slightly colored crystalline powder. It contains 3 moles of water of solvation and is slightly soluble in water.

The stability of esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25°C and about 8 hours at 37°C.

NEXIUM is supplied as Delayed-Release Capsules for oral administration. Each delayed-release capsule contains 20 mg or 40 mg of esomeprazole (present as 22.3 mg or 44.5 mg esomeprazole magnesium trihydrate) in the form of enteric-coated pellets with the following inactive ingredients: glyceryl monostearate 40-50, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C Yellow #10.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

NEXIUM Delayed-Release Capsules contain an enteric-coated pellet formulation of esomeprazole magnesium. After oral administration peak plasma levels (C_{max}) occur at approximately 1.5 hours (T_{max}). The C_{max} increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 μmol*hr/L on day 1 to 11.2 μmol*hr/L on day 5 after 40 mg once daily dosing.

The AUC after administration of a single 40 mg dose of esomeprazole is decreased by 43-53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals.

The pharmacokinetic profile of esomeprazole was determined in 36 patients with symptomatic gastroesophageal reflux disease following repeated once daily administration of 20 mg and 40 mg capsules of NEXIUM over a period of five days. The results are shown in the following table:

Pharmacokinetic Parameters of NEXIUM Following Oral Dosing for 5 days

Parameter	NEXIUM 40 mg	NEXIUM 20 mg
AUC (μmol*h/L)	12.6	4.2
Coefficient of variation	42%	59%
C_{max} (μmol/L)	4.7	2.1
T_{max} (h)	1.6	1.6
$t_{1/2}$ (h)	1.5	1.2

Values represent the geometric mean, except the T_{max}, which is the arithmetic mean.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 μmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed Poor metabolizers. At steady state, the ratio of AUC in Poor metabolizers to AUC in the rest of the population (Extensive metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion

The plasma elimination half-life of esomeprazole is approximately 1-1.5 hours. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

Special Populations

Geriatric

The AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Pediatric

The pharmacokinetics of esomeprazole have not been studied in patients < 18 years of age.

Gender

The AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Dosage adjustment based on gender is not necessary.

Hepatic Insufficiency

The steady state pharmacokinetics of esomeprazole obtained after administration of 40 mg once daily to 4 patients each with mild (Child Pugh A), moderate (Child Pugh Class B), and severe (Child Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver function. In

patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded (See **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency

The pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of esomeprazole is excreted unchanged in urine.

Pharmacokinetics: Combination Therapy with Antimicrobials

Esomeprazole magnesium 40 mg once daily was given in combination with clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for 7 days to 17 healthy male and female subjects. The mean steady state AUC and C_{max} of esomeprazole increased by 70% and 18%, respectively during triple combination therapy compared to treatment with esomeprazole alone. The observed increase in esomeprazole exposure during co-administration with clarithromycin and amoxicillin is not expected to produce significant safety concerns.

The pharmacokinetic parameters for clarithromycin and amoxicillin were similar during triple combination therapy and administration of each drug alone. However, the mean AUC and C_{max} for 14-hydroxyclarithromycin increased by 19% and 22%, respectively, during triple combination therapy compared to treatment with clarithromycin alone. This increase in exposure to 14-hydroxyclarithromycin is not considered to be clinically significant.

Pharmacodynamics

Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related

up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

Antisecretory Activity

The effect of esomeprazole on intragastric pH was determined in patients with symptomatic gastroesophageal reflux disease in two separate studies. In the first study of 36 patients, NEXIUM 40 mg and 20 mg capsules were administered over 5 days. The results are shown in the following table:

Effect on Intragastric pH on Day 5 (N=36)

Parameter	NEXIUM 40 mg	NEXIUM 20 mg
% Time Gastric pH >4† (Hours)	70%* (16.8 h)	53% (12.7 h)
Coefficient of variation	26%	37%
Median 24 Hour pH	4.9*	4.1
Coefficient of variation	16%	27%

† Gastric pH was measured over a 24-hour period
*p< 0.01 NEXIUM 40 mg vs NEXIUM 20 mg

In a second study, the effect on intragastric pH of NEXIUM 40 mg administered once daily over a five day period was similar to the first study, (% time with pH>4 was 68% or 16.3 hours).

Serum Gastrin Effects

The effect of NEXIUM on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6-12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Enterochromaffin-like (ECL) Cell Effects

In 24-month carcinogenicity studies of omeprazole in rats, a dose-related significant occurrence of gastric ECL cell carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see **PRECAUTIONS,** Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3,000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with

time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients.

In over 1,000 patients treated with NEXIUM (10, 20 or 40 mg/day) up to 6-12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

Endocrine Effects

NEXIUM had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of NEXIUM on the endocrine system were assessed using omeprazole studies. Omeprazole given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

Microbiology

Esomeprazole magnesium, amoxicillin and clarithromycin triple therapy has been shown to be active against most strains of *Helicobacter pylori (H. pylori) in vitro* and in clinical infections as described in the **Clinical Studies** and **INDICATIONS AND USAGE** sections.

Helicobacter

Helicobacter pylori: Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin using agar dilution methodology, and minimum inhibitory concentrations (MICs) were determined.

Pretreatment Resistance: Clarithromycin pretreatment resistance rate (MIC $\geq$ 1 μg/mL) to *H. pylori* was 15% (66/445) at baseline in all treatment groups combined. A total of > 99% (394/395) of patients had *H. pylori* isolates which were considered to be susceptible (MIC $\leq$ 0.25 μg/mL) to amoxicillin at baseline. One patient had a baseline *H. pylori* isolate with an amoxicillin MIC = 0.5 μg/mL.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes: The baseline *H. pylori* clarithromycin susceptibility results and the *H. pylori* eradication results at the Day 38 visit are shown in the table below:

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes[a] for Triple Therapy - (Esomeprazole magnesium 40 mg once daily/amoxicillin 1000 mg twice daily/clarithromycin 500 mg twice daily for 10 days)

Clarithromycin Pretreatment Results	*H. pylori* negative (Eradicated)	*H. pylori* positive (Not Eradicated) Post-treatment susceptibility results			
		S[b]	I[b]	R[b]	No MIC
Susceptible[b] 182	162	4	0	2	14
Intermediate[b] 1	1	0	0	0	0
Resistant[b] 29	13	1	0	13	2

[a]Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results

[b]Susceptible (S) MIC ≤ 0.25 μg/mL, Intermediate (I) MIC = 0.5 μg/mL, Resistant (R) MIC ≥ 1.0 μg/mL

Patients not eradicated of *H. pylori* following esomeprazole magnesium/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, when possible. Patients with clarithromycin resistant *H. pylori* should not be re-treated with a clarithromycin-containing regimen.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes: In the esomeprazole magnesium/amoxicillin/clarithromycin clinical trials, 83% (176/212) of the patients in the esomeprazole magnesium/amoxicillin/clarithromycin treatment group who had pretreatment amoxicillin susceptible MICs (≤ 0.25 μg/mL) were eradicated of *H. pylori*, and 17% (36/212) were not eradicated of *H. pylori*. Of the 36 patients who were not eradicated of *H. pylori* on triple therapy, 16 had no post-treatment susceptibility test results and 20 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Fifteen of the patients who were not eradicated of *H. pylori* on triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs. There were no patients with *H. pylori* isolates who developed treatment emergent resistance to amoxicillin.

Susceptibility Test for Helicobacter pylori: The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs. One to three microliters of an inoculum equivalent to a No.2 McFarland standard (1×10^7 - 1×10^8 CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a

microaerobic environment produced by a gas generating system suitable for *Campylobacter*. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

Clarithromycin MIC (μg/mL) [a]	Interpretation	
≤ 0.25	Susceptible	(S)
0.5	Intermediate	(I)
≥1.0	Resistant	(R)

Amoxicillin MIC (μg/mL) [a,b]	Interpretation	
≤ 0.25	Susceptible	(S)

[a] These are breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.

[b] There were not enough organisms with MICs > 0.25 μg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

Microorganism	Antimicrobial Agent	MIC (μg/mL) [a]
H. pylori ATCC 43504	Clarithromycin	0.016 – 0.12 (μg/mL)
H. pylori ATCC 43504	Amoxicillin	0.016 – 0.12 (μg/mL)

[a] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

Clinical Studies

Healing of Erosive Esophagitis

The healing rates of NEXIUM 40 mg, NEXIUM 20 mg, and omeprazole 20 mg (the approved dose for this indication) were evaluated in patients with endoscopically diagnosed erosive esophagitis in four multicenter, double-blind, randomized studies. The healing rates at weeks 4 and 8 were evaluated and are shown in the table below:

Erosive Esophagitis Healing Rate (Life-Table Analysis)

Study	No. of Patients	Treatment Groups	Week 4	Week 8	Significance Level *
1	588	NEXIUM 20 mg	68.7%	90.6%	N.S.
	588	Omeprazole 20 mg	69.5%	88.3%	
2	654	NEXIUM 40 mg	75.9%	94.1%	$p < 0.001$
	656	NEXIUM 20 mg	70.5%	89.9%	$p < 0.05$
	650	Omeprazole 20 mg	64.7%	86.9%	
3	576	NEXIUM 40 mg	71.5%	92.2%	N.S.
	572	Omeprazole 20 mg	68.6%	89.8%	
4	1216	NEXIUM 40 mg	81.7%	93.7%	$p < 0.001$
	1209	Omeprazole 20 mg	68.7%	84.2%	

*log-rank test vs omeprazole 20 mg
N.S. = not significant ($p > 0.05$).

In these same studies of patients with erosive esophagitis, sustained heartburn resolution and time to sustained heartburn resolution were evaluated and are shown in the table below:

Sustained Resolution[‡] of Heartburn (Erosive Esophagitis Patients)

			Cumulative Percent[#] with Sustained Resolution		
Study	No. of Patients	Treatment Groups	Day 14	Day 28	Significance Level *
1	573	NEXIUM 20 mg	64.3%	72.7%	N.S.
	555	Omeprazole 20 mg	64.1%	70.9%	
2	621	NEXIUM 40 mg	64.8%	74.2%	$p <0.001$
	620	NEXIUM 20 mg	62.9%	70.1%	N.S.
	626	Omeprazole 20 mg	56.5%	66.6%	
3	568	NEXIUM 40 mg	65.4%	73.9%	N.S.
	551	Omeprazole 20 mg	65.5%	73.1%	
4	1187	NEXIUM 40 mg	67.6%	75.1%	$p <0.001$
	1188	Omeprazole 20 mg	62.5%	70.8%	

[‡]Defined as 7 consecutive days with no heartburn reported in daily patient diary.
[#]Defined as the cumulative proportion of patients who have reached the start of sustained resolution
*log-rank test vs omeprazole 20 mg
N.S. = not significant ($p > 0.05$).

In these four studies, the range of median days to the start of sustained resolution (defined as 7 consecutive days with no heartburn) was 5 days for NEXIUM 40 mg, 7-8 days for NEXIUM 20 mg and 7-9 days for omeprazole 20 mg.

There are no comparisons of 40 mg of NEXIUM with 40 mg of omeprazole in clinical trials assessing either healing or symptomatic relief of erosive esophagitis.

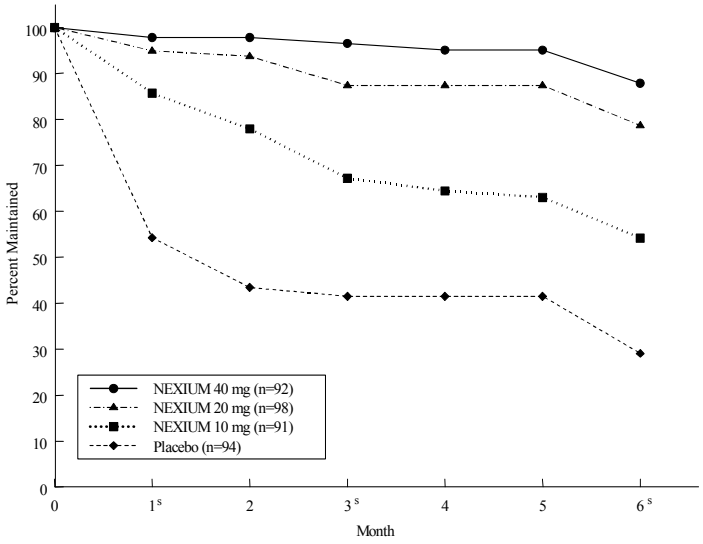
Long-Term Maintenance of Healing of Erosive Esophagitis

Two multicenter, randomized, double-blind placebo-controlled 4-arm trials were conducted in patients with endoscopically confirmed, healed erosive esophagitis to evaluate NEXIUM 40 mg (n=174), 20 mg (n=180), 10 mg (n= 168) or placebo (n=171) once daily over six months of treatment.

No additional clinical benefit was seen with NEXIUM 40 mg over NEXIUM 20 mg.

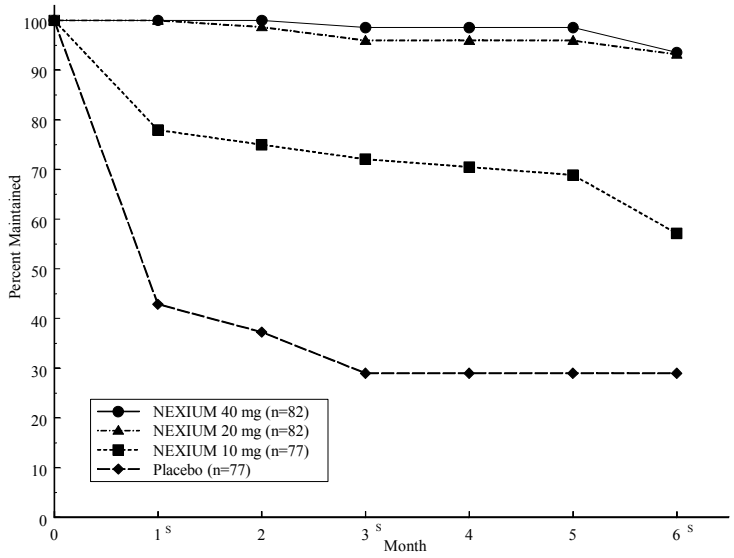
The percentage of patients that maintained healing of erosive esophagitis at the various time points are shown in the figures below:

Maintenance of Healing Rates by Month (Study 177)



s= scheduled visit

Maintenance of Healing Rates by Month (Study 178)



s= scheduled visit

Patients remained in remission significantly longer and the number of recurrences of erosive esophagitis was significantly less in patients treated with NEXIUM compared to placebo.

In both studies, the proportion of patients on NEXIUM who remained in remission and were free of heartburn and other GERD symptoms was well differentiated from placebo.

In a third multicenter open label study of 808 patients treated for 12 months with NEXIUM 40 mg, the percentage of patients that maintained healing of erosive esophagitis was 93.7% for six months and 89.4% for one year.

Symptomatic Gastroesophageal Reflux Disease (GERD)

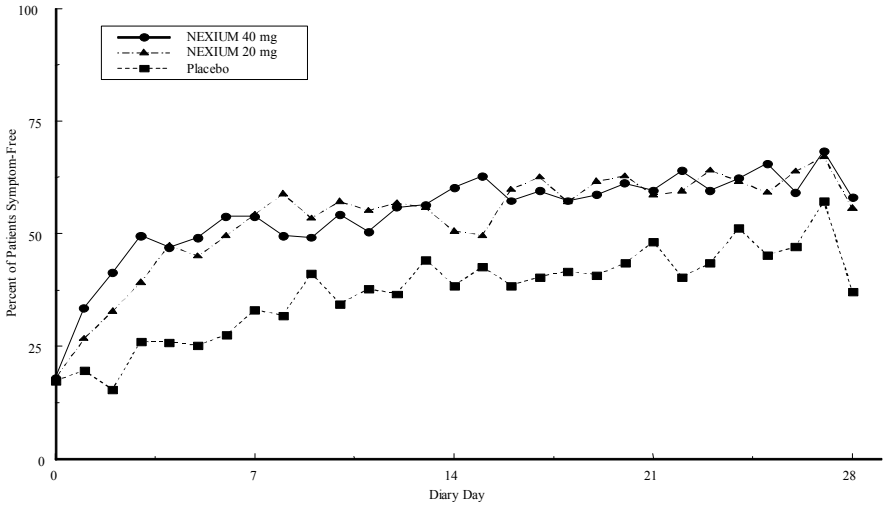
Two multicenter, randomized, double-blind, placebo-controlled studies were conducted in a total of 717 patients comparing four weeks of treatment with NEXIUM 20 mg or 40 mg once daily versus placebo for resolution of GERD symptoms. Patients had ≥ 6-month history of heartburn episodes, no erosive esophagitis by endoscopy, and heartburn on at least four of the seven days immediately preceding randomization.

The percentage of patients that were symptom-free of heartburn was significantly higher in the NEXIUM groups compared to placebo at all follow-up visits (Weeks 1, 2, and 4).

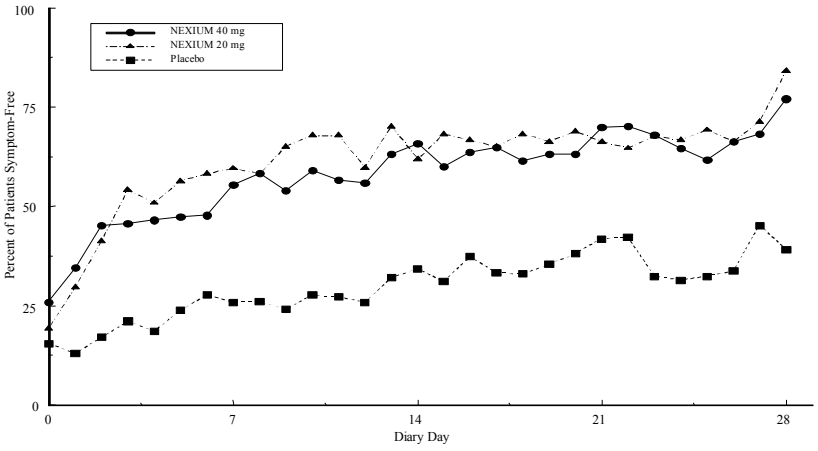
No additional clinical benefit was seen with NEXIUM 40 mg over NEXIUM 20 mg.

The percent of patients symptom-free of heartburn by day are shown in the figures below:

Percent of Patients Symptom-Free of Heartburn by Day (Study 225)



Percent of Patients Symptom-Free of Heartburn by Day (Study 226)



In three European symptomatic GERD trials, NEXIUM 20 mg and 40 mg and omeprazole 20 mg were evaluated. No significant treatment related differences were seen.

Risk Reduction of NSAID-Associated Gastric Ulcer

Two multicenter, double-blind, placebo-controlled studies were conducted in patients at risk of developing gastric and/or duodenal ulcers associated with continuous use of non-selective and COX-2 selective NSAIDs. A total of 1429 patients were randomized across the 2 studies. Patients ranged in age from 19 to 89 (median age 66.0 years) with 70.7% female, 29.3% male, 82.9% Caucasian, 5.5% Black, 3.7% Asian, and 8.0% Others. At baseline, the patients in these studies were endoscopically confirmed not to have ulcers but were determined to be at risk for ulcer occurrence due to their age ($\geq$60 years) and/or history of a documented gastric or duodenal ulcer within the past 5 years. Patients receiving NSAIDs and treated with NEXIUM 20 mg or 40 mg once-a-day experienced significant reduction in gastric ulcer occurrences relative to placebo treatment at 26 weeks. No additional benefit was seen with NEXIUM 40 mg over NEXIUM 20 mg. These studies did not demonstrate significant reduction in the development of NSAID-associated duodenal ulcer due to the low incidence.

Cumulative percentage of patients without gastric ulcers at 26 weeks:

Study	No. of Patients	Treatment Group	% of Patients Remaining Gastric Ulcer Free[1]
1	191 194 184	NEXIUM 20 mg NEXIUM 40 mg Placebo	95.4 96.7 88.2
2	267 271 257	NEXIUM 20 mg NEXIUM 40 mg Placebo	94.7 95.3 83.3

[1] %= Life Table Estimate. Significant difference from placebo ($p<0.01$).

Helicobacter pylori *(H. pylori) Eradication in Patients with Duodenal Ulcer Disease*

Triple Therapy (NEXIUM/amoxicillin/clarithromycin): Two multicenter, randomized, double-blind studies were conducted using a 10 day treatment regimen. The first study (191) compared NEXIUM 40 mg once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily to NEXIUM 40 mg once daily plus clarithromycin 500 mg twice daily. The second study (193) compared NEXIUM 40 mg once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice

daily to NEXIUM 40 mg once daily. *H. pylori* eradication rates, defined as at least two negative tests and no positive tests from CLOtest®, histology and/or culture, at 4 weeks post-therapy were significantly higher in the NEXIUM plus amoxicillin and clarithromycin group than in the NEXIUM plus clarithromycin or NEXIUM alone group. The results are shown in the following table:

H. pylori Eradication Rates at 4 Weeks after 10 Day Treatment Regimen
% of Patients Cured
[95% Confidence Interval]
(Number of patients)

Study	Treatment Group	Per-Protocol†	Intent-to-Treat ‡
191	NEXIUM plus amoxicillin and clarithromycin	84%* [78, 89] (n=196)	77%* [71, 82] (n=233)
	NEXIUM plus clarithromycin	55% [48, 62] (n=187)	52% [45, 59] (n=215)
193	NEXIUM plus amoxicillin and clarithromycin	85%** [74, 93] (n=67)	78%** [67, 87] (n=74)
	NEXIUM	5% [0, 23] (n=22)	4% [0, 21] (n=24)

† Patients were included in the analysis if they had *H. pylori* infection documented at baseline, had at least one endoscopically verified duodenal ulcer ≥ 0.5 cm in diameter at baseline or had a documented history of duodenal ulcer disease within the past 5 years, and were not protocol violators. Patients who dropped out of the study due to an adverse event related to the study drug were included in the analysis as not *H. pylori* eradicated.
‡ Patients were included in the analysis if they had documented *H. pylori* infection at baseline, had at least one documented duodenal ulcer at baseline, or had a documented history of duodenal ulcer disease, and took at least one dose of study medication. All dropouts were included as not *H. pylori* eradicated.
*$p < 0.05$ compared to NEXIUM plus clarithromycin
**$p < 0.05$ compared to NEXIUM alone

The percentage of patients with a healed baseline duodenal ulcer by 4 weeks after the 10 day treatment regimen in the NEXIUM plus amoxicillin and clarithromycin group was 75% (n=156) and 57% (n=60) respectively, in the 191 and 193 studies (per-protocol analysis).

INDICATIONS AND USAGE

Treatment of Gastroesophageal Reflux Disease (GERD)

Healing of Erosive Esophagitis

NEXIUM is indicated for the 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 4-8 weeks of treatment, an additional 4-8-week course of NEXIUM may be considered.

Maintenance of Healing of Erosive Esophagitis

NEXIUM is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.

Symptomatic Gastroesophageal Reflux Disease

NEXIUM is indicated for treatment of heartburn and other symptoms associated with GERD.

Risk Reduction of NSAID-Associated Gastric Ulcer

NEXIUM is indicated for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers. Patients are considered to be at risk due to their age ($\geq$ 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months.

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy (NEXIUM plus amoxicillin and clarithromycin):
NEXIUM, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See **Clinical Studies** and **DOSAGE AND ADMINISTRATION**.)

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See **CLINICAL PHARMACOLOGY, Microbiology** and the clarithromycin package insert, **CLINICAL PHARMACOLOGY, Microbiology**.)

CONTRAINDICATIONS

NEXIUM is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles.

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic.

Concomitant administration of clarithromycin with pimozide is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with pimozide resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsade de pointes) most likely due to inhibition of hepatic metabolism of pimozide by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin.)

Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin. (Please refer to full prescribing information for amoxicillin.)

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (See WARNINGS in prescribing information for clarithromycin.)

Amoxicillin: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND

AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General

Symptomatic response to therapy with NEXIUM does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which NEXIUM is an enantiomer.

Information for Patients

Patients should be informed of the following:

NEXIUM Delayed-Release Capsules should be taken at least one hour before meals.

For patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the NEXIUM Delayed-Release Capsule can be opened, and the pellets inside the capsule carefully emptied onto the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or

crushed. The pellet/applesauce mixture should not be stored for future use.

Antacids may be used while taking NEXIUM.

Drug Interactions

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.

In vitro and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin. Post-marketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of diazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance.

Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole.

Concomitant administration of esomeprazole may reduce the plasma levels of atazanavir.

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant changes in the pharmacokinetic profiles of esomeprazole or these NSAIDs.

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where

gastric pH is an important determinant of bioavailability (eg, ketoconazole, iron salts, and digoxin).

Combination Therapy with Clarithromycin

Co-administration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin. (See **CLINICAL PHARMACOLOGY**, **Pharmacokinetics: Combination Therapy with Antimicrobials.)**

Concomitant administration of clarithromycin with pimozide is contraindicated. (See clarithromycin package insert.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times the human dose of 20 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 5.6 times the human dose on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test. Omeprazole was positive in the *in vitro* human lymphocyte

chromosome aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test.

The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

Pregnancy

Teratogenic Effects. Pregnancy Category B

Teratology studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Teratology studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.5 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human doses on a body surface area basis). There are no adequate and well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy.

Amoxicillin

Pregnancy Category B. See full prescribing information for amoxicillin before using in pregnant women.

Clarithromycin

Pregnancy Category C. See **WARNINGS** (above) and full prescribing information for clarithromycin before using in pregnant women.

Nursing Mothers

The excretion of esomeprazole in milk has not been studied. However, omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. Because esomeprazole is likely to be excreted in human milk, because of the potential for serious adverse reactions in nursing infants from esomeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of patients who received NEXIUM in clinical trials, 1459 were 65 to 74 years of age and 354 patients were ≥ 75 years of age.

No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The safety of NEXIUM was evaluated in over 15,000 patients (aged 18-84 years) in clinical trials worldwide including over 8,500 patients in the United States and over 6,500 patients in Europe and Canada. Over 2,900 patients were treated in long-term studies for up to 6-12 months. In general, NEXIUM was well tolerated in both short and long-term clinical trials.

The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1,240 patients on NEXIUM 20 mg, 2,434 patients on NEXIUM 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse events (≥1%) in all three groups was headache (5.5, 5.0, and 3.8, respectively) and diarrhea (no

difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking NEXIUM or omeprazole.

Additional adverse events that were reported as possibly or probably related to NEXIUM with an incidence < 1% are listed below by body system:

Body as a Whole*:** abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, chest pain substernal, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors; ***Cardiovascular*:** flushing, hypertension, tachycardia; ***Endocrine*:** goiter; ***Gastrointestinal*:** bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting; ***Hearing: earache, tinnitus; ***Hematologic*:** anemia, anemia hypochromic, cervical lymphoadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia; ***Hepatic*:** bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased; ***Metabolic/Nutritional:*** glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease; ***Musculoskeletal*:** arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica; ***Nervous System/Psychiatric*:** anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect; ***Reproductive*:** dysmenorrhea, menstrual disorder, vaginitis; ***Respiratory*:** asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis; ***Skin and Appendages*:** acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria; ***Special Senses:*** otitis media, parosmia, taste loss, taste perversion; ***Urogenital*:** abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria; ***Visual*:** conjunctivitis, vision abnormal.

Endoscopic findings that were reported as adverse events include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration,

esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration.

The incidence of treatment-related adverse events during 6-month maintenance treatment was similar to placebo. There were no differences in types of related adverse events seen during maintenance treatment up to 12 months compared to short-term treatment.

Two placebo-controlled studies were conducted in 710 patients for the treatment of symptomatic gastroesophageal reflux disease. The most common adverse events that were reported as possibly or probably related to NEXIUM were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Postmarketing Reports - There have been spontaneous reports of adverse events with postmarketing use of esomeprazole. These reports occurred rarely and are listed below by body system:

Blood And Lymphatic System Disorders*:* agranulocytosis, pancytopenia; ***Eye Disorders:*** blurred vision; ***Gastrointestinal Disorders:*** pancreatitis; ***Hepatobiliary Disorders:*** hepatitis with or without jaundice; ***Immune System Disorders:*** anaphylactic reaction/shock; ***Musculoskeletal And Connective Tissue Disorders:*** myalgia; ***Psychiatric Disorders:*** depression; ***Skin and Subcutaneous Tissue Disorders:*** alopecia, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN, some fatal).

Other adverse events not observed with NEXIUM, but occurring with omeprazole can be found in the omeprazole package insert, **ADVERSE REACTIONS** section.

Combination Treatment with Amoxicillin and Clarithromycin

In clinical trials using combination therapy with NEXIUM plus amoxicillin and clarithromycin, no adverse events peculiar to these drug combinations were observed. Adverse events that occurred have been limited to those that had been observed with either NEXIUM, amoxicillin, or clarithromycin alone.

The most frequently reported drug-related adverse events for patients who received triple therapy for 10 days were diarrhea (9.2%), taste perversion (6.6%), and abdominal pain (3.7%). No treatment-emergent adverse events were observed at higher rates with triple therapy than were observed with NEXIUM alone.

For more information on adverse events with amoxicillin or clarithromycin, refer to their package inserts, **ADVERSE REACTIONS** sections.

Laboratory Events

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to NEXIUM, were reported in ≤ 1% of patients: increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone (see **CLINICAL PHARMACOLOGY**, *Endocrine Effects* for further information on thyroid effects). Decreases were seen in hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroxine.

In clinical trials using combination therapy with NEXIUM plus amoxicillin and clarithromycin, no additional increased laboratory abnormalities particular to these drug combinations were observed.

For more information on laboratory changes with amoxicillin or clarithromycin, refer to their package inserts, **ADVERSE REACTIONS** section.

OVERDOSAGE

A single oral dose of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions.

There have been some reports of overdosage with esomeprazole. Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - **ADVERSE REACTIONS**). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

DOSAGE AND ADMINISTRATION

The recommended adult dosages are outlined in the table below. NEXIUM Delayed-Release Capsules should be swallowed whole and taken at least one hour before eating.

For patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the NEXIUM Delayed-Release Capsule can be opened, and the pellets inside the capsule carefully emptied onto the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellet/applesauce mixture should not be stored for future use.

For patients who have a nasogastric tube in place, NEXIUM Delayed-Release Capsules can be opened and the intact granules emptied into a 60 mL syringe and mixed with 50 mL of water. Replace the plunger and shake the syringe vigorously for 15 seconds. Hold the syringe with the tip up and check for granules remaining in the tip. Attach the syringe to a nasogastric tube and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the granules, the nasogastric tube should be flushed with additional water. Do not administer the pellets if they have dissolved or disintegrated.

The suspension must be used immediately after preparation.

Recommended Adult Dosage Schedule of NEXIUM

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	20 mg or 40 mg	Once Daily for 4 to 8 Weeks*
Maintenance of Healing of Erosive Esophagitis	20 mg	Once Daily**
Symptomatic Gastroesophageal Reflux Disease	20 mg	Once Daily for 4 Weeks***
Risk Reduction of NSAID-Associated Gastric Ulcer	20 mg or 40 mg	Once Daily for up to 6 months**
***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**		
Triple Therapy:		
NEXIUM	40 mg	Once Daily for 10 Days
Amoxicillin	1000 mg	Twice Daily for 10 Days
Clarithromycin	500 mg	Twice Daily for 10 Days

*(see **CLINICAL STUDIES**). The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4-8 weeks, an additional 4-8 weeks of treatment may be considered.

**Controlled studies did not extend beyond six months.

***If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.

Please refer to amoxicillin and clarithromycin full prescribing information for **CONTRAINDICATIONS, WARNINGS** and dosing in elderly and renally-impaired patients.

Special Populations

Geriatric

No dosage adjustment is necessary. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**)

Renal Insufficiency

No dosage adjustment is necessary. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics**.)

Hepatic Insufficiency

No dosage adjustment is necessary in patients with mild to moderate liver impairment (Child Pugh Classes A and B). For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg of

NEXIUM should not be exceeded (See **CLINICAL PHARMACOLOGY, Pharmacokinetics**.)

Gender
No dosage adjustment is necessary. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**)

HOW SUPPLIED

NEXIUM Delayed-Release Capsules, 20 mg, are opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and NEXIUM 20 mg in yellow on the body. They are supplied as follows:

NDC 0186-5020-31 unit of use bottles of 30
NDC 0186-5022-28 unit dose packages of 100
NDC 0186-5020-54 bottles of 90
NDC 0186-5020-82 bottles of 1000

NEXIUM Delayed-Release Capsules, 40 mg, are opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and NEXIUM 40 mg in yellow on the body. They are supplied as follows:

NDC 0186-5040-31 unit of use bottles of 30
NDC 0186-5042-28 unit dose packages of 100
NDC 0186-5040-54 bottles of 90
NDC 0186-5040-82 bottles of 1000

Storage

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). [See USP Controlled Room Temperature]. Keep container tightly closed. Dispense in a tight container if the product package is subdivided.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Fifth Edition: Approved Standard NCCLS Document M7-A5, Vol. 20, no. 2, NCCLS, Wayne, PA, January 2000.

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Clinical Study Protocol Amendment	
Amendment Number	01
Drug Substance	Esomeprazole
Study Code	D9614C00007
Date	[redacted]

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Sponsor:

AstraZeneca LP, 1800 Concord Pike, Wilmington, DE 19850-5437, USA

Centres affected by the Amendment:

All participating centres

The protocol for the study is to be amended as follows:

Section of protocol affected:

Page 2

Previous text:

ASTRAZENECA PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

In the case of a medical emergency you may contact the Study Delivery Operations Specialist. If the Study Delivery Operations Specialist is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Role in the study	**Name**	**Address and Telephone number**
Study Delivery Operations Specialist	[redacted]	[redacted]
Study Delivery Leader	[redacted]	[redacted]
Study Team Physician	[redacted]	[redacted]
Covance Central Laboratories Project Manager	[redacted]	[redacted]

Revised text:

ASTRAZENECA PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

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Study Delivery Leader	[redacted]	[redacted]
Study Team Physician	[redacted]	[redacted]
Covance Central Laboratories Project Manager	[redacted]	[redacted]

Section of Protocol Affected:

3.1.1 Screening Period (Visit 1)

Previous text:

In order to establish eligibility to participate in this study, patients will undergo all screening procedures and assessments within 21 days prior to Day 1. Patients who have had a prior endoscopy can be included in the study if the endoscopy has been performed within 14 days of enrollment (Visit 1). Patients and/or their parent/guardian will have the study design fully explained to them. Each patients' parent/guardian will provide written informed consent with assent from the patient (if appropriate) prior to any study related procedures or assessments. If a patient is taking prescribed PPI therapy and/or H_2RAs he/she must be able to stop taking

these therapies 7 days prior to randomization on Day 1 for PPIs and 3 days prior to randomization on Day 1 for H_2RA.

Revised text:

In order to establish eligibility to participate in this study, patients will undergo all screening procedures and assessments within 21 days prior to Day 1. Patients who have had a prior endoscopy can be included in the study if the endoscopy has been performed within 42 days of enrollment (Visit 1). Patients and/or their parent/guardian will have the study design fully explained to them. Each patients' parent/guardian will provide written informed consent with assent from the patient (if appropriate) prior to any study related procedures or assessments. If a patient is taking prescribed PPI therapy and/or H_2RAs he/she must be able to stop taking these therapies 7 days prior to randomization on Day 1 for PPIs and 3 days prior to randomization on Day 1 for H_2RA.

Section of the protocol affected:

3.1 Overall Study Design

Previous text:

Table 1 Study plan

Assessment/Procedure	**Screening Period (Within 21 days prior to randomization (Visit 1)**	**Day 1 (Dosing and PK Day) (Visit 2)**	**Follow-Up Visit (7-14 days after Day 1) (Visit 3)**
Informed consent/assent	X		
Demographics	X		
Review inclusion/exclusion	X	X	
Full Medical History including surgical history	X		
Complete physical exam	X		X
Vital signs [a]	X	X	X
Concomitant medications	X	X	X
Clinical chemistry, hematology, urinalysis	X		X
Urine pregnancy test [b]		X	
Endoscopic examination [c]	X		
Randomization		X	
Study drug administration [d]		X	

Blood samples for esomeprazole concentration [e]		X	
Meals [f]		X	
Adverse Events		X	X
Serious Adverse Events	X	X	X

a. Blood pressure and pulse will be evaluated in the seated position. Vital signs will also include respiratory rate and either oral, rectal or tympanic temperature evaluations. On Study Day 1 vital signs evaluations will occur prior to dosing.
b. A urine pregnancy test will be required for all post-menarchal females on Day 1 prior to study drug administration.
c. Endoscopy will be performed during the screening period unless the patient has had a prior endoscopy within 14 days prior to enrollment (Visit 1) into the study.
d. Study drug will be administered by CRC personnel.
e. Blood samples (0.8 mL-1mL each) will be collected as follows: pre-dose, 0.5, 1.0. 1.5, 2.0, 3.0, 4.0 and 6 hours post dose.
f. A light low-fat breakfast will be served 1-hour post dose (for patients 1-5) and 2 hours post dose (for patients 6-11) following study drug administration. Lunch will be provided following the 4-hour post dose PK sample collection.

Revised text:

Table 2 Study plan

Assessment/Procedure	**Screening Period (Within 21 days prior to randomization (Visit 1)**	**Day 1 (Dosing and PK Day) (Visit 2)**	**Follow-Up Visit (7-14 days after Day 1) (Visit 3)**
Informed consent/assent	X		
Demographics	X		
Review inclusion/exclusion	X	X	
Full Medical History including surgical history	X		
Complete physical exam	X		X
Vital signs [a]	X	X	X
Concomitant medications	X	X	X
Clinical chemistry, hematology, urinalysis	X		X
Urine pregnancy test [b]		X	
Endoscopic examination [c]	X		
Randomization		X	
Study drug administration [d]		X	
Blood samples for esomeprazole concentration [e]		X	
Meals [f]		X	
Adverse Events		X	X

Serious Adverse Events	X	X	X

a. Blood pressure and pulse will be evaluated in the seated position. Vital signs will also include respiratory rate and either oral, rectal or tympanic temperature evaluations. On Study Day 1 vital signs evaluations will occur prior to dosing.
b. A urine pregnancy test will be required for all post-menarchal females on Day 1 prior to study drug administration.
c. Endoscopy will be performed during the screening period unless the patient has had a prior endoscopy within 42 days prior to enrollment (Visit 1) into the study.
d. Study drug will be administered by CRC personnel.
e. Blood samples (0.8 mL-1mL each) will be collected as follows: pre-dose, 0.5, 1.0. 1.5, 2.0, 3.0, 4.0 and 6 hours post dose.
f. A light low-fat breakfast will be served 1-hour post dose (for patients 1-5) and 2 hours post dose (for patients 6-11) following study drug administration. Lunch will be provided following the 4-hour post dose PK sample collection

Section of the protocol affected:

3.3.2 Inclusion criteria – Inclusion criteria # 5

Previous text:

> Patients may be diagnosed with endoscopically-proven GERD by the investigator during the screening period (Visit 1). In addition patients with a previous (within 14 days of Visit 1) endoscopic diagnosis of GERD induced esophagitis will not be required to have another endoscopy to be enrolled into this study. The diagnosis of esophagitis can be made by the Principal Investigator or may be referred from other endoscopy specialists or centers. Endoscopic evidence will be accepted if there is adequate documentation (ie, complete endoscopic reports, pathology reports or photo documentation). Patients with extra-esophageal and/or atypical symptoms (ie failure to thrive, reactive airway disease, etc.) who are candidates for endoscopy will qualify for inclusion provided they have endoscopic signs of GERD.

Revised text:

> Patients may be diagnosed with endoscopically-proven GERD by the investigator during the screening period (Visit 1). In addition patients with a previous (within 42 days of Visit 1) endoscopic diagnosis of GERD induced esophagitis will not be required to have another endoscopy to be enrolled into this study. The diagnosis of esophagitis can be made by the Principal Investigator or may be referred from other endoscopy specialists or centers. Endoscopic evidence will be accepted if there is adequate documentation (ie, complete endoscopic reports, pathology reports or photo documentation). Patients with extra-esophageal and/or atypical symptoms (ie failure to thrive, reactive airway disease, etc.) who are candidates for endoscopy will qualify for inclusion provided they have endoscopic signs of GERD.

Section of the protocol affected:

5.6 Study timetable and end of study

Previous text:

The study is expected to start in June 2006 and to be completed by January 2007

Revised text:

The study is expected to start in June 2006 and to be completed by August 2007

Section of the protocol affected:

5.7.1 Case report forms

Previous text:

Data from the completed pCRFs will be entered into AstraZeneca's clinical study database (AMOS) and validated under the direction of the Data Manager in accordance with the Data Entry Instructions. After data entry the data will be verified and cleaned with electronic data checks comprised of validated computer programs such as SPOLA and manual data review. Any data requiring coding will be classified using both MedDRA and AZDD. Later questions and corrections will be noted and verified by the investigator. Any missing, impossible or inconsistent recordings in the pCRFs will be referred back to the Investigator using a data query form (DQF) and be documented for each individual subject before clean file status is declared. Responses should be received by Data Management and updated within an agreed number of days upon generating the data queries. (These timelines will be reduced nearing Clean File). Clean File will be declared when all of the following have been completed; all data discrepancies are resolved or accepted; all coding is complete and has been medically reviewed and approved; data checks has been run and discrepancies resolved, and quality control of the database against the CRF, any scheduled and relevant data sources has been completed.

Revised text:

After collection of the CRFs, data will be entered continuously throughout the study into an AstraZeneca authorized and approved database managed by the CRO. Data will be entered in accordance with the Data Entry Instructions through the data entry application designed by the CRO. After entry, data will be proofread or verified against CRF data to ensure consistency. Any data requiring coding will be classified using both MedDRA and AZDD.

Data verification and validation checks will be performed utilizing edit checks comprised of validated computer programs and manual data review in accordance with the CRO's Data Validation Manual. Any data discrepancies will be referred back in a query format to the Investigator for any missing, inconsistent or illegible entries. These queries will be resolved at the Investigative site and the Investigator will sign and date the query resolution. Original query forms with resolutions will be returned to the CRO within the specified timeframe and, where necessary, the database will be updated as required. All data handling instructions will be documented in an approved Data Management Plan for the study.

The CRO will submit batches of Clean Data to AstraZeneca R&D Data Management at time points specified within the contract/third part vendor (TPV) Agreement. Clean Data is declared when data validation is complete, all data query forms (DQFs) are resolved and the quality and consistency of coding are checked. AstraZeneca R&D will assume ownership of the data from the CRO once Clean Data has been sent.

Section of the protocol affected:

8.1 AstraZeneca emergency contact procedure

Previous text:

In the case of a medical emergency, contact AstraZeneca personnel shown below.

- [redacted] Phone: [redacted] /Fax: [redacted]
- [redacted] Phone: [redacted]

Revised text:

In the case of a medical emergency, contact AstraZeneca personnel shown below.

- [redacted] Phone: [redacted] /Fax: [redacted]
- [redacted] Phone: [redacted]

Reason for Amendment:

The reason for this amendment is to allow a larger enrolment window as a result of current slow recruitment. The incidence of endoscopically-proven GERD including erosive esophagitis (EE) in children is not fully known but considered rare the younger the age of the child. In a population based study from the Pediatric Endoscopy Database System (Peds CORI), *Gilger et al* reviewed 8038 endoscopy records from 1999-2002 and reported 1070 (13.3%) cases with EE, and from the latter group, only 106 patients were in the age range from 0-2 years old (9.9%). 73 patients were age 3-5 years old (6.8%) and 277 were age 6-12 years old (25.9%).

Presently, there have been significant enrolment difficulties; mostly as a result of acutely capturing patients with this infrequent endoscopic diagnosis. By extending the diagnostic window for up to 6 weeks (42 days), we allow Principal Investigators to enrol most patients available to them or their colleagues who are presently being treated for this condition, and in this way the study will not be solely looking for the more rare newly diagnosed case.

This change does not impact the actual study design in that it has no bearing on the PK parameters (primary objectives) and it still complies with the FDA written request general condition of including patients with endoscopically-proven GERD. Finally, since this is not an efficacy or healing study, the timing of diagnosis will have no bearing on the study outcome or patient safety.

This amendment also provides updated AstraZeneca Study Personnel contact information, updated timeline and a corrected description of the data management section.

Persons who initiated the Amendment:

[redacted], Study Physician

[redacted], Study Delivery Program Leader

1. REFERENCES

1. Gilger MA., El-Serag HB., Dietrich CL., The prevalence of erosive esophagitis in children: A population based study. Gastrointestinal Endoscopy 2004 April: 59(5): AB104.

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

[redacted]

Date
(Day Month Year)

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[redacted]

[redacted]

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[redacted]

[redacted]

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SIGNATURE OF PRINCIPAL INVESTIGATOR

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review

I agree to the terms of this amendment.

Centre No.:

Signature:

Name: _____ Date (Day Month Year) _____

Title:

Address:

Telephone:

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Clinical Pharmacology Study Protocol Amendment	
Amendment Number	02
Drug Substance	Esomeprazole
Study Code	D9614C00007
Date	[redacted]

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Sponsor:

AstraZeneca LP, 1800 Concord Pike, Wilmington, DE 19850-5437, USA

Centres affected by the Amendment:

All participating centers

The protocol for the study is to be amended as follows:

Section of protocol affected:

Protocol Synopsis, page 3

Previous text:

Study period		Phase of development
Estimated date of first subject enrolled	[redacted]	Phase I
Estimated date of last subject completed	[redacted]	

Revised text:

Study period		**Phase of development**
Estimated date of first subject enrolled	[redacted]	Phase I
Estimated date of last subject completed	[redacted]	

Section of protocol affected:

Protocol Synopsis – Statistical Methods, page 5

Previous text:

The aim of this study is to determine the area under the plasma concentration–time curve (AUC) of esomeprazole after a single oral dose of 5 mg, 10 mg or 20 mg esomeprazole. Plasma concentration data, pharmacokinetic data, safety information obtained from laboratory assessments, and adverse events will be summarized using descriptive statistics by weight group and dose.

Revised text:

The aim of this study is to determine the area under the plasma concentration–time curve (AUC) of esomeprazole after a single oral dose of 5 mg, 10 mg or 20 mg esomeprazole. Plasma concentration data, pharmacokinetic data, safety information obtained from laboratory assessments, and adverse events will be summarized using descriptive statistics by weight group and dose. **An interim analysis will be performed on the patients in the completed Groups (Groups C and D).**

Section of protocol affected:

TABLE OF CONTENTS, page 8

Previous text:

6.5 Interim analyses (Not applicable)

Revised text:

6.5 Interim analyses

Section of protocol affected:

3.1.1 Screening Period (Visit1), page 15

Previous text:

In order to establish eligibility to participate in this study, patients will undergo all screening procedures and assessments within 21 days prior to Day 1. Patients who have had a prior endoscopy can be included in the study if the endoscopy has been performed within 42 days of enrollment (Visit 1). Patients and/or their parent/guardian will have the study design fully explained to them. Each patients' parent/guardian will provide written informed consent with assent from the patient (if appropriate) prior to any study related procedures or assessments. If a patient is taking prescribed PPI therapy and/or H_2RAs he/she must be able to stop taking these therapies 7 days prior to randomization on Day 1 for PPIs and 3 days prior to randomization on Day 1 for H_2RA.

Revised text:

In order to establish eligibility to participate in this study, patients will undergo all screening procedures and assessments within 21 days prior to Day 1. Patients who have had a prior endoscopy can be included in the study if the endoscopy has been performed within 42 days of enrollment (Visit 1). **Patients weighing less than 20 kg with a previous endoscopy performed within 90 days of Visit 1 will be included.** Patients and/or their parent/guardian will have the study design fully explained to them. Each patients' parent/guardian will provide written informed consent with assent from the patient (if appropriate) prior to any study related procedures or assessments. If a patient is taking prescribed PPI therapy and/or H_2RAs he/she must be able to stop taking these therapies 7 days prior to randomization on Day 1 for PPIs and 3 days prior to randomization on Day 1 for H_2RA.

Section of the protocol affected:

3.1 Overall Study Design, Table 1, page 18

Previous text:

Table 1 Study plan

Assessment/Procedure	**Screening Period (Within 21 days prior to randomization (Visit 1)**	**Day 1 (Dosing and PK Day) (Visit 2)**	**Follow-Up Visit (7-14 days after Day 1) (Visit 3)**
Informed consent/assent	X		
Demographics	X		
Review inclusion/exclusion	X	X	
Full Medical History including surgical history	X		
Complete physical exam	X		X
Vital signs [a]	X	X	X

Concomitant medications	X	X	X
Clinical chemistry, hematology, urinalysis	X		X
Urine pregnancy test [b]		X	
Endoscopic examination [c]	X		
Randomization		X	
Study drug administration [d]		X	
Blood samples for esomeprazole concentration [e]		X	
Meals [f]		X	
Adverse Events		X	X
Serious Adverse Events	X	X	X

a. Blood pressure and pulse will be evaluated in the seated position. Vital signs will also include respiratory rate and either oral, rectal or tympanic temperature evaluations. On Study Day 1 vital signs evaluations will occur prior to dosing.
b. A urine pregnancy test will be required for all post-menarchal females on Day 1 prior to study drug administration.
c. Endoscopy will be performed during the screening period unless the patient has had a prior endoscopy within 42 days prior to enrollment (Visit 1) into the study.
d. Study drug will be administered by CRC personnel.
e. Blood samples (0.8 mL-1mL each) will be collected as follows: pre-dose, 0.5, 1.0. 1.5, 2.0, 3.0, 4.0 and 6 hours post dose.
f. A light low-fat breakfast will be served 1-hour post dose (for patients 1-5) and 2 hours post dose (for patients 6-11) following study drug administration. Lunch will be provided following the 4-hour post dose PK sample collection.

Revised text:

Table 2 Study plan

Assessment/Procedure	**Screening Period (Within 21 days prior to randomization (Visit 1)**	**Day 1 (Dosing and PK Day) (Visit 2)**	**Follow-Up Visit (7-14 days after Day 1) (Visit 3)**
Informed consent/assent	X		
Demographics	X		
Review inclusion/exclusion	X	X	
Full Medical History including surgical history	X		
Complete physical exam	X		X
Vital signs [a]	X	X	X

Concomitant medications	X	X	X
Clinical chemistry, hematology, urinalysis	X		X
Urine pregnancy test [b]		X	
Endoscopic examination [c]	X		
Randomization		X	
Study drug administration [d]		X	
Blood samples for esomeprazole concentration [e]		X	
Meals [f]		X	
Adverse Events		X	X
Serious Adverse Events	X	X	X

a Blood pressure and pulse will be evaluated in the seated position. Vital signs will also include respiratory rate and either oral, rectal or tympanic temperature evaluations. On Study Day 1 vital signs evaluations will occur prior to dosing.

b A urine pregnancy test will be required for all post-menarchal females on Day 1 prior to study drug administration.

c. Endoscopy will be performed during the screening period unless the patient has had a prior endoscopy within 42 days prior to enrollment (Visit 1) into the study. **Patients weighing less than 20 kg may have had a prior endoscopy within 90 days of enrollment (Visit 1).**

d. Study drug will be administered by CRC personnel.

e. Blood samples (0.8 mL-1mL each) will be collected as follows: pre-dose, 0.5, 1.0. 1.5, 2.0, 3.0, 4.0 and 6 hours post dose.

f A light low-fat breakfast will be served 1-hour post dose (for patients 1-5) and 2 hours post dose (for patients 6-11) following study drug administration. Lunch will be provided following the 4-hour post dose PK sample collection.

Section of protocol affected:

3.3.2 Inclusion criteria – Inclusion criteria # 4

Previous text:

The patient's weight for height percentile should be less than the 90th percentile and/or the BMI must be between the 5th and 85th percentile for age.

Revised text:

The patient's weight for height percentile should be less than the 90th percentile **or** the BMI must be between the 5th and **95th** percentile for age.

Section of protocol affected:

3.3.2 Inclusion criteria – Inclusion criteria # 5

Previous text:

Patients may be diagnosed with endoscopically-proven GERD by the investigator during the screening period (Visit 1). In addition patients with a previous (within 42 days of Visit 1) endoscopic diagnosis of GERD induced esophagitis will not be required to have another endoscopy to be enrolled into this study. The diagnosis of esophagitis can be made by the Principal Investigator or may be referred from other endoscopy specialists or centers. Endoscopic evidence will be accepted if there is adequate documentation (ie, complete endoscopic reports, pathology reports or photo documentation). Patients with extra-esophageal and/or atypical symptoms (ie failure to thrive, reactive airway disease, etc.) who are candidates for endoscopy will qualify for inclusion provided they have endoscopic signs of GERD.

Revised text:

Patients may be diagnosed with endoscopically-proven GERD by the investigator during the screening period (Visit 1). In addition patients with a previous (within 42 days of Visit 1) endoscopic diagnosis of GERD induced esophagitis will not be required to have another endoscopy to be enrolled into this study. **Patients weighing less than 20 kg with a previous endoscopy performed within 90 days of Visit 1 are eligible for enrollment**. The diagnosis of esophagitis can be made by the Principal Investigator or may be referred from other endoscopy specialists or centers. Endoscopic evidence will be accepted if there is adequate documentation (ie, complete endoscopic reports, pathology reports or photo documentation). Patients with extra-esophageal and/or atypical symptoms (ie failure to thrive, reactive airway disease, etc.) who are candidates for endoscopy will qualify for inclusion provided they have endoscopic signs of GERD.

Section of protocol affected:

3.3.3 Exclusion criteria – Exclusion criteria # 9

Previous text:

Patients with a history or a current need for resectional or reconstructive surgery of the GI tract (eg, esophagus, stomach, duodenum, jejunum or colon).

Revised text:

Patients with a history or a current need for resectional or reconstructive surgery of the GI tract (eg, esophagus, stomach, duodenum, jejunum or colon) **will be excluded except for those who require surgery for a diagnosis of esophageal atresia (any variant) or pyloric stenosis**.

Section of protocol affected:

4.4.1 Laboratory safety measurements

Previous text:

Urinalysis assessments will include: Specific gravity, pH, protein, glucose, blood, ketones, nitrates, and a microscopic evaluation.

Revised text:

Urinalysis assessments will include: Specific gravity, pH, protein, glucose, blood, ketones, **nitrites**, and a microscopic evaluation.

Section of protocol affected:

5.6 Study timetable and end of study

Previous text:

The study is expected to start in [redacted] and to be completed by [redacted].

Revised text:

The study is expected to start in [redacted] and to be completed by [redacted]

Section of protocol affected:

6.5 Interim analyses

Previous text:

6.5 Interim analyses (Not applicable)

Revised text:

6.5 Interim analyses

An interim analysis will be performed on the patients in the completed Groups (Groups C and D). The analysis will use the methods described in section 6.4.

Reason for Amendment:

Rationale for changes to the eligibility criteria:

Two inclusion and one exclusion criteria have been modified. These include an extension in the period of previous endoscopic diagnosis of GERD from 42 days to 90 days for patients weighing less than 20 kg, an increase in the BMI (Body Mass Index) upper range from the 85th percentile to the 95th percentile and the inclusion of patients with esophageal atresia and pyloric stenosis into the study. These changes are a result of a careful review of the protocol and the feedback received from opinion leaders participating as principal investigators. These changes do not impact the safety or the design of the study

The main reason for implementing the extension of the diagnosis of endoscopically-proven GERD stems from the well-known fact that endoscopically–proven GERD (i.e. reflux induced esophagitis) is extremely infrequent in the pediatric age groups especially children 1-5 years old. Although, this complication of GERD is being increasingly recognized and reported, it's true prevalence is not known due to the lack of sufficiently large studies. There are presently, limited reports in the literature addressing the findings of erosive esophagitis (EE) in children. One such report, available only in abstract form, indicated that (13.3%) of all registered children during the 3-year study period who were endoscoped had EE. The mean age of children with EE was 12.6 (+/-5.6) yrs and EE was found in 9.9% children aged 0-2 years and 6.8% children aged 3-5 years. This report by the Peds Cori (Pediatric Endoscopic Database) Group reflects the low probability of finding endoscopically- proven GERD in young children. This change is specific to the patients who weigh less than 20 kg because the Groups which include patients greater than 20 kg are completed and patients who weigh less than 20 kg usually fall into the 1-5 year age group which as stated above has a low incidence of EE.

In addition to the inherent difficulties in locating young patients with this diagnosis, it has been difficult for the centers to enroll patients into this study due to the protocol weight restrictions. Increasing the BMI upper range up to the 95th percentile may facilitate enrollment from key centers who attend to a population where malnutrition or failure to thrive is uncommon.

Lastly, it is well known that patients with congenital esophageal anomalies, specifically those related to esophageal atresia, are more prone to developing the complications of GERD and therefore these patients should be allowed in the study. The protocol will also allow patients with a past history of pyloric stenosis due to the simple nature of the surgical repair, which will not represent a safety risk to the patient if enrolled in the study.

It is our hope that these changes will facilitate the enrollment in the younger Groups, which have been difficult to recruit in for the entire length of the study.

Rationale for interim analysis:

Since the study has experienced slower than expected recruitment an interim analysis will be performed on the patients in the completed Groups (Groups C and D) to ensure the that the data from these Groups is available according to the timeframe required by the FDA's Written Request.

This amendment also includes two administrative changes, which include the following:

The urinalysis assessment of nitrates was changed to nitrites to be consistent with the actual assessment being performed by the central lab.

The study period and timetable were updated to reflect the timeline extension.

Persons who initiated the Amendment:

The D9614C00007 Study Delivery Team

1. REFERENCES

1 Gilger MA., El-Serag HB., Dietrich CL. The prevalence of erosive esophagitis in children: A population-based study. Gastrointestinal Endoscopy 2004 April;59 (5): AB104.

2 Gilger MA., El-Serag HB., Dietrich CL., Gold BD., Hassall EG. Endoscopic manifestations of erosive esophagitis in children. Gastrointestinal Endoscopy 2004 April;59 (5):AB143.

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

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This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol amendment.

AstraZeneca Research and Development site representative

[redacted]

Date
(Day Month Year)

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[redacted]

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AstraZeneca Research and Development site representativ[redacted]

[redacted]

Date
(Day Month Year)

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SIGNATURE OF PRINCIPAL INVESTIGATOR

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This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review

I agree to the terms of this amendment.

Centre No.:

Signature:

Name: _____ Date (Day Month Year) _____

Title:

Address:

Telephone:

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