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Subject: Proton Pump Inhibitors BPCA Drug Use Review and
Duration of Use Analysis

Drug Name(s): Aciphex® (rabeprazole), Prevacid® (lansoprazole), Nexium®
(esomeprazole), Prilosec® (omeprazole), Protonix®
(pantoprazole), and Kapidex® (dexlansoprazole)

Application
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OSE RCM #: 2010-306

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EXECUTIVE SUMMARY

This review examines drug utilization patterns in the pediatric population (patients aged <1, 1-12, 13-17 years) and adults (18+ years) for proton pump inhibitors. Proton pump inhibitors (PPIs) are indicated for the treatment of gastroesophageal reflux disease (GERD), erosive esophagitis (EE), duodenal ulcers, benign gastric ulcers, and pathological hypersecretory conditions including Zollinger-Ellison syndrome (ZES). Since approximately 69-86% of the proton pump inhibitor market share was sold to U.S. outpatient retail settings, this review focuses on the outpatient setting. Outpatient proprietary drug use databases licensed by FDA were used to examine drug use patterns from years 2002-2009. In addition, to assess off-label use of these products in neonates (birth to 4 weeks), duration of use analysis is provided which includes an unprojected sample of health plan claims data from outpatient retail settings during years 2007-2008.

Summary of Findings:

- The total number of dispensed prescriptions for proton pump inhibitors increased by 28% from approximately 74 million prescriptions in year 2002 to 95 million prescriptions in year 2009.
- Proton pump inhibitor use in the pediatric population increased nearly 3-fold from 940,000 prescriptions (1.3%) in 2002 to 2.6 million prescriptions (2.7%) in year 2009.
- Among pediatric patients less than 1 year old, there were around 404,000 dispensed prescriptions and 145,000 patients (projected number) who filled a prescription for a proton pump inhibitor in year 2009. The proportion of *new patient prescriptions* decreased in this age group for all agents from years 2002 to 2009.
- A subgroup analysis for infants and young children showed that the median age of initiation for pediatric patients less than two years old on proton pump inhibitors was 226 days with a median duration of use of 60 days.
- General Practice, Family Medicine, Doctor of Osteopathy was the top prescribing specialty for proton pump inhibitors.
- “Esophageal Disorder Nec” (ICD-9 530.8) was the top diagnosis code recorded for all age groups for the review period.

BACKGROUND

1.1 INTRODUCTION

The Office of Pediatric Therapeutics (OPT) and Pediatric and Maternal Health Staff (PMHS) have requested a review of the drug utilization patterns and the duration of use for the proton pump inhibitors (PPIs) in preparation for mandatory safety reporting at the June 2010 Pediatric Advisory Committee Meeting and the subsequent proton pump inhibitor science Advisory Committee (AC) Meeting. The drug utilization data are requested to provide background and context for discussions at the advisory committee meetings. The four products with mandatory reporting are Aciphex (rabeprazole), Prevacid (lansoprazole), Nexium (esomeprazole), Prilosec (omeprazole). To better

understand the use of these products in pediatrics, data for Protonix (pantoprazole), and Kapidex (dexlansoprazole) was also requested.

While there are no specific pediatric safety concerns slated for discussion at the AC meetings, there are a number of studies which have shown that there are potential risks associated with PPIs, including gastric cancer, bone fractures, increases in rates of infection, and gastric polyps. Some studies have shown that long term use may be a risk factor in the development of PPI adverse events. However, these studies were conducted primarily in adults and the safety profile of the PPIs may be different in children¹. An FDA Adverse Event Reporting System database (AERS) search conducted for the BPCA review failed to identify previously undescribed pediatric specific signals of concern².

In order to provide contextual background for the AC members, the OPT and PMHS requested data on the utilization of the proton pump inhibitors in the pediatric population (age 0-17 years). OPT and PMHS requested data on indication of use, prescriber specialty, and duration of use within the pediatric population, with a specific request to examine off-label use in patients age birth to 1 year old.

1.2 PRODUCT LABELING

Approved pediatric indications and ages differ among the 6 available PPI products. All are approved for the treatment of gastroesophageal reflux disease (GERD) and erosive esophagitis (EE) in the pediatric population with the exception of rabeprazole which is approved only for GERD. Lansoprazole, esomeprazole and omeprazole are approved for use in patients 1 year of age and older; rabeprazole is approved for patients 12 years of age and older; pantoprazole is approved for patients 5 years of age and older; dexlansoprazole is not approved for use in pediatric patients. The details of pediatric product approvals are given in Table 1.

Table 1. Approved pediatric usage of the available proton pump inhibitors.

Aciphex® (rabeprazole) is a proton pump inhibitor indicated for adolescent patients 12 years of age and above for short term treatment of symptomatic (GERD).
Prevacid® (lansoprazole) is a proton pump inhibitor indicated in pediatric patients for: (1) short-term treatment of symptomatic GERD in 1 to 17 year olds (July 31, 2002); and (2) short-term treatment of (EE) in 1 to 11 year olds (June 17, 2004).
Nexium® (esomeprazole) is a proton pump inhibitor indicated in pediatric patients for: (1) treatment of GERD in pediatric patients 1 year and older; healing of EE in

¹ Francesca Lodato, Francesco Azzaroli, Laura Turco, Natalia Mazzella, Federica Buonfiglioli, Marco Zoli, Giuseppe Mazzella, Adverse effects of proton pump inhibitors, Best Practice & Research Clinical Gastroenterology, Volume 24, Issue 2, Adverse Effects of Gastrointestinal Drugs, April 2010, Pages 193-201, ISSN 1521-6918, DOI: 10.1016/j.bpg.2009.11.004.

² Ann Corken Mackey, RPh, MPH, Safety Evaluator, DPV 1/OSE, review dated 4/18/2010, filed in DAARTS

pediatric patients 1 to 11 years; and (2) short-term treatment (up to 8 weeks) in pediatric patients 1 to 17 years

Prilosec® (omeprazole) is a proton pump inhibitor indicated in pediatric patients for treatment of GERD and maintenance of healing of EE. It is not approved for use in children less than one year of age. The original approval is dated 14 September 1989. Approval of the delayed-release oral suspension, an age-appropriate pediatric formulation is dated 20 March 2008. The sponsor has a study ongoing for the treatment of GERD and EE in pediatric patients ages birth to 1 year. Study reports are due December 31, 2010.

Protonix® (pantoprazole sodium) is a proton pump inhibitor indicated in adults and pediatric patients 5 years and older for the following: short-term treatment of EE associated with GERD.

Kapidx® (dexlansoprazole sodium) is a proton pump inhibitor. Safety and effectiveness has not been established in pediatric patients.

2 REVIEW METHODS AND MATERIALS

2.1 DRUG UTILIZATION

2.1.1 Determining settings of care

The IMS Health, IMS National Sales Perspectives™ (see Appendix 1 for database descriptions) was used to determine the various retail and non-retail channels of distribution for the proton pump inhibitors.³ With the exception of pantoprazole products, the examination of wholesale sales data by Eaches (bottles, packets, etc.) in year 2009 indicates that the majority of proton pump inhibitors were distributed to outpatient pharmacy settings (69% to 86%). Outpatient pharmacy settings include chain, independent, and food stores with pharmacies. Pantoprazole products were primarily distributed to non-retail pharmacy settings (76%), mainly non-federal hospitals. Mail order sales distribution ranged from approximately 4% to 14% of sales for all agents studied. Thus, we examined outpatient utilization patterns. Mail order and non-retail pharmacy settings were not included in this analysis.

2.1.2 Drug Utilization Data Sources

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

Outpatient use and patient demographics (stratified by ages <1, 1-12, 13-17 and 18+ years) were measured from SDI, Vector One®; National (VONA) and Total Patient Tracker (TPT) (*Appendix 1*). Indications for use were obtained from the SDI's Physician's Drug and Diagnosis Audit (PDDA) (*Appendix 1*). From these data sources,

³ IMS Health, IMS Nationals Sales Perspectives™, Year 2009, Data extracted 3-24-10. File: 1003ppis.xls

estimates of the number of dispensed prescriptions, the number of patients who received a prescription for a proton pump inhibitor, and the number of drug mentions by office-based physicians, were obtained from years 2002 through 2009, inclusive. Proton pump inhibitor products were searched by USC code: 23420 and grouped by chemical name.

We analyzed dispensed prescriptions from years 2002 through 2009 to evaluate which of those were being dispensed to new patients, continuing patients, or switch/add-on patients. Prescriptions were classified as *new patient prescriptions* if no prescriptions for a proton pump inhibitor were dispensed to a patient within the previous 6 months. Prescriptions were classified as *continuing patient prescriptions* if a prescription for a proton pump inhibitor was dispensed to a patient in the previous 6 months. Lastly, prescriptions were classified as *switch/add-on patient prescriptions* if a prescription for a different proton pump inhibitor was dispensed to a patient in the previous 6 months; these prescriptions were either added on to a current proton pump inhibitor or switched from one therapy to another.

2.2 DURATION OF USE ANALYSIS

2.2.1 Data source

Data for this analysis were derived from IMS' Health Plan Claims database (PharMetrics). This database consists of paid health plan claims data representing over 95 managed care plans and covering approximately 60 million de-identified patients. The database maintains unique person-level identifiers across all years of data and thus provided the ability to track patients longitudinally. The medical claims are captured from medical encounters in doctor's offices, retail and mail order pharmacies, patient visits to specialists and hospitalizations including diagnoses, ER visits, office visits, home care, diagnostic tests, procedures and injections. The data are not nationally projected; however, it represents approximately 9 percent of the U.S. commercially insured population based on year 2007 U.S. Census.

2.2.2 Subject Age Estimation

The PharMetrics database only contains the year of birth, and the patient's age is estimated by subtracting the service date from the year of birth (fixed as January 1st). However, this method results in estimated ages that may differ from the patient's true age by up to two years. Due to this limitation, we conducted a subgroup analysis of patients with a PharMetrics assigned age of 2 years or less. In this subgroup we generated an estimated birth date by identifying the first occurrence of a diagnosis or procedure code associated with the live birth (Appendix 3) when that diagnosis occurred on the same day as the reported first day of insurance eligibility. The age in days at each PPI drug claim was calculated using PPI date of service minus the determined date of birth for all patients whose first claim date was the same as the first birth associated claim date.

2.2.3 Measures of Exposure

Drug exposure

The PPIs were identified from pharmacy claims data using the NDC (national drug code) coding system. Data for drugs captured through pharmacy claims consist of the NDC code, dispensing date and days supply.

Episodes of therapy

Episodes of therapy for proton pump inhibitors were constructed using days' supply and allowing a gap of $\leq 25\%$ of the prior prescription between prescription dispensing date and the latest ending date. The duration of each episode of therapy for a drug was calculated using two methods.

- Definition 1- Sum of all prescription days supply ignoring overlap days of therapy - Overlaps in the dispensing days were eliminated assuming that leftover supplies from previous prescription were discarded to begin the early refill prescription. Gaps between prescriptions are not included in the episode duration.
- Definition 2- Sum of all prescription days' supply. Overlaps in the dispensing days were summed assuming that the patient continued taking the drug from previous refills as part of the same regimen (e.g., an early refill). Gaps between prescriptions are not included in the episode duration.

Episodes for individual PPI drugs were combined to construct episodes of therapy for each individual drug product as well as for the entire class of PPIs as a whole.

Appendix 4 shows examples to illustrate the methods used for calculating the episode duration.

3 RESULTS

3.1 DRUG UTILIZATION

3.1.1 Proton Pump Inhibitor Market Utilization

Total dispensed prescriptions for proton pump inhibitor products increased by 28% from approximately 74 million prescriptions in year 2002 to 95 million prescriptions in year 2009. In year 2009, omeprazole products accounted for the largest proportion of the total market share at 40 million prescriptions (42%) followed by esomeprazole products with 26 million prescriptions (28%) and lansoprazole products with 15 million prescriptions (16%). Pantoprazole, rabeprazole and dexlansoprazole products accounted for the remainder of the prescription share with a combined 14 million prescriptions (14%). The prescription

share for esomeprazole products doubled from 13 million dispensed prescriptions in year 2002 to 26 million dispensed prescriptions in year 2009. For omeprazole products, there was a decreasing trend in dispensed prescriptions between years 2002-2005, then a rapid increase during the past 4 years (*Appendix 1: Figure 1*); the net increase was 99% between year 2002 and 2009. In contrast, lansoprazole and rabeprazole products decreased by one-third while pantoprazole products declined by 22% in the outpatient setting between years 2002-2009 (*Appendix 1: Table 1*).

3.1.2 Proton Pump Inhibitor Utilization by Patient Age

Proton pump inhibitor use in the pediatric population increased nearly 3-fold in the past 8 years from 940,000 prescriptions (1.3%) in 2002 to 2.6 million prescriptions (2.7%) in 2009. Among the pediatric population, patients in the age 1-12 year group accounted for the largest proportion of prescriptions with approximately 1.4 million prescriptions (54%) compared to 788,000 prescriptions (30%) in the age 13-17 year group in 2009. Pediatric patients in the age 0-1 year group accounted for 404,000 prescriptions (15%) for the same period (*Appendix 2: Table 2 and Figure 2*).

In year 2002, omeprazole products were the most commonly dispensed products for pediatric patients in the age less than 1 year and 1-12 year groups. However, during years 2003 through 2009, market share shifted from omeprazole products to lansoprazole products in both of these age group. By year 2009, lansoprazole products accounted for the majority of total prescription share at 86% and 78%, respectively, for patients aged less than 1 year and patients aged 1-12 years old. Omeprazole products were a distant second with approximately 12% and 14% of prescription share for these respective age groups. For patients aged 13-17 years, lansoprazole was the most commonly dispensed PPI product throughout the time period, followed by omeprazole. By year 2009, lansoprazole and omeprazole accounted for approximately 39% and 34%, respectively, of prescription share in this age group; esomeprazole accounted for approximately 21% of total prescription share. Among adults aged 18 years and older, lansoprazole (31%) was the most commonly dispensed product followed by omeprazole (27%) during year 2002. However, by year 2009, omeprazole held the highest share at 43% followed by esomeprazole at 28% and lansoprazole at 15% (*Appendix 2: Table 2*).

Trends for patient data were similar to that of dispensed prescription data. In the pediatric population, patients in the age 1-12 year group accounted for the largest proportion of patients with approximately 461,000 patients (51%) compared to 314,000 patients (35%) for patients in the age 13-17 year group in 2009. Pediatric patients in the age 0-1 year group accounted for 145,000 patients (16%) for the same period. Compared to dispensed prescription data, analysis of patient-level data by pediatric sub-age groups revealed slight differences in product use trends. For patients aged less than 1 and 1-12 years, product use trends by patient counts were similar to dispensed prescription data. For patients aged 13-17 years, more patients received lansoprazole among all the PPI products from years 2002 – 2008; by year 2009, more patients received omeprazole among all the PPI products. Among adults aged 18 years and older, patients receiving lansoprazole (35%) accounted for the largest share of PPI use followed by omeprazole

(26%) during year 2002. However, by year 2009, patients receiving omeprazole held the highest share at 46% followed by esomeprazole at 28% and pantoprazole at 18% (*Appendix 2: Table 3 and Figure 3*).

3.1.3 Proton Pump Inhibitor Utilization by Prescribing Specialty

For the entire review period, General Practice, Family Medicine, Doctor of Osteopathy (GP/FM/DO) was the top prescribing specialty for proton pump inhibitors with 32-35% of dispensed prescriptions. Internal Medicine was the second most common prescribing specialty with approximately 28-29% of dispensed prescriptions, for the same period. The total number of dispensed prescriptions from Pediatricians increased each year for the review period and accounted for 1-3% of the prescription share. Prescription dispensing by each specialists generally increased for all over the time period, except for Pulmonary Diseases specialists (*Appendix 2: Table 4*).

3.1.4 Diagnosis Associated With the Use of Proton Pump Inhibitors

According to office-based physician practices in the U.S., “Esophageal Disorder Nec” (ICD-9 530.8)⁴ was the top diagnosis code recorded for all age groups for the review period. “Abdominal Pain” (ICD-9 789.0) and “Gastritis/Duodenitis Nos” (ICD-9 535.5) were the second and third most common diagnosis codes recorded for all age groups except in patients less than 1 year old. All other diagnosis codes recorded in pediatric age groups were below the acceptable count allowable to provide a reliable estimate of national use (*Appendix 2: Table 5*).

3.1.5 New, Continuing, Switch/Add-On Patient Rx

We also analyzed dispensed prescriptions from years 2005 through 2009 to evaluate which of those were being dispensed to new patients, continuing patients, or switch/add-on patients. Prescriptions were classified as *new patient prescriptions* if no prescriptions for proton pump inhibitors were dispensed to a patient within the previous 6 months. Prescriptions were classified as *continuing patient prescriptions* if a prescription for a proton pump inhibitor was dispensed to a patient in the previous 6 months. Lastly, prescriptions were classified as *switch/add-on patient prescriptions* if a different prescription for a proton pump inhibitor was dispensed to a patient in the previous 6 months; these prescriptions were either added on to current therapy or switched from one therapy to another (*Appendix 2: Table 6*).

Over the five year period from year 2005 through 2009, the proportion of *new patient prescriptions* for proton pump inhibitors in the age 0-1 year group generally decreased for all agents. Despite relatively small new prescription totals, rabeprazole accounted for the highest proportion of *new patient prescriptions* throughout the study period in this

⁴ ICD-9 530.8 Esophageal Disorder contains the following sub-diagnoses: Esophageal reflux (530.81), esophageal hemorrhage (530.82), esophageal leukoplakia (530.83), trachesophageal fistula (530.84), Barrett’s esophagus (530.85), infection of esophagostomy (530.86), mechanical complication of esophagostomy (530.87), and other diseases of esophagus (530.89)

age group, ranging from nearly 50% to 65% of new patient prescriptions. Omeprazole and esomeprazole accounted for the lowest share of *new patient prescriptions*, ranging from approximately 17-27% and 16-35%, respectively. *Continuing patient prescriptions* accounted for nearly 50% of new prescriptions for all products except for rabeprazole (30%) in this age group. Esomeprazole accounted for a slightly higher proportion of *switch/add-on patient prescriptions*, ranging from 34-44% compared to lansoprazole and omeprazole with 22-30% for the review period.

Among the age 1-12 year group, the proportion of *new patient prescriptions* for proton pump inhibitors increased for omeprazole and esomeprazole and generally decreased for the all other agents. Despite relatively small new prescription totals, dexlansoprazole and rabeprazole accounted for a slightly higher proportion of *new patient prescriptions* throughout the study period in this age group, ranging from nearly 40% to 46% for rabeprazole and 39% for dexlansoprazole of *new patient prescriptions*. Omeprazole accounted for roughly 29-44% of *new patient prescriptions* and esomeprazole accounted for roughly a third of *new patient prescriptions*. *Continuing patient prescriptions* accounted for nearly 40-57% of new prescriptions for all products except for dexlansoprazole (23%) in this age group. *Switch/add-on patient prescriptions* accounted for approximately 10-23% for all agents except for dexlansoprazole (37%).

Among the age 13-17 year group, the proportion of *new patient prescriptions* for proton pump inhibitors increased for omeprazole and slightly decreased for the all other agents. Omeprazole accounted for the highest proportion of *new patient prescriptions* throughout the study period in this age group, ranging from 48% to 54% of *new patient prescriptions*. *Continuing patient prescriptions* accounted for 35% to 45% of new prescriptions for all products except for dexlansoprazole (23%) in this age group. *Switch/add-on patient prescriptions* accounted for approximately 8-20% for all agents except for dexlansoprazole (31%).

3.2 DURATION OF USE ANALYSIS

3.2.1 Study population

The study sample consisted of patients newly initiated on PPI therapy from January 2007 through December 31, 2008. Follow-up time for eligible patients began on their first PPI prescription date (i.e., index date) until the end of the study period (December 31, 2008), or the end of continuous enrollment.

Patients who had a claim for at least one PPI prescription from 2007-2008 were identified. Patients were included in the study if they met the following inclusion criteria:

1. Had a PPI prescription claim from January 1, 2007, through December 31, 2008, with the date of the first PPI prescription fill in this period defined as the index date
2. Did not have any PPI prescription claim in the 180 days prior to the index date ("new starters")

3. Were continuously enrolled at least 365 days prior to the index date
4. Had a minimum of 180 days of continuous enrollment after the index date

3.2.2 Study Results

We identified 1,273,171 new starters of PPI therapy. The median age was 53 years (range 0-109 years old) and the mean was 51.3 years (SD 16.9). The percentage of females in the sample was 57.7%. Patient demographic characteristics of the study population are presented in Table 3.2-1.

Table 3.2-1. Characteristics of patients who are new starters of proton pump inhibitor therapy, IMS' Health Plan Claims database (PharMetrics), 2007-2008

Characteristics	N (1,273,171)	%
Age (years)		
0-<1	638	0.1
1-12	32,467	2.6
13-17	24,380	1.9
18+	1,215,686	95.5
Gender		
Male	538,134	42.3
Female	734,913	57.7
Unknown	124	0.0

Drug duration of use

The mean number of episodes of PPI therapy per patient ranged from 1.7 among those under 1 year of age to 2.2 for patients age 18 years and older. When prescription overlaps are ignored (Definition 1) the median duration of each episode using definition 1 was 30 days for each age category (means from 47.7 for ages 1-12 years and 69.1 for ages 18+). When prescription overlaps are not ignored (definition 2), the median episode length was again 30 days for all age groups. The means ranged from 47.2 days among 12-17 year olds, to 74.9 days for those 18 years of age and older.

Table 3.2-2 Number of episodes per patient and episode length (duration) for all proton pump inhibitors combined

Age category (years)	Episodes per patient		Episode duration length (days) definition 1		Episode duration length (days) definition 2	
	Mean	Median	Mean	Median	Mean	Median
<1	1.7	1	54.4	30	58.4	30
1-12	1.9	1	47.7	30	50.7	30
13-17	1.9	1	44.3	30	47.2	30
18+	2.2	2	69.1	30	74.9	30

Episode Duration definition:
1. Period of overlap not included
2. Period of overlap included

The median total duration of therapy (the sum of all episodes for each patient) under definition 1 (Table 3.2-3) was 60 days for patients in the 0-1 year age group (mean 85.3 days), 42 days for patients 1-12 years old (mean 84.5 days), 30 days for patients age 13-17 years (mean 76.9 days), and 89 days for patients age 18 years and older (mean 145.9 days). Using definition 2, the median duration was 60 days for patients in the 0-1 age group (mean 91.6), 56 days for the 1-12 year old group (mean 89.9), 30 days for the 13-17 year old group (mean 82.0) and 90 days for patients age 18 and older (mean 158.1 days).

Table 3.2-3 Total duration of therapy for all proton pump inhibitors combined

Age (in years)	Total days of Therapy Definition 1		Total days of therapy Definition 2	
	Mean	Median	Mean	Median
<1	85.3	60	91.6	60
1-12	84.5	42	89.9	56
13-17	76.9	30	82.0	30
18+	145.9	89	158.1	90

Episode Duration of therapy definition:

1. Period of overlap not included
2. Period of overlap included

When episodes of PPI therapy were stratified by PPI drug, the mean number of episodes (Table 3.2-4) were similar among the PPI products ranging from 2.1 for pantoprazole to 2.3 for esomeprazole, lansoprazole, and rabeprazole. The median number of episodes per patient was 2 for all drugs in this analysis. The median length of each episode using definition 1 was 30 days for all the drug products, while the means ranged from 64.4 days for lansoprazole to 70.3 for rabeprazole. Under definition 2, the median episode duration was 30 days for all drugs. The means ranged from 70.1 for lansoprazole to 77.6 for rabeprazole.

Table 3.2-4. Number of episodes per patient and episode length by proton pump inhibitor

	Episodes per patient		Episode Duration (days) Definition 1		Episode duration (days) Definition 2	
	Mean	Median	Mean	Median	Mean	Median
Esomeprazole	2.3	2	71.7	30	78.8	30

Lansoprazole	2.2	2	64.4	30	70.1	30
Omeprazole	2.2	2	66.2	30	70.7	30
Pantoprazole	2.1	2	69.8	30	76.6	30
Rabeprazole	2.3	2	70.3	30	77.6	30

Episode Duration definition:

1. Period of overlap not included
2. Period of overlap included

The total patient duration (length) of use for each proton pump inhibitor (Table 3.2-5) using definition 1 ranged from a median of 60 days for lansoprazole (mean 133.2 days) to 90 days for esomeprazole and rabeprazole (means 156.2 and 159.5 respectively). For definition 2, the median duration ranged from 75 days for lansoprazole (mean 145.0 days) to 90 days for esomeprazole, pantoprazole and rabeprazole (means of 171.6, 152.4, 176.0, respectively)

Table 3.2-5 Total duration of use of proton pump inhibitors, by generic drug name

	Total days of Therapy Definition 1		Total days of therapy Definition 2	
	Mean	Median	Mean	Median
esomeprazole	156.2	90	171.6	90
lansoprazole	133.2	60	145.0	75
omeprazole	135.8	74	145.0	88
pantoprazole	140.7	86	152.4	90
rabeprazole	159.5	90	176.0	90

Episode Duration definition:

1. Period of overlap not included
2. Period of overlap included

Subgroup Analysis on Children Under 2 Years Old

The results of the subgroup analysis on children less than 2 years old are presented in table 3.2-6. For patients with an IMS assigned age of birth through 1 year of age, 1,384 (32.9 %) had birth codes which allowed us to estimate the date of birth.

Table 3.2-6 Patient characteristics for children less than 2 years old on proton pump inhibitors included and excluded from duration of use subgroup analysis.

Characteristics	N		N	
	Included	%	Excluded	%

	(n=1384)		(n=2824)	
IMS assigned Age (years)				
Median	1		1	
Mean	0.5		0.9	
Derived age at initiation (median days)	226			
Sex				
Male	816	59.0	1246	59.7
Female	568	41.0	841	40.3
Unknown	0	0	2	0.1

Children less than 2 years old for whom we were able to estimate a birth date (hereafter called included patients) had an average of 1.7 episodes each with a median number of episodes of 1 while patients without definable birth codes had a mean of 2.4 and a median of 2 episodes (Table 3.2-7). Under definition 1, included patients had a median episode length of 30 days (mean 55.4). Excluded patients had a median of 30 days (mean 60.7). Under definition 2, the median episode duration was 30 for both the included and excluded patients (means of 59.6 and 64.9, respectively).

Table 3.2-7 Number of therapy episodes per child and episode length for all proton pump inhibitors combined

	Episodes per patient		Episode Duration (days) Definition 1		Episode duration (days) Definition 2	
	Mean	Median	Mean	Median	Mean	Median
Included patients	1.7	1	55.4	30	59.6	30
Excluded patients	2.4	2	60.7	30	64.9	30
Episode Duration definition:						
1. Period of overlap not included						
2. Period of overlap included						

Table 3.2-8 shows the median duration of PPI use for the included patients to be 60 days under definition 1 and 2 (means 88.9 and 95.8, respectively). For excluded patients, the median duration for definition 1 was 66 days (mean 128.2); under definition 2 the median was 137.1 days (median 78 days).

Table 3.2-8 Total duration of use of for children less than 2 years old on proton pump inhibitors included and excluded from the subgroup analysis

	Total days of Therapy Definition 1		Total days of therapy Definition 2	
	Mean	Median	Mean	Median
Included	88.9	60	95.8	60
Excluded	128.2	66	137.1	78

Episode Duration definition:

1. Period of overlap not included
2. Period of overlap included

4 DISCUSSION

4.1 DRUG UTILIZATION PATTERNS

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that proton pump inhibitors are distributed primarily to the inpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these non-federal hospital channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Indications for use were obtained using SDI's PDDA, a monthly survey of 3,100 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

4.2 DURATION OF USE

In general, we found that the PPIs were used less often and for shorter durations in patients under age 18, when compared to adults. This is as expected given the approved labeling in children is for diagnoses in which relatively short term use would be the norm. In our subset of patients for which we were able to derive an estimated birth date, we found that the use in neonates (birth to 30 days) was rare, with only one identified

patient. The majority of use in the under 2 year old population occurred after 6 months of age.

Given that the PPI drugs may be used for patients on an as needed basis, we expected that a duration of use definition that allowed for early and late refills would be more appropriate (i.e. definition 2). However, we found that under definition 2, the durations of use were not substantially longer than for duration 1.

The analysis of the duration of use by patient age was complicated due to the IMS method of reporting patient age. Our method of identifying newborns/infants using billing codes associated with birth allowed us to examine use within a subset of the newborns/infants in the dataset. However, we were only able to assign a birth date to roughly one third of patients with an IMS assigned age of 0-2 years of age.

5 CONCLUSIONS

In the outpatient retail pharmacy setting, proton pump inhibitor use in the pediatric population has increased over the past 8 years. However, the proportion of new patient prescriptions in the 0-1 year age group decreased between years 2005 and 2009 for all proton pump inhibitors.

Overall, patients receiving proton pump inhibitors stay on therapy for a median of roughly 180 days. The duration of use increases with patient age. In our study, infants were placed on proton pump inhibitor therapy at a median of 9 months of age and received therapy for roughly 90 days. The duration of use does not differ greatly between products, although omeprazole and lansoprazole had slightly shorter durations of use when compared to the other products in this analysis.

6 RECOMMENDATIONS

Given the apparent low levels of off label use of these products in patients under 1 year of age and the inability to precisely estimate the use in this population, we have no recommendation for safety related changes to the product labeling at this time.

7 APPENDICES

7.1 APPENDIX 1: DATABASE DESCRIPTIONS

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

SDI's Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then

projected nationally by physician specialty and region to reflect national prescribing patterns.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

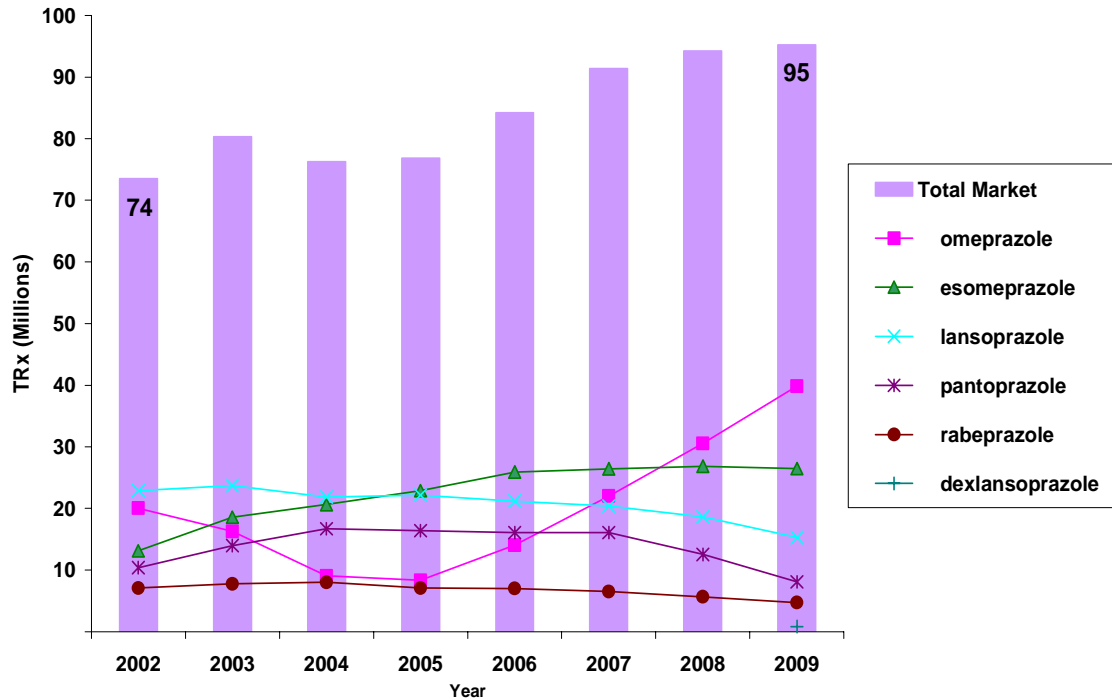
The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS LifeLink™ Health Plan Claims Database

The IMS Health Plan Claims Database is a health plan claims database representing approximately 101 managed care plans and covering approximately 65.8 million de-identified patients. The medical claims are captured from doctor's offices, retail and mail order pharmacies, patient visits to specialists and hospitalizations including diagnoses, ER visits, office visits, home care, diagnostic tests, procedures and injections. The data are not nationally projected, however, it represents approximately 9 percent of the U.S. commercially insured population based on year 2007 U.S. Census.

7.2 APPENDIX 2: DRUG UTILIZATION DATA

Figure 1. Total number of dispensed prescriptions for proton pump inhibitors in U.S. outpatient retail pharmacies, 2002-2009



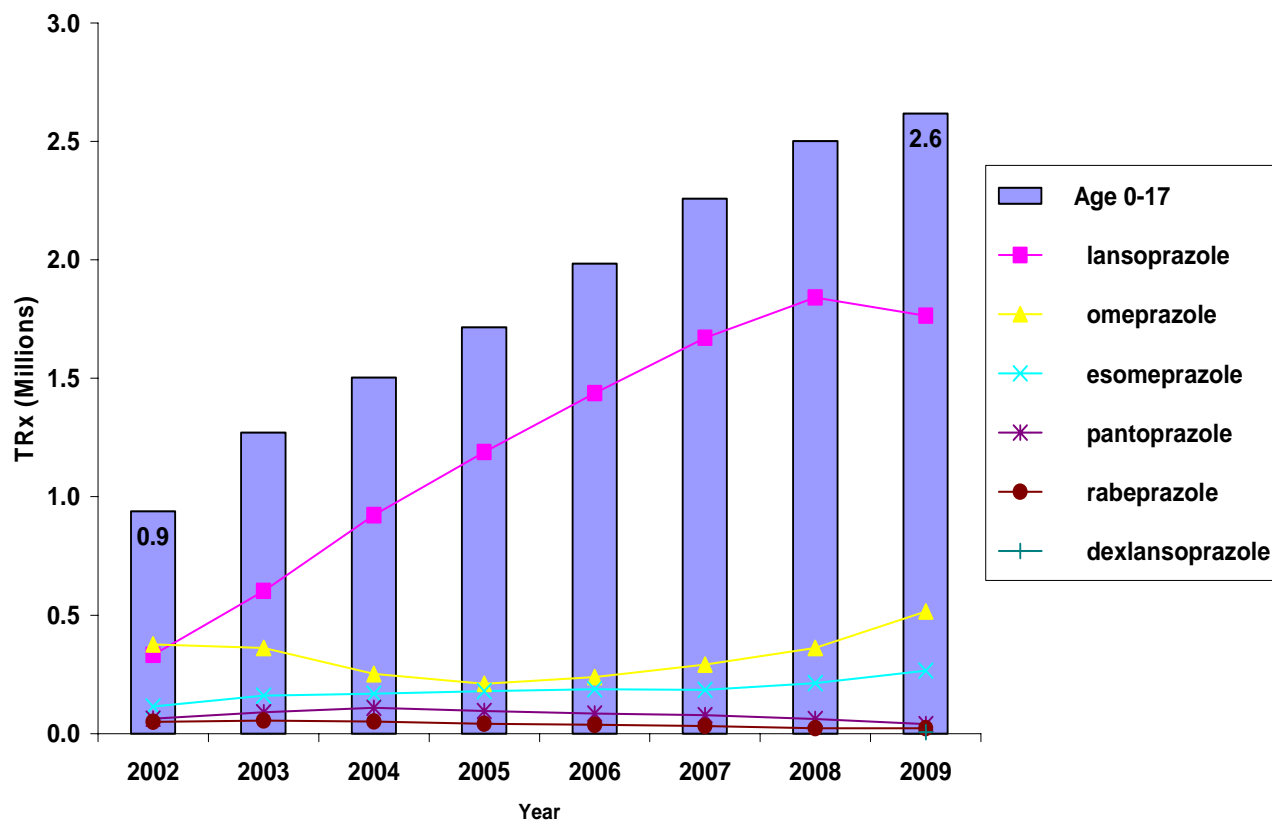
Source: SDI Vector One®: National, Data Extracted March 2010

Table 1. Total number of dispensed prescriptions for proton pump inhibitor market in U.S. outpatient retail pharmacies, 2002-2009

	2002		2003		2004		2005		2006		2007		2008		2009	
	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %
Total Market	73,526,613	100.0%	80,303,067	100.0%	76,264,668	100.0%	76,863,116	100.0%	84,226,100	100.0%	91,411,552	100.0%	94,248,217	100.0%	95,210,165	100.0%
omeprazole	20,061,106	27.3%	16,288,950	20.3%	9,058,343	11.9%	8,343,720	10.9%	14,047,096	16.7%	22,014,656	24.1%	30,562,537	32.4%	39,844,084	41.8%
esomeprazole	13,123,981	17.8%	18,552,274	23.1%	20,649,888	27.1%	22,883,314	29.8%	25,917,256	30.8%	26,425,420	28.9%	26,855,862	28.5%	26,463,830	27.8%
lansoprazole	22,874,805	31.1%	23,701,752	29.5%	21,842,220	28.6%	22,152,419	28.8%	21,180,277	25.1%	20,397,320	22.3%	18,642,948	19.8%	15,298,002	16.1%
pantoprazole	10,381,124	14.1%	13,983,363	17.4%	16,710,386	21.9%	16,402,444	21.3%	16,089,288	19.1%	16,066,286	17.6%	12,512,118	13.3%	8,072,428	8.5%
rabeprazole	7,085,597	9.6%	7,776,728	9.7%	8,003,831	10.5%	7,081,219	9.2%	6,992,183	8.3%	6,507,870	7.1%	5,674,752	6.0%	4,719,455	5.0%
dexlansoprazole	--	--	--	--	--	--	--	--	--	--	--	--	--	--	812,367	0.9%
															13,604,250	14.3%

Source: SDI Vector One®: National, Data Extracted March 2010. File: VONA 2010-306 PPIs TRx by age_form 03-12-10.xls

Figure 2. Total number of dispensed prescriptions for proton pump inhibitors by patient age 0-17 years in U.S. outpatient retail pharmacies, 2002-2009



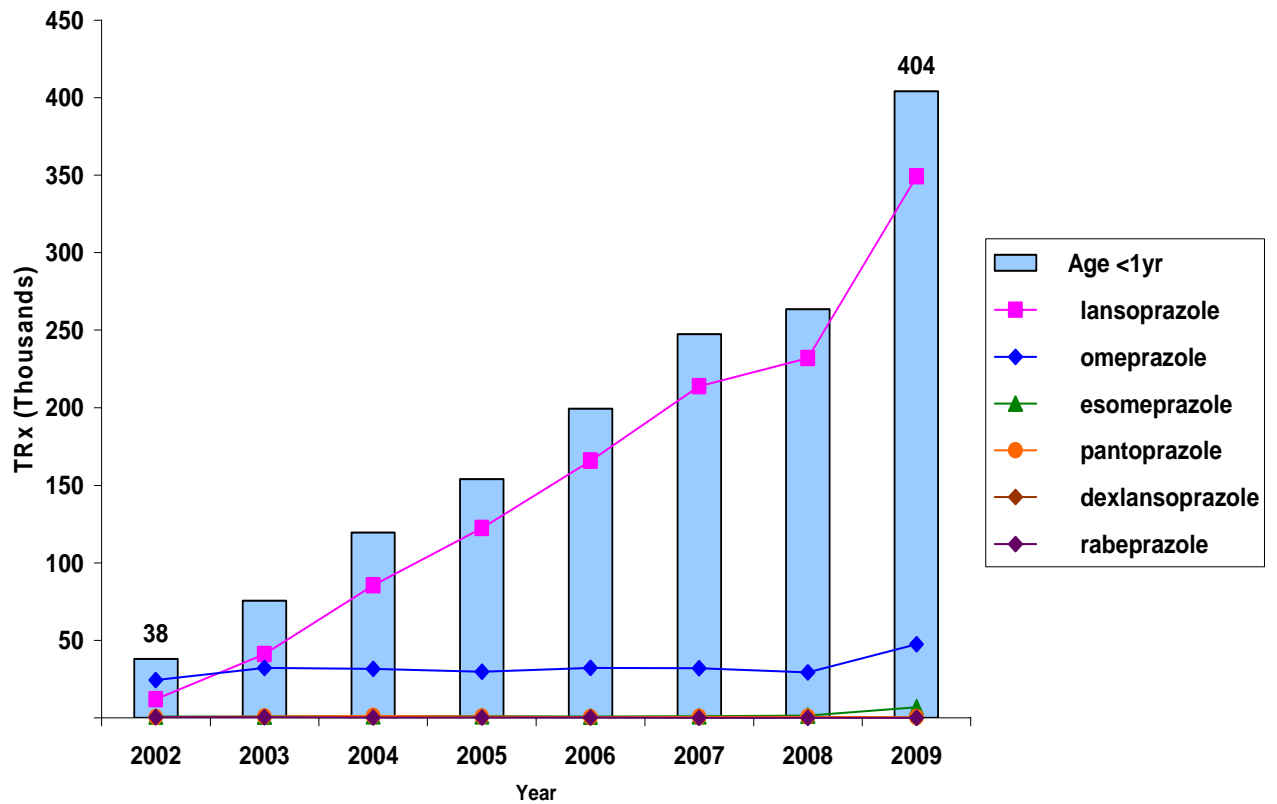
Source: SDI Vector One®: National, Data Extracted April 2010.

Table 2. Total number of dispensed prescriptions for proton pump inhibitor market by patient age (<1, 1-12, 13-17, 18+) in U.S. outpatient retail pharmacies, 2002-2009

	2002		2003		2004		2005		2006		2007		2008		2009	
	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %
Total Market	73,527,457	100.0%	80,303,284	100.0%	76,264,587	100.0%	76,863,011	100.0%	84,226,121	100.0%	91,411,518	100.0%	94,248,041	100.0%	95,210,165	100.0%
Age 0-17 yrs	938,937	1.3%	1,270,415	1.6%	1,503,430	2.0%	1,715,298	2.2%	1,715,298	2.0%	2,258,138	2.5%	2,501,853	2.7%	2,616,887	2.7%
<1 yr	38,034	4.1%	75,466	5.9%	119,461	7.9%	154,015	9.0%	199,449	11.6%	247,402	11.0%	263,694	10.5%	404,067	15.4%
lansoprazole	12,025	31.6%	41,175	54.6%	85,516	71.6%	122,394	79.5%	165,815	83.1%	213,778	86.4%	232,111	88.0%	349,282	86.4%
omeprazole	24,379	64.1%	32,266	42.8%	31,627	26.5%	29,683	19.3%	32,252	16.2%	31,933	12.9%	29,405	11.2%	47,470	11.7%
esomeprazole	788	2.1%	866	1.1%	1,001	0.8%	990	0.6%	809	0.4%	906	0.4%	1,511	0.6%	6,669	1.7%
pantoprazole	544	1.4%	796	1.1%	1,119	0.9%	834	0.5%	475	0.2%	725	0.3%	593	0.2%	558	0.1%
dexlansoprazole	--	--	--	--	--	--	--	--	--	--	--	--	--	--	55	0.0%
rabeprazole	298	0.8%	363	0.5%	198	0.2%	114	0.1%	98	0.0%	60	0.0%	74	0.0%	33	0.0%
1-12 yrs	465,379	49.6%	659,179	51.9%	822,822	54.7%	964,652	56.2%	1,151,625	67.1%	1,326,706	58.8%	1,497,347	59.8%	1,424,784	54.4%
lansoprazole	173,035	37.2%	350,577	53.2%	572,637	69.6%	753,969	78.2%	941,691	81.8%	1,106,437	83.4%	1,245,200	83.2%	1,104,139	77.5%
omeprazole	223,294	48.0%	212,139	32.2%	149,238	18.1%	117,912	12.2%	123,852	10.8%	138,297	10.4%	160,654	10.7%	204,523	14.4%
esomeprazole	38,817	8.3%	55,520	8.4%	58,106	7.1%	59,552	6.2%	58,075	5.0%	56,683	4.3%	71,429	4.8%	97,499	6.8%
pantoprazole	15,944	3.4%	24,847	3.8%	29,413	3.6%	23,642	2.5%	19,172	1.7%	18,442	1.4%	15,412	1.0%	12,530	0.9%
rabeprazole	14,289	3.1%	16,096	2.4%	13,428	1.6%	9,577	1.0%	8,835	0.8%	6,847	0.5%	4,652	0.3%	4,954	0.3%
dexlansoprazole	--	--	--	--	--	--	--	--	--	--	--	--	--	--	1,139	0.1%
13-17 yrs	435,524	46.4%	535,770	42.2%	561,147	37.3%	596,631	34.8%	633,571	36.9%	684,030	30.3%	740,812	29.6%	788,036	30.1%
lansoprazole	147,534	33.9%	210,708	39.3%	263,438	46.9%	312,431	52.4%	329,124	51.9%	350,427	51.2%	363,380	49.1%	310,666	39.4%
omeprazole	129,258	29.7%	117,807	22.0%	70,940	12.6%	62,495	10.5%	82,475	13.0%	121,711	17.8%	171,921	23.2%	264,259	33.5%
esomeprazole	75,502	17.3%	104,130	19.4%	109,290	19.5%	119,242	20.0%	128,634	20.3%	127,791	18.7%	140,897	19.0%	161,927	20.5%
pantoprazole	46,996	10.8%	64,171	12.0%	79,274	14.1%	70,805	11.9%	64,848	10.2%	58,878	8.6%	46,110	6.2%	27,893	3.5%
rabeprazole	36,234	8.3%	38,954	7.3%	38,205	6.8%	31,658	5.3%	28,490	4.5%	25,223	3.7%	18,504	2.5%	18,138	2.3%
dexlansoprazole	--	--	--	--	--	--	--	--	--	--	--	--	--	--	5,152	0.7%
Age 18+ yrs	72,314,489	98.4%	78,730,056	98.0%	74,148,758	97.2%	74,497,066	96.9%	81,977,187	97.3%	88,971,558	97.3%	91,583,706	97.2%	92,433,829	97.1%
omeprazole	19,598,073	27.1%	15,857,302	20.1%	8,733,823	11.8%	8,081,838	10.8%	13,783,718	16.8%	21,688,606	24.4%	30,155,571	32.9%	39,282,389	42.5%
esomeprazole	12,972,453	17.9%	18,335,866	23.3%	20,328,123	27.4%	22,480,137	30.2%	25,643,136	31.3%	26,194,368	29.4%	26,600,379	29.0%	26,158,267	28.3%
lansoprazole	22,449,188	31.0%	23,003,940	29.2%	20,712,731	27.9%	20,704,369	27.8%	19,647,687	24.0%	18,669,921	21.0%	16,755,670	18.3%	13,473,662	14.6%
pantoprazole	10,277,012	14.2%	13,831,681	17.6%	16,462,044	22.2%	16,211,979	21.8%	15,956,862	19.5%	15,950,211	17.9%	12,425,537	13.6%	8,021,987	8.7%
rabeprazole	7,017,763	9.7%	7,701,267	9.8%	7,912,037	10.7%	7,018,743	9.4%	6,945,784	8.5%	6,468,452	7.3%	5,646,549	6.2%	4,691,954	5.1%
dexlansoprazole	--	--	--	--	--	--	--	--	--	--	--	--	--	--	805,570	0.9%
Unknown Age	274,031	0.4%	302,813	0.4%	612,399	0.8%	650,647	0.8%	264,289	0.3%	181,822	0.2%	162,482	0.2%	159,450	0.2%
lansoprazole	93,358	34.1%	95,487	31.5%	207,906	33.9%	259,215	39.8%	95,940	36.3%	56,734	31.2%	46,533	28.6%	60,254	37.8%
omeprazole	86,317	31.5%	69,452	22.9%	72,664	11.9%	51,764	8.0%	24,851	9.4%	34,162	18.8%	44,978	27.7%	45,443	28.5%
esomeprazole	36,536	13.3%	55,929	18.5%	153,311	25.0%	223,394	34.3%	86,601	32.8%	45,600	25.1%	41,567	25.6%	39,468	24.8%
pantoprazole	40,767	14.9%	61,906	20.4%	138,529	22.6%	95,155	14.6%	47,905	18.1%	38,021	20.9%	24,402	15.0%	9,460	5.9%
rabeprazole	17,053	6.2%	20,039	6.6%	39,989	6.5%	21,119	3.2%	8,992	3.4%	7,305	4.0%	5,002	3.1%	4,375	2.7%
dexlansoprazole	--	--	--	--	--	--	--	--	--	--	--	--	--	--	450	0.3%

Source: SDI Vector One®: National, Data Extracted March 2010. File: VONA 2010-306 PPIs TRx by age_form 03-12-10.xls

Figure 3. Total number of dispensed prescriptions for proton pump inhibitors by patient age 0-1 year in U.S. outpatient retail pharmacies, 2002-2009



Source: SDI Vector One®: National, Data Extracted March 2010.

Table 3. Total number of projected patients (ages <1, 1-12, 13-17, 18+) who filled a prescription for proton pump inhibitor market in U.S. outpatient retail pharmacies, 2002-2009

	2002		2003		2004		2005		2006		2007		2008		2009	
	Patient	Share	Patient	Share	Patient	Share	Patient	Share	Patient	Share	Patient	Share	Patient	Share	Patient	Share
	Count		Count		Count		Count		Count		Count		Count		Count	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Grand Total	16,906,196	100.0%	18,929,081	100.0%	17,144,202	100.0%	16,920,143	100.0%	18,476,807	100.0%	19,246,489	100.0%	20,850,574	100.0%	20,862,596	100.0%
Age 0-17 yrs	356,838	2.1%	509,569	2.7%	603,618	3.5%	657,651	3.9%	717,886	3.9%	798,958	4.2%	888,230	4.3%	907,386	4.3%
<1 yr	18,212	5.1%	38,202	7.5%	56,818	9.4%	75,235	11.4%	94,190	13.1%	115,614	14.5%	118,576	13.3%	145,289	16.0%
lansoprazole	6,413	35.2%	22,698	59.4%	42,660	75.1%	62,014	82.4%	80,971	86.0%	102,623	88.8%	106,565	89.9%	128,676	88.6%
omeprazole	11,257	61.8%	15,313	40.1%	13,868	24.4%	13,349	17.7%	14,285	15.2%	14,388	12.4%	13,073	11.0%	17,579	12.1%
esomeprazole	505	2.8%	773	2.0%	858	1.5%	836	1.1%	555	0.6%	551	0.5%	920	0.8%	2,991	2.1%
pantoprazole	407	2.2%	603	1.6%	934	1.6%	906	1.2%	330	0.4%	401	0.3%	375	0.3%	415	0.3%
rabeprazole	209	1.1%	266	0.7%	180	0.3%	109	0.1%	91	0.1%	41	0.0%	55	0.0%	35	0.0%
dexlansoprazole														28	0.0%	
1-12 yrs	163,625	45.9%	251,234	49.3%	311,657	51.6%	348,920	53.1%	397,828	55.4%	449,662	56.3%	515,873	58.1%	461,068	50.8%
lansoprazole	71,354	43.6%	154,218	61.4%	240,265	77.1%	290,452	83.2%	336,976	84.7%	383,651	85.3%	435,551	84.4%	354,485	76.9%
omeprazole	73,778	45.1%	73,262	29.2%	47,787	15.3%	37,632	10.8%	42,784	10.8%	50,819	11.3%	63,185	12.2%	83,772	18.2%
esomeprazole	15,916	9.7%	21,084	8.4%	20,669	6.6%	20,802	6.0%	19,726	5.0%	19,489	4.3%	25,245	4.9%	34,560	7.5%
pantoprazole	7,683	4.7%	11,455	4.6%	13,174	4.2%	9,216	2.6%	7,480	1.9%	6,735	1.5%	6,798	1.3%	5,872	1.3%
rabeprazole	6,395	3.9%	7,802	3.1%	5,594	1.8%	3,999	1.1%	3,657	0.9%	2,823	0.6%	1,947	0.4%	2,119	0.5%
dexlansoprazole														590	0.1%	
13-17 yrs	184,388	51.7%	236,373	46.4%	260,069	43.1%	264,438	40.2%	261,239	36.4%	276,296	34.6%	298,263	33.6%	314,180	34.6%
omeprazole	53,456	29.0%	51,095	21.6%	31,556	12.1%	26,900	10.2%	38,857	14.9%	59,727	21.6%	83,242	27.9%	126,643	40.3%
lansoprazole	71,118	38.6%	107,070	45.3%	136,970	52.7%	151,634	57.3%	140,745	53.9%	143,492	51.9%	146,049	49.0%	111,911	35.6%
esomeprazole	34,185	18.5%	46,058	19.5%	48,210	18.5%	55,355	20.9%	55,841	21.4%	55,216	20.0%	55,460	18.6%	65,699	20.9%
pantoprazole	24,112	13.1%	33,460	14.2%	44,774	17.2%	33,223		28,966	11.1%	25,084	9.1%	25,521	8.6%	21,857	7.0%
rabeprazole	17,930	9.7%	19,431	8.2%	18,145	7.0%	14,499	5.5%	13,596	5.2%	11,106	4.0%	7,939	2.7%	7,939	2.5%
dexlansoprazole														2,881	0.9%	
Age 18+ yrs	16,530,097	97.8%	18,334,223	96.9%	16,369,128	95.5%	16,095,266	95.1%	17,675,259	95.7%	18,391,173	95.6%	19,896,701	95.4%	19,645,298	94.2%
omeprazole	4,310,371	26.1%	3,794,674	20.7%	2,050,103	12.5%	1,912,043	11.9%	3,589,613	20.3%	5,396,964	29.3%	7,423,800	37.3%	9,017,224	45.9%
esomeprazole	3,761,730	22.8%	4,872,260	26.6%	4,869,165	29.7%	5,127,003	31.9%	5,945,273	33.6%	5,820,136	31.6%	5,874,928	29.5%	5,489,433	27.9%
pantoprazole	3,177,727	19.2%	4,159,037	22.7%	4,427,807	27.0%	4,175,517	25.9%	4,136,386	23.4%	3,853,547	21.0%	3,995,550	20.1%	3,491,040	17.8%
lansoprazole	5,846,770	35.4%	6,061,945	33.1%	5,033,927	30.8%	4,997,907	31.1%	4,657,197	26.3%	4,141,788	22.5%	3,742,572	18.8%	2,768,547	14.1%
rabeprazole	1,965,410	11.9%	2,172,796	11.9%	2,033,205	12.4%	1,758,495	10.9%	1,781,263	10.1%	1,521,111	8.3%	1,296,081	6.5%	1,060,965	5.4%
dexlansoprazole														311,549	1.6%	
Unknown Age	127,442	0.8%	309,802	1.6%	501,898	2.9%	511,489	3.0%	373,204	2.0%	363,883	1.9%	393,946	1.9%	987,627	4.7%
omeprazole	29,991	23.5%	55,967	18.1%	58,126	11.6%	49,359	9.7%	75,469	20.2%	112,415	30.9%	152,871	38.8%	519,866	52.6%
esomeprazole	18,362	14.4%	55,387	17.9%	116,997	23.3%	151,587	29.6%	102,041	27.3%	85,343	23.5%	87,913	22.3%	197,989	20.0%
pantoprazole	31,261	24.5%	88,004	28.4%	144,540	28.8%	118,774	23.2%	88,569	23.7%	85,466	23.5%	85,980	21.8%	184,351	18.7%
lansoprazole	41,337	32.4%	95,693	30.9%	165,415	33.0%	182,923	35.8%	101,674	27.2%	77,227	21.2%	66,382	16.9%	115,821	11.7%
rabeprazole	11,195	8.8%	26,370	8.5%	36,888	7.3%	26,236	5.1%	19,466	5.2%	17,259	4.7%	15,428	3.9%	32,358	3.3%
dexlansoprazole														4,497	0.5%	

*Subtotals may not sum exactly, due to rounding. Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts. Source: SDI Total Patient Tracker. File: TPT 2010-306 PPIs total 3-24-10.xls

Table 4. Total number of dispensed prescriptions for proton pump inhibitor market in outpatient retail pharmacies by top 10 prescribing specialties, 2002-2009

	2002		2003		2004		2005		2006		2007		2008		2009	
	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %
Total Market	73,526,621	100.0%	80,303,145	100.0%	76,264,655	100.0%	76,863,130	100.0%	84,226,057	100.0%	91,411,580	100.0%	94,248,188	100.0%	95,210,165	100.0%
GP/FM/DO	23,797,314	32.4%	26,386,571	32.9%	24,108,890	31.6%	24,537,834	31.9%	28,771,722	34.2%	31,411,149	34.4%	32,320,177	34.3%	33,398,984	35.1%
Internal Medicine	20,618,787	28.0%	22,671,038	28.2%	21,037,700	27.6%	21,379,330	27.8%	24,085,358	28.6%	26,001,376	28.4%	26,678,299	28.3%	27,370,342	28.7%
Gastroenterology	8,556,872	11.6%	8,966,964	11.2%	8,096,444	10.6%	7,997,922	10.4%	8,781,451	10.4%	9,376,528	10.3%	9,498,023	10.1%	9,301,392	9.8%
Nurse Practitioner	849,568	1.2%	1,216,292	1.5%	1,338,691	1.8%	1,549,321	2.0%	2,031,740	2.4%	2,557,233	2.8%	3,076,028	3.3%	3,791,102	4.0%
Physician Assistant	625,947	0.9%	854,507	1.1%	950,015	1.2%	1,090,954	1.4%	1,413,613	1.7%	1,764,039	1.9%	2,114,490	2.2%	2,775,125	2.9%
Pediatrics	988,878	1.3%	1,298,590	1.6%	1,417,323	1.9%	1,626,460	2.1%	1,998,040	2.4%	2,322,503	2.5%	2,637,121	2.8%	2,766,773	2.9%
Cardiology	1,776,986	2.4%	1,895,549	2.4%	1,775,628	2.3%	1,797,088	2.3%	2,014,393	2.4%	2,123,237	2.3%	2,062,958	2.2%	1,922,565	2.0%
Otolaryngology	978,026	1.3%	1,145,921	1.4%	1,120,614	1.5%	1,180,733	1.5%	1,372,937	1.6%	1,438,360	1.6%	1,475,574	1.6%	1,452,717	1.5%
Pulmonary Diseases	923,009	1.3%	974,883	1.2%	876,693	1.1%	868,309	1.1%	952,487	1.1%	990,928	1.1%	955,695	1.0%	910,362	1.0%
All Others	7,517,404	10.2%	8,239,285	10.3%	7,666,106	10.1%	7,654,290	10.0%	8,574,271	10.2%	9,019,935	9.9%	8,816,346	9.4%	8,240,800	8.7%
Unknown Specialty	6,893,830	9.4%	6,653,545	8.3%	7,876,551	10.3%	7,180,889	9.3%	4,230,045	5.0%	4,406,292	4.8%	4,613,477	4.9%	3,280,004	3.4%

Source: SDI Vector One®: National, Data Extracted March 2010. File: VONA_2010-306_PPis_MDs_03-24-10(1).xls *GP/FM/DO – General Practice, Family Medicine, Doctor of Osteopathy

Table 5. Diagnoses associated with the use* of the proton pump inhibitor market by patient age (<1, 1-12, 13-17, 18+) as reported by office-based physician practices, 2002-2009

	01/2002-12/2009	
	Uses (000)	Share %
Total Market	214,649	100.0%
<1 yr	1,352	0.6%
5308 ESOPHAGEAL DISORDER NEC [†]	1,232	91.2%
V202 ROUTIN CHILD HEALTH EXAM	26	1.9%
All Others	94	6.9%
1-12 yrs	3,408	1.6%
5308 ESOPHAGEAL DISORDER NEC	1,793	52.6%
7890 ABDOMINAL PAIN	526	15.4%
5355 GASTRITIS/DUODENITIS NOS	302	8.9%
7870 NAUSEA AND VOMITING	80	2.4%
5368 STOMACH FUNCTION DIS NEC	51	1.5%
5301 ESOPHAGITIS	45	1.3%
0418 BACTERIAL INFECTION NEC	41	1.2%
7143 JUV CHRON POLYARTHRITIS	38	1.1%
7862 COUGH	35	1.0%
All Others	498	14.6%
13-17 yrs	2,825	1.3%
5308 ESOPHAGEAL DISORDER NEC	1,013	35.9%
7890 ABDOMINAL PAIN	487	17.2%
5355 GASTRITIS/DUODENITIS NOS	343	12.2%
5368 STOMACH FUNCTION DIS NEC	97	3.4%
5301 ESOPHAGITIS	97	3.4%
7870 NAUSEA AND VOMITING	82	2.9%
5339 PEPTIC ULCER NOS	70	2.5%
7865 CHEST PAIN	57	2.0%
5589 NONINF GASTROENTERIT NEC	38	1.3%
7871 HEARTBURN	36	1.3%
5350 ACUTE GASTRITIS	34	1.2%
All Others	472	16.7%
18+ yrs	200,836	93.6%
5308 ESOPHAGEAL DISORDER NEC	111,016	55.3%
7890 ABDOMINAL PAIN	12,771	6.4%
5355 GASTRITIS/DUODENITIS NOS	10,395	5.2%
5368 STOMACH FUNCTION DIS NEC	5,979	3.0%
5339 PEPTIC ULCER NOS	5,836	2.9%
5301 ESOPHAGITIS	5,575	2.8%
5789 GASTROINTEST HEMORR NOS	4,993	2.5%
7872 DYSPHAGIA	4,764	2.4%
7871 HEARTBURN	4,098	2.0%
7865 CHEST PAIN	3,686	1.8%
7870 NAUSEA AND VOMITING	2,104	1.1%
5319 STOMACH ULCER NOS	2,068	1.0%
All Others	27,552	13.7%
Unknown Age	6,229	2.9%
5308 ESOPHAGEAL DISORDER NEC	3,563	57.2%
5355 GASTRITIS/DUODENITIS NOS	443	7.1%
5368 STOMACH FUNCTION DIS NEC	327	5.3%
7890 ABDOMINAL PAIN	325	5.2%
7872 DYSPHAGIA	150	2.4%
7871 HEARTBURN	132	2.1%
5789 GASTROINTEST HEMORR NOS	124	2.0%
5301 ESOPHAGITIS	123	2.0%
5339 PEPTIC ULCER NOS	107	1.7%
7865 CHEST PAIN	85	1.4%
All Others	849	13.6%

Source: SDI Physician Drug and Diagnosis Audit, Extracted March 2010.

File: PDDA 2010-306 PPIs_AgeDx4 3-24-1-.xls

* Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease.

[†]ICD-9 530.8 Esophageal Disorder contains the following sub-diagnoses: Esophageal reflux (530.81), esophageal hemorrhage (530.82), esophageal leukoplakia (530.83), trachesophageal fistula (530.84), Barrett's esophagus (530.85), infection of esophagostomy (530.86), mechanical complication of esophagostomy (530.87), and other diseases of esophagus (530.89)

Table 6. New, Continuing and Switch/Add-on patient prescriptions for proton pump inhibitors by patient age in U.S. outpatient retail pharmacies, 2002-2009

	2005		2006		2007		2008		2009	
	NRxs N	Share %	NRxs N	Share %	NRxs N	Share %	NRxs N	Share %	NRxs N	Share %
Total Market	25,573,909	100.0%	28,968,117	100.0%	30,161,589	100.0%	31,083,522	100.0%	30,999,630	100.0%
<1 yr	102,115	0.4%	130,418	0.5%	159,236	0.5%	170,345	0.5%	232,438	0.7%
lansoprazole	81,330	79.6%	108,666	83.3%	137,118	86.1%	149,083	87.5%	199,403	85.8%
New Patient Rx	24,701	30.4%	29,647	27.3%	38,349	28.0%	40,179	27.0%	41,238	20.7%
Continuing Patient Rx	33,189	40.8%	49,041	45.1%	61,012	44.5%	68,589	46.0%	98,095	49.2%
Switch/Add-On Patient Rx	23,440	28.8%	29,978	27.6%	37,757	27.5%	40,315	27.0%	60,070	30.1%
omeprazole	19,683	19.3%	20,825	16.0%	21,066	13.2%	19,709	11.6%	28,649	12.3%
New Patient Rx	5,343	27.1%	4,583	22.0%	4,529	21.5%	3,391	17.2%	6,636	23.2%
Continuing Patient Rx	8,844	44.9%	10,099	48.5%	10,669	50.6%	10,617	53.9%	15,655	54.6%
Switch/Add-On Patient Rx	5,496	27.9%	6,143	29.5%	5,868	27.9%	5,701	28.9%	6,358	22.2%
esomeprazole magnesium	557	0.5%	524	0.4%	555	0.3%	1,080	0.6%	3,975	1.7%
New Patient Rx	194	34.8%	158	30.2%	139	25.0%	218	20.2%	632	15.9%
Continuing Patient Rx	173	31.1%	175	33.4%	172	31.0%	384	35.6%	1,825	45.9%
Switch/Add-On Patient Rx	190	34.1%	191	36.5%	244	44.0%	478	44.3%	1,518	38.2%
pantoprazole	461	0.5%	321	0.2%	450	0.3%	408	0.2%	350	0.2%
New Patient Rx	194	42.1%	156	48.6%	153	34.0%	182	44.6%	102	29.1%
Continuing Patient Rx	198	43.0%	140	43.6%	216	48.0%	155	38.0%	194	55.6%
Switch/Add-On Patient Rx	69	15.0%	25	7.8%	81	18.0%	71	17.4%	53	15.3%
rabeprazole sodium	84	0.1%	82	0.1%	47	0.0%	65	0.0%	32	0.0%
New Patient Rx	52	61.9%	54	65.9%	31	66.0%	32	49.2%	15	48.7%
Continuing Patient Rx	18	21.4%	24	29.3%	15	31.9%	25	38.5%	8	25.5%
Switch/Add-On Patient Rx	14	16.7%	4	4.9%	1	2.1%	8	12.3%	8	25.8%
dexlansoprazole	--	--	--	--	--	--	--	--	30	0.0%
New Patient Rx	--	--	--	--	--	--	--	--	3	10.7%
Continuing Patient Rx	--	--	--	--	--	--	--	--	16	54.1%
Switch/Add-On Patient Rx	--	--	--	--	--	--	--	--	10	35.2%
1-12 yrs	448,164	1.8%	531,619	1.8%	597,027	2.0%	684,753	2.2%	642,067	2.1%
lansoprazole	360,050	80.3%	439,702	82.7%	498,549	83.5%	566,279	82.7%	484,457	75.5%
New Patient Rx	147,686	41.0%	176,049	40.0%	195,263	39.2%	221,056	39.0%	182,749	37.7%
Continuing Patient Rx	178,941	49.7%	228,868	52.1%	266,209	53.4%	306,156	54.1%	231,011	47.7%
Switch/Add-On Patient Rx	33,423	9.3%	34,785	7.9%	37,077	7.4%	39,067	6.9%	70,697	14.6%
omeprazole	48,397	10.8%	54,864	10.3%	63,566	10.6%	77,273	11.3%	103,201	16.1%
New Patient Rx	13,776	28.5%	17,989	32.8%	22,423	35.3%	29,240	37.8%	45,447	44.0%
Continuing Patient Rx	27,448	56.7%	28,611	52.1%	31,486	49.5%	36,224	46.9%	41,233	40.0%
Switch/Add-On Patient Rx	7,173	14.8%	8,264	15.1%	9,657	15.2%	11,809	15.3%	16,521	16.0%
esomeprazole magnesium	24,746	5.5%	24,410	4.6%	23,717	4.0%	31,830	4.6%	45,707	7.1%
New Patient Rx	7,370	29.8%	7,371	30.2%	6,886	29.0%	9,226	29.0%	14,737	32.2%
Continuing Patient Rx	13,088	52.9%	12,726	52.1%	12,441	52.5%	16,236	51.0%	22,874	50.0%
Switch/Add-On Patient Rx	4,288	17.3%	4,313	17.7%	4,390	18.5%	6,368	20.0%	8,095	17.7%
pantoprazole	10,729	2.4%	8,526	1.6%	8,057	1.3%	7,142	1.0%	5,428	0.8%
New Patient Rx	4,239	39.5%	2,978	34.9%	2,740	34.0%	2,507	35.1%	1,503	27.7%
Continuing Patient Rx	4,698	43.8%	4,020	47.1%	3,817	47.4%	2,838	39.7%	2,652	48.9%
Switch/Add-On Patient Rx	1,792	16.7%	1,528	17.9%	1,500	18.6%	1,797	25.2%	1,272	23.4%
rabeprazole sodium	4,242	0.9%	4,117	0.8%	3,138	0.5%	2,229	0.3%	2,620	0.4%
New Patient Rx	1,823	43.0%	1,880	45.7%	1,428	45.5%	932	41.8%	1,049	40.0%
Continuing Patient Rx	1,722	40.6%	1,619	39.3%	1,269	40.4%	895	40.2%	955	36.4%
Switch/Add-On Patient Rx	697	16.4%	618	15.0%	441	14.1%	402	18.0%	616	23.5%
dexlansoprazole	--	--	--	--	--	--	--	--	654	0.1%
New Patient Rx	--	--	--	--	--	--	--	--	257	39.3%
Continuing Patient Rx	--	--	--	--	--	--	--	--	153	23.4%
Switch/Add-On Patient Rx	--	--	--	--	--	--	--	--	244	37.3%
13-17 yrs	294,157	1.2%	316,606	1.1%	338,248	1.1%	369,955	1.2%	394,799	1.3%
omeprazole	30,248	10.3%	44,946	14.2%	67,378	19.9%	97,208	26.3%	150,482	38.1%
New Patient Rx	14,354	47.5%	23,231	51.7%	35,568	52.8%	50,787	52.2%	80,489	53.5%
Continuing Patient Rx	11,280	37.3%	14,805	32.9%	21,792	32.3%	33,279	34.2%	52,494	34.9%
Switch/Add-On Patient Rx	4,614	15.3%	6,910	15.4%	10,018	14.9%	13,142	13.5%	17,499	11.6%
lansoprazole	158,766	54.0%	164,332	51.9%	169,824	50.2%	174,469	47.2%	141,608	35.9%
New Patient Rx	77,139	48.6%	79,052	48.1%	79,223	46.7%	82,219	47.1%	60,140	42.5%
Continuing Patient Rx	68,307	43.0%	72,895	44.4%	77,781	45.8%	78,984	45.3%	63,939	45.2%
Switch/Add-On Patient Rx	13,320	8.4%	12,385	7.5%	12,820	7.5%	13,266	7.6%	17,529	12.4%
esomeprazole magnesium	55,229	18.8%	61,155	19.3%	61,152	18.1%	66,363	17.9%	77,746	19.7%
New Patient Rx	22,583	40.9%	25,075	41.0%	24,883	40.7%	26,659	40.2%	30,657	39.4%
Continuing Patient Rx	24,682	44.7%	27,810	45.5%	27,784	45.4%	30,208	45.5%	36,470	46.9%
Switch/Add-On Patient Rx	7,964	14.4%	8,270	13.5%	8,485	13.9%	9,496	14.3%	10,619	13.7%
pantoprazole	34,438	11.7%	31,834	10.1%	27,832	8.2%	23,173	6.3%	12,655	3.2%
New Patient Rx	16,101	46.8%	14,119	44.4%	12,167	43.7%	10,597	45.7%	5,211	41.2%
Continuing Patient Rx	13,532	39.3%	12,839	40.3%	11,568	41.6%	7,461	32.2%	5,168	40.8%
Switch/Add-On Patient Rx	4,805	14.0%	4,876	15.3%	4,097	14.7%	5,115	22.1%	2,275	18.0%
rabeprazole sodium	15,476	5.3%	14,339	4.5%	12,062	3.6%	8,742	2.4%	9,087	2.3%
New Patient Rx	7,709	49.8%	7,350	51.3%	5,989	49.7%	4,132	47.3%	3,998	44.0%
Continuing Patient Rx	5,715	36.9%	5,117	35.7%	4,477	37.1%	3,241	37.1%	3,420	37.6%
Switch/Add-On Patient Rx	2,052	13.3%	1,872	13.1%	1,596	13.2%	1,369	15.7%	1,669	18.4%
dexlansoprazole	--	--	--	--	--	--	--	--	3,221	0.8%
New Patient Rx	--	--	--	--	--	--	--	--	1,475	45.8%
Continuing Patient Rx	--	--	--	--	--	--	--	--	753	23.4%
Switch/Add-On Patient Rx	--	--	--	--	--	--	--	--	994	30.8%
18+ yrs	24,521,279	95.9%	27,893,730	96.3%	28,999,310	96.1%	29,795,200	95.9%	29,672,289	95.7%
UNSPEC	208,194	0.8%	95,744	0.3%	67,768	0.2%	63,269	0.2%	58,037	0.2%

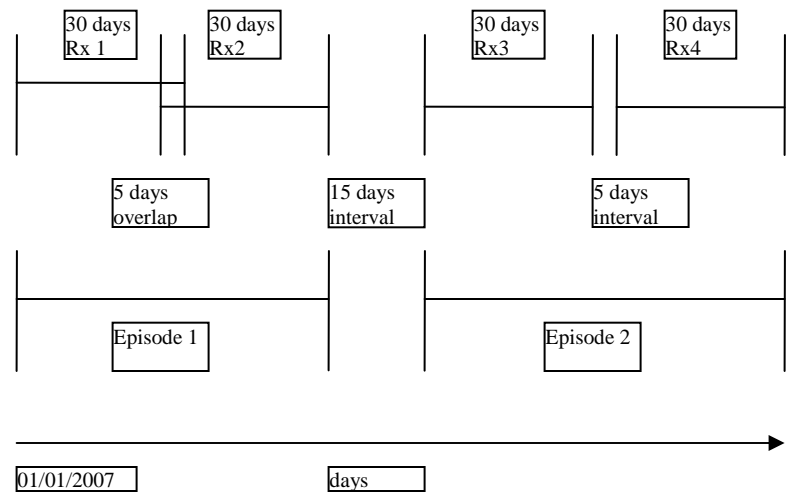
Source: SDI Vector One®: National, Data Extracted March 2010. File: VONA 2010-306 PPIs RxType_03-24-10.xls.xls

7.3 APPENDIX 3: DIAGNOSIS AND HCPCS CODES USED TO IDENTIFY NEWBORNS

V30.xx Single Liveborn
V31.xx Twin Birth, Mate Liveborn
V32.xx Twin Birth, Mate Stillborn
V33.xx Twin Birth, Unspecified Whether Mate Liveborn Or Stillborn
V34.xx Other Multiple Birth (three Or More), Mates All Liveborn
V35.xx Other Multiple Birth (three Or More), Mates All Stillborn
V36.xx Other Multiple Birth (three Or More), Mates Liveborn And Stillborn
V37.xx Other Multiple Birth (three Or More), Unspecified Whether Mates Liveborn or stillborn
V39.xx Liveborn, Unspecified Whether Single, Twin, Or Multiple
V29.xx Observation And Evaluation Of Newborns And Infants For Suspected Conditions Not Found
742.3 Congenital Hydrocephalus Aqueduct of Sylvius: anomaly, obstruction congenital, stenosis; Atresia of foramina of Magendie and Luschka; Hydrocephalus in newborn
747.83 Persistent fetal circulation persistent pulmonary hypertension, primary pulmonary hypertension of newborn
760.xx Fetus Or Newborn Affected By Maternal Conditions Which May Be Unrelated To Present Pregnancy
761.xx Fetus Or Newborn Affected By Maternal Complications Of Pregnancy
762.xx Fetus Or Newborn Affected By Complications Of Placenta, Cord, And Membranes
763.xx Fetus Or Newborn Affected By Other Complications Of Labor And Delivery
764.xx Slow Fetal Growth And Fetal Malnutrition
765.xx Disorders Relating To Short Gestation And Low Birthweight
766.xx Disorders Relating To Long Gestation And High Birthweight
767.xx Birth Trauma
768.xx Intrauterine Hypoxia And Birth Asphyxia
769 Respiratory Distress Syndrome In Newborn Cardiorespiratory distress syndrome of newborn; Hyaline membrane disease (pulmonary); Idiopathic respiratory distress syndrome [IRDS or RDS] of newborn; Pulmonary hypoperfusion syndrome
770.xx Other Respiratory Conditions Of Fetus And Newborn
771.xx Infections Specific To The Perinatal Period
772.xx Fetal And Neonatal Hemorrhage
773.xx Hemolytic Disease Of Fetus Or Newborn, Due To Isoimmunization
774.xx Other Perinatal Jaundice
775.xx Endocrine And Metabolic Disturbances Specific To The Fetus And Newborn
776.xx Hematological Disorders Of Newborn
777.xx Perinatal Disorders Of Digestive System
778.xx Conditions Involving The Integument And Temperature Regulation Of Fetus And Newborn
779.xx Other And Ill-defined Conditions Originating In The Perinatal Period
799.82 Apparent life threatening event in infant ALTE; Apparent life threatening event in newborn and infant

7.4 APPENDIX 4

Figure 1. Cumulative days of therapy calculation for the two duration of therapy definitions when allowed grace period is 25% of prescription days supply



	Definition 1 sum of duration, overlap ignored	Definition 2 sum of duration, overlap included
Episode 1	55	60
Episode 2	60	60
Total duration	115	120

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
NDA-22020	ORIG-1	WYETH PHARMACEUTICA LS INC	PROTONIX DELAYED RELEASE GRANULES
NDA-22101	ORIG-1	ASTRAZENECA LP	NEXIUM
NDA-22056	ORIG-1	ASTRAZENECA LP	PRILOSEC FOR DELAYED- RELEASE ORAL SUSP
NDA-20973	SUPPL-22	EISAI INC	ACIPHEX(RABEPRAZOLE SODIUM)10MG/20MG TAB
NDA-21428	SUPPL-17	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	PREVACID(LANSOPRAZOLE) 15/30 MG TABLETS
NDA-22287	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	DEXLANSOPRAZOLE

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/s/

PATTY A GREENE

05/03/2010

data cleared by database vendors 5/3/10

SOLOMON IYASU

05/04/2010