

## 9 Long-Term Potential for Gastro-Intestinal Cellular Alterations

An important function of the gastric mucosa is the secretion of concentrated hydrochloric acid. This function plays an important but nonessential role in digestion, but also contributes to eradication of potentially pathogenic bacteria ingested with food. Unfortunately, the caustic nature of gastric acid often plays a central role in the pathogenesis of a number of acid-related diseases as well as heartburn and other symptoms associated with gastroesophageal reflux.

The discovery and introduction of acid-suppressing drugs in the H<sub>2</sub>RA and PPI classes during the past 20 years revolutionized the treatment of acid-related diseases. These drug therapies remain the treatment of first choice for patients diagnosed with these disorders. However, from the time of the introduction of acid-suppressing drugs, especially omeprazole, concerns about the safety of pharmacological inhibition of gastric acid secretion have been raised. When omeprazole is used to treat “Rx” indications that often require long-term acid inhibition, one has to consider possible effects on gastric mucosal cell biology. The accumulation of more than 20 years of worldwide clinical experience with omeprazole (including longitudinal studies in which a cohort of patients has been treated continuously with omeprazole for up to 14 years) has largely allayed these concerns. In addition, the PPI class is now generally recognized as being as safe as the H<sub>2</sub>RA class, as well as being among the safest of all medications in use today. Moreover, this experience with the use of omeprazole in both long-term clinical trials (continuous use for 2 to up to 14 years) and in the marketed Rx setting (since 1988) provides very strong support for the safety of OTC usage that will be on a much more short-term basis.

This portion of the briefing document addresses the relationship among long-term acid inhibitory therapy and demonstrated or theoretical gastrointestinal epithelial effects:

1. Hypergastrinemia and gastric enterochromaffin-like (ECL) cell changes such as hyperplasia and carcinoids;
2. Fundic gland polyps;
3. Colon adenomatous polyps and adenocarcinoma; and
4. Atrophic gastritis and the potential for progression to intestinal metaplasia, dysplasia, and gastric adenocarcinoma.

The conclusions addressing each of the above entities are supported by the results of review of the published medical literature, safety data from long-term clinical studies, and post-marketing AE reports.

During nonclinical investigations, increased serum gastrin secondary to inhibition of gastric acid secretion following prolonged administration of omeprazole resulted in hyperplasia of gastric ECL cells and ECL cell carcinoids in Sprague-Dawley rats. These findings led to a thorough examination, during the course of the omeprazole development program and

following approval of the original NDA, of the potential for similar findings in humans, as well as for the above-described gastrointestinal epithelial effects, during omeprazole treatment.

## **9.1 Physiology of Gastrin, Hypergastrinemia, and ECL Cells**

Endocrine cells are located throughout the human gastrointestinal tract and produce several hormones and neurotransmitters. The ECL cells, the most dominant gastric endocrine cell population, secrete histamine. The cells lie in close proximity to the acid-producing parietal cells of the oxyntic mucosa of the gastric body. ECL cells are biochemically sensitive to the effects of gastrin.

Gastrin is an endocrine hormone that is secreted by G cells that are located in the pyloric-antral mucosa of the stomach. G cells play a role in regulating hydrochloric acid secretion within the stomach by releasing gastrin into the bloodstream, thereby activating the release of histamine from ECL cells. Histamine subsequently stimulates the nearby parietal cells to produce hydrochloric acid. Generally, further gastrin secretion will then be inhibited by the presence of gastric acid (negative feedback loop). However, drug-induced acid inhibition has been shown to disrupt the normal negative feedback of gastric acid on the gastrin-producing G cells. When drug therapy shifts the intragastric pH toward neutral, an increase in serum gastrin, or hypergastrinemia occurs because gastrin is released into the bloodstream in an attempt to increase acid production as a homeostatic mechanism. Negative feedback inhibition of gastrin secretion is disrupted in certain disease states, such as Zollinger-Ellison syndrome (ZES), when gastrin is autonomously produced by tumor cells.

## **9.2 Hypergastrinemia and Possible Effects on the Gastric ECL Cell and the Gastrointestinal Tract Epithelium**

Hypergastrinemia and ECL cell hyperplasia are expected outcomes associated with long-term treatment with omeprazole and other antisecretory therapies, and are established manifestations of acid hypersecretory conditions, including ZES and multiple endocrine neoplasia (MEN), as well as of pernicious anemia. These events are asymptomatic and are not associated with other known deleterious tissue effects or outcomes when they arise as a result of long-term treatment with omeprazole. Gastric ECL cell carcinoids are manifestations of ZES, MEN syndrome, and pernicious anemia, but there is no evidence to support a causal relationship between the use of omeprazole and the development of carcinoids.

Gastric ECL cell carcinoid tumors in humans are rare, usually indolent and do not necessarily occur in association with antisecretory therapy.<sup>61</sup> Carcinoid tumors usually occur in patients with chronic autoimmune gastritis, which can progress to pernicious anemia, or in those patients with ZES, a rare neoplastic disease associated with hypergastrinemia secondary to gastrin-producing tumors (e.g., gastrinoma) and gastric acid hypersecretion that occurs as a consequence.<sup>62,63</sup> Patients with ZES appear to be at risk for carcinoid tumors if their disease arises as part of the MEN-1 syndrome, an inherited, autosomal dominant condition.<sup>64</sup> Sporadic ZES (arising in patients without MEN-1) is rarely associated with gastric carcinoid tumors, suggesting that inactivation of both copies of the MEN-1 gene are necessary for

carcinoids to arise, even in the context of hypergastrinemia.<sup>65</sup> These observations are consistent with modern understanding of the pathogenesis of human malignancy, the development of which requires a combination of inherited or acquired genetic abnormalities coupled with abnormalities of cell proliferation. Therefore, the trophic, or proliferative, stimulus of increased circulating gastrin levels on ECL cells is insufficient to independently produce formation of ECL cell carcinoid tumors without a coincident genetic abnormality. ECL cell carcinoids very rarely occur in humans who do not have either of these rare preexisting conditions. ZES and pernicious anemia can be characterized by extreme elevations in serum gastrin. However, there are factors beyond gastrin elevation that appear to be required for the emergence of ECL cell carcinoid tumors. Moreover, hypergastrinemia in these diseases is not associated with any other clinically significant adverse effects.

In humans, although acid suppression with therapeutic doses of omeprazole and other acid suppressing drugs can result in an elevation of serum gastrin levels above the normal range, these elevations are usually not marked and are not of the same magnitude as those that may be observed in patients with ZES or pernicious anemia.

ECL cell carcinoids arise in a background of diffuse endocrine cell hyperplasia in the oxyntic mucosa. The Solcia classification of ascending grades of severity of ECL cell pathology are delineated in Table 9.1 below.<sup>66</sup> This classification has been of benefit in the assessment of gastric biopsies obtained from humans on chronic omeprazole therapy. It is important to note that apart from those patients with ZES or other predisposing conditions, no patients on chronic omeprazole therapy in controlled clinical trials have been observed to develop ECL cell dysplasia or carcinoid tumors.

<b>TABLE 9.1</b> <b>SOLCIA CLASSIFICATION OF ECL CELL PATHOLOGY<sup>a</sup></b>	
<b>CLASSIFICATION</b>	<b>CELL PATHOLOGY</b>
0	Normal
1	Simple (diffuse) hyperplasia
2	Linear or chain forming hyperplasia
3	Micronodular hyperplasia
4	Adenomatoid hyperplasia
5	Dysplastic (“precarcinoid”) growths
6	Intramucosal neoplasm (intramucosal carcinoid)
7	Invasive neoplasm (invasive carcinoid)

<sup>a</sup> ADAPTED FROM SOLCIA et al.<sup>67</sup>

### **9.3 Long Term Use of Omeprazole – Data from Clinical Trials**

The most pertinent clinical trials for assessing the risk of neoplastic complications are two US and six Non-US trials of approximately 1,100 patients who were treated for time periods ranging from 2 to 14 years (see Table 9.2). Special reference to possible changes in the alimentary tract epithelium are addressed based on these long-term clinical data. It should be noted that exceptionally high doses of omeprazole were administered in two of the trials: (1) 80 mg per day for 2 years in Study #3 and (2) 80 mg per day for 1 year followed by 40 mg per day for 1 year in Study #1, compared to the usual daily adult dose of 20 mg approved for GERD indications. Descriptive information regarding these clinical trials and the type of data collected is presented in tabular form in Table 9.2.

The following sections examine the available data from these long term trials relative to specific considerations of high gastrin levels, fundic gland polyps, colon adenomatous polyps, adenocarcinoma, and atrophic gastritis. In addition, relevant post-market reports are summarized in each section.

**TABLE 9.2**  
**TABLE OF LONG-TERM CLINICAL TRIALS REVIEWED**  
 (Page 1 of 8)

TRIAL # / LOCATION	TRIAL DESIGN AND OBJECTIVE	TREATMENT GROUPS	NUMBER OF PATIENTS RANDOMIZED	ASSESSMENTS PERFORMED
1 / US	<p>TRIAL DESIGN: A double-blind multi-center parallel group trial</p> <p>OBJECTIVE: To determine whether long-term therapy with omeprazole or an H<sub>2</sub>-antagonist will alter the natural course of Barrett's esophagus and result in regression of the area of esophageal involvement</p> <p>COMPLETION DATE: 4/94</p>	<p>TRIAL DURATION: 24 months</p> <p>1. Omeprazole 40 mg bid for 12 months then 20 mg bid for another 12 months</p> <p>2. Ranitidine 300 mg bid for 24 months</p> <p>Total:</p>	<p>57</p> <p>49</p> <p>106</p>	<p>Serum gastrin; gastric/esophageal biopsy (with histologic assessments of ECL cells and presence or absence of atrophic gastritis and intestinal/esophageal metaplasia) at baseline and every six months; colonoscopy for evaluation of colon polyps at baseline and 24 months; and overall clinical safety assessments.</p> <p>The number of patients with at least one endoscopy performed <math>\geq</math> six months after baseline was 53 in the omeprazole group and 44 in the ranitidine group.</p>

**TABLE 9.2 (Cont.)  
TABLE OF LONG-TERM CLINICAL TRIALS REVIEWED**

**(Page 2 of 8)**

TRIAL # / LOCATION	TRIAL DESIGN AND OBJECTIVE	TREATMENT GROUPS	NUMBER OF PATIENTS RANDOMIZED	ASSESSMENTS PERFORMED
2 / US	<p>TRIAL DESIGN: A double blind, randomized, multi-center group trial conducted in three phases</p> <p>OBJECTIVE: To investigate the efficacy of 2 oral doses of omeprazole vs. placebo in the maintenance treatment of patients with active duodenal ulcers healed by omeprazole; to evaluate the long-term safety of omeprazole</p>	<p>TRIAL DURATION: 24 months</p> <p>Phase 1: (4 weeks) 20 mg omeprazole qam open label</p> <p>Phase 2: (weeks 1-52)</p> <ol style="list-style-type: none"> <li>1. Omeprazole 20 mg od</li> <li>2. Omeprazole 10 mg od</li> <li>3. Placebo</li> </ol> <p>Phase 3: (weeks 53-104)</p> <ol style="list-style-type: none"> <li>1. Omeprazole 20 mg od</li> <li>2. Omeprazole 10 mg od</li> <li>3. Placebo</li> </ol>	<p>1,170</p> <p>362</p> <p>372</p> <p>179</p> <p>170</p> <p>138</p> <p>27</p>	<p>Endoscopy was performed at baseline, weeks 4, 6, 26, 52, and 104. Gastric fundus biopsy for histologic assessments of ECL cells was performed at baseline, weeks 4, 52 and 104. Serum gastrin was performed at baseline, week 4, 26, 52 and 104. Overall clinical safety assessments were also performed.</p> <p>Note: 335 patients <b>completed</b> Phase 3 138 in omeprazole 10 mg; 170 in omeprazole 20 mg and 27 in placebo groups respectively.</p>

**TABLE 9.2 (Cont.)  
TABLE OF LONG-TERM CLINICAL TRIALS REVIEWED**

**(Page 3 of 8)**

TRIAL # / LOCATION	TRIAL DESIGN AND OBJECTIVE	TREATMENT GROUPS	NUMBER OF PATIENTS RANDOMIZED	ASSESSMENTS PERFORMED
3 / Non-US	<p>TRIAL DESIGN: Randomized, double-blind, double dummy, parallel group design.</p> <p>OBJECTIVE: To compare the effects of the different treatments on histological parameters and parameters of premalignant change in Barrett's epithelium and relate these to the degree of acid gastro-esophageal reflux.</p> <p>COMPLETION DATE: 4/96</p>	<p>TRIAL DURATION: 24 months</p> <ol style="list-style-type: none"> <li>1. Omeprazole 40 mg bid</li> <li>2. Ranitidine 150 mg bid</li> <li>3. Open label Omeprazole 40 mg bid</li> </ol> <p>Total:</p>	<p>33</p> <p>35</p> <p>4</p> <p>72</p>	<p>Gastric biopsies were taken at the first and last visit for histologic assessments of ECL cells and gastritis status, including activity, inflammation and atrophy. Serum gastrin was evaluated at baseline and at 3, 9, 15 and 24 months. <i>H. pylori</i> status was determined by serum IgG. Overall clinical safety assessments were also performed.</p> <p>Note: 26 patients completed in the omeprazole group and 27 patients completed in the ranitidine group.</p>

**TABLE 9.2 (Cont.)**  
**TABLE OF LONG-TERM CLINICAL TRIALS REVIEWED**  
**(Page 4 of 8)**

TRIAL # / LOCATION	TRIAL DESIGN AND OBJECTIVE	TREATMENT GROUPS	NUMBER OF PATIENTS RANDOMIZED	ASSESSMENTS PERFORMED
4 / Non-US	<p>TRIAL DESIGN: Open, parallel group trial</p> <p>OBJECTIVE: To compare omeprazole treatment with surgical treatment (anti-reflux surgery) in long-term management of peptic esophagitis</p> <p>COMPLETION DATE: Interim data from 36 months - 1997</p>	<p>TRIAL DURATION: 60 months (Data included here is from an interim report after 36 month). Patients who had recurrent erosive or ulcerative esophagitis and were suitable candidates for surgery were healed with omeprazole 20 or 40 mg daily. Healed patients were then randomized to:</p> <ol style="list-style-type: none"> <li>1. Omeprazole 20 mg daily</li> <li>2. Anti-reflux surgery</li> </ol>	<p>155</p> <p>155</p>	<p>Endoscopies with gastric biopsies were performed at baseline, 12 and 36 months. <i>H. pylori</i> status was determined by biopsy. Histologic assessments of ECL cells and gastritis status, including activity, inflammation and atrophy were evaluated. Serum gastrin levels were performed at baseline, 12 and 36 months. Overall clinical safety assessments were also performed.</p> <p>Note: 139 omeprazole patients completed 36 months of treatment and 130 patients in the anti-reflux group completed 36 months of the study.</p>



**TABLE 9.2 (Cont.)**  
**TABLE OF LONG-TERM CLINICAL TRIALS REVIEWED**  
**(Page 5 of 8)**

TRIAL # / LOCATION	TRIAL DESIGN AND OBJECTIVE	TREATMENT GROUPS	NUMBER OF PATIENTS RANDOMIZED	ASSESSMENTS PERFORMED
5 / Non-US	<p>TRIAL DESIGN: Open label treatment</p> <p>OBJECTIVE: To document the efficacy and safety of omeprazole in the long-term treatment of patients with severe peptic ulcer and reflux esophagitis disease who were refractory to treatment with H<sub>2</sub>-receptor antagonists and ineligible for surgery. (This was a Compassionate Use Study since no maintenance indication was approved).</p> <p>Original study was designed for 5 years and patients were asked to extend.</p> <p>COMPLETION DATE: 4/97</p>	<p>TRIAL DURATION: 60 – 144 months</p> <p>Phase 1 (healing phase) 4-8 weeks: Omeprazole 40 mg OD (open label)</p> <p>Phase 2 (prophylaxis phase) over 11 years: Omeprazole 20 mg every morning (dosing of up to 80 mg could be used in cases of recurrence)</p>	<p>Total of 265 patients:</p> <p>73 treated for 0-5 yrs</p> <p>173 treated for 5-10 yrs</p> <p>19 treated for 10-12 yrs</p>	<p>Endoscopy with gastric biopsy and histologic assessments of ECL cells and gastritis status, including non-atrophic, sub-atrophic or atrophic gastritis were performed annually. Serum gastrin levels were performed annually. <i>H. pylori</i> status was also determined by biopsy. Overall clinical safety assessments were also performed.</p> <p>Note: 70% of patients were followed for more than 5 years. 133 patients withdrew from the study for various reasons.</p>

**TABLE 9.2 (Cont.)**  
**TABLE OF LONG-TERM CLINICAL TRIALS REVIEWED**  
**(Page 6 of 8)**

TRIAL # / LOCATION	TRIAL DESIGN AND OBJECTIVE	TREATMENT GROUPS	NUMBER OF PATIENTS RANDOMIZED	ASSESSMENTS PERFORMED
6 / Non-US	<p>TRIAL DESIGN: Open label healing phase with omeprazole treatment for up to 12 weeks followed by prophylaxis against recurrence of peptic ulcer or esophagitis.</p> <p>OBJECTIVE: To determine the efficacy and safety of treatment with omeprazole for a period of up to 5 years in patients with peptic ulcer disease or severe esophagitis resistant to treatment with high doses of ranitidine. The study was continued for up to 14 years</p> <p>COMPLETION DATE: 1/98</p>	<p>TRIAL DURATION: 60 – 168 months</p> <p>Phase 1 (healing phase) up to 12 weeks: Omeprazole 40 mg daily</p> <p>Phase 2 (prophylaxis phase) up to 5 years planned with extension of up to 14 years.: Omeprazole 20 – 40 mg daily</p> <p>Note: Average treatment period was 9.6 yrs</p>	<p>Note: the 2 centers filed individual interim study reports. Patient data was combined for a report covering 5-14 years of treatment</p> <p>83 patients extended past 5 years (5-14 years of treatment)</p> <p>66 patients treated &gt; 8 yrs</p> <p>33 patients treated &gt;10 yrs</p> <p>11 patients treated &gt;12 yrs</p>	<p>Endoscopy with gastric biopsy, histologic assessments of ECL cells and gastritis status, including activity, inflammation and atrophy was performed annually. <i>H. pylori</i> status was determined by biopsy. Serum gastrin levels were performed annually. Overall clinical safety assessments were also performed.</p>

**TABLE 9.2 (Cont.)**  
**TABLE OF LONG-TERM CLINICAL TRIALS REVIEWED**  
**(Page 7 of 8)**

TRIAL # / LOCATION	TRIAL DESIGN AND OBJECTIVE	TREATMENT GROUPS	NUMBER OF PATIENTS RANDOMIZED	ASSESSMENTS PERFORMED
7 / Non-US	<p>TRIAL DESIGN: Double-blind, double-dummy parallel group study consisting of an 8 week healing period followed by a 24 month maintenance period.</p> <p>OBJECTIVE: To compare the efficacy of omeprazole and ranitidine in the healing of duodenal ulcers.</p> <p>COMPLETION DATE: 4/94</p>	<p>TRIAL DURATION: 24 months</p> <p>Phase 1: Healing period (8 weeks) Omeprazole 20 mg or Ranitidine 150 mg BID</p> <p>Phase 2: Maintenance period (24 months) with patients treated with omeprazole 10mg daily, omeprazole 20mg daily, or ranitidine 150mg daily</p> <p>Patients were randomized to three treatment groups:</p> <p>Omeprazole 20mg/Omeprazole 10mg</p> <p>Omeprazole20mg/Omeprazole 20mg</p> <p>Ranitidine 150mg BID/ Ranitidine 150mg</p> <p>Total:</p>	<p>40</p> <p>40</p> <p>40</p> <p>120</p>	<p>Endoscopy was performed at the start of healing, 2, and 8 weeks of healing period. During the maintenance, endoscopy was carried out every 6 months. The appearance of the esophagus, stomach, and duodenum was recorded. Biopsies of the four quadrants of the gastric body were taken at the time of endoscopy. Histologic assessments of ECL cells, atrophic gastritis, and intestinal metaplasia were made. Serum gastrin was evaluated at the end of the healing period and every 6 months of the maintenance period. Overall clinical safety assessments were also performed; but a full evaluation was not conducted.</p>

**TABLE 9.2 (Cont.)**  
**TABLE OF LONG-TERM CLINICAL TRIALS REVIEWED**  
**(Page 8 of 8)**

TRIAL # / LOCATION	TRIAL DESIGN AND OBJECTIVE	TREATMENT GROUPS	NUMBER OF PATIENTS RANDOMIZED	ASSESSMENTS PERFORMED
8 / Non-US	<p>TRIAL DESIGN: Open, non-randomized design with 8 or 16 week omeprazole healing periods and 48 months omeprazole or ranitidine maintenance periods.</p> <p>OBJECTIVE: To evaluate the efficacy and safety of omeprazole and ranitidine in patients with gastro-esophageal reflux disease with complications of Barrett's esophagus and/or stricture.</p> <p>COMPLETION DATE: 9/95</p>	<p>TRIAL DURATION: 48 months</p> <p>The allocation of patients was dependent on disease state (with or without active esophagitis) and previous treatment.</p> <ol style="list-style-type: none"> <li>1. Active esophagitis on entry-healing period, omeprazole 20mg for 8 weeks followed by omeprazole 40mg for 8 weeks if unhealed. Healed patients entered maintenance with omeprazole 20 mg daily.</li> <li>2. No esophagitis on entry and assessed as suitable for ranitidine alone- maintenance period, ranitidine 300 mg daily.</li> <li>3. No esophagitis on entry and assessed as unsuitable for ranitidine alone- maintenance period, omeprazole 20mg daily.</li> </ol>	<p>Total patients:109</p> <p>Note: 51 of 81 Barrett's esophagus pts received omeprazole and 30 received ranitidine, 25 of 29 stricture pts received omeprazole and 4 ranitidine.</p> <p>Two patients entered the initial healing phase, 73 entered omeprazole maintenance, and 34 ranitidine maintenance.</p>	<p>Endoscopy was performed at study entry and every 8 weeks during the healing period. During maintenance, it was performed at 6, 12, 18, 24, 36, and 48 months. Gastric biopsy was performed at each endoscopy. Two to three biopsies were taken from the gastric body mucosa. Histologic assessments of ECL cells and gastritis status (includes activity, inflammation, and atrophy) were made. Serum gastrin levels were performed at Baseline and week 8 during the healing period. During the maintenance period, serum gastrin levels were obtained at Baseline and every 6 months up to 2 years, then yearly thereafter. Overall clinical safety assessments were also performed; but a full evaluation was not conducted.</p>

### 9.3.1 Clinical Trial Data and Post-Marketing Reports Concerning Hypergastrinemia

Omeprazole has been shown to elevate serum gastrin levels during the first 1 to 2 weeks of treatment in patients with acid-related disorders; however, these levels appear to stabilize quickly and are reversible upon discontinuation of drug therapy. During the course of long-term treatment with omeprazole, some patients develop ECL cell hyperplasia. However, hypergastrinemia has not always been associated with growth alterations of the ECL cell or with changes in the density of ECL cells. More importantly, analyses of gastric biopsy specimens in humans have not shown evidence of ECL cell hyperplasia progressing to ECL cell dysplasia or carcinoids.

In long-term clinical studies assessing the effects of omeprazole on serum gastrin level in patients with gastroesophageal reflux disease (GERD) or peptic ulcer disease, it was noted that the majority of patients had gastrin levels exceeding the upper limits of normal, but that only in a minority of patients were gastrin levels markedly elevated. In groups randomized by *H. pylori* status, these very high gastrin values were only noted in *H. pylori* positive patients.

In Trial 2, a two year study conducted in duodenal ulcer patients, median gastrin levels increased with omeprazole therapy but remained within the normal range. Gastrin levels in excess of 150% of the upper limit of normal (> 250 pg/mL) were observed in up to 14.5% of patients in the omeprazole 20 mg group (N=152). In Trial 4, a three year study of GERD patients, less than 10% of patients (N=155) treated with omeprazole 20 mg or 40 mg daily had serum gastrin levels exceeding 100 pmol/L. Patients in the omeprazole group had greater increases in their serum gastrin levels when compared with those in the anti-reflux surgery group.

Serum gastrin levels have also been assessed during omeprazole treatment in patients with severe GERD or peptic ulcer disease. In Trial 5, serum gastrin levels were analyzed annually over 5 years. The median serum gastrin level at Year 1 was increased from Baseline by a little over two-fold (N=43). Thereafter, at Year 2, 3, 4, and 5, the median serum gastrin level was relatively consistent across the 12-year study period. Trial 6, assessing serum gastrin levels over twelve years, yielded comparable results. Serum gastrin levels exceeded 400 pmol/L in only a minority of patients treated with omeprazole 20 mg or 40 mg daily (total number of patients treated was 73). The time trend analysis was flat for the median serum gastrin levels over the 12-year study period.

In addition, two 24-month studies of patients with Barrett's esophagus treated with omeprazole have revealed that only a small percentage of patients develop a serum gastrin level that exceeds 400 pmol/L. In Trial 1, 106 patients were randomized (57 in omeprazole group and 49 in ranitidine group). At the end of the double-blind phase there were 46 patients in the omeprazole group and 30 in the ranitidine group. In this study, between 51% and 69% of patients treated with omeprazole, and between 18% and 28% of the ranitidine patients had increases from baseline of more than 40 pg/mL. Only 1 patient (80 mg group) treated with omeprazole 20 mg or 40 mg twice daily had a serum gastrin level exceeding 400 pg/mL. In a separate foreign study, Trial 3, it was observed that serum gastrin levels of > 400 ng/L occurred only in patients with *H. pylori*-positive status. Serum gastrin levels were available for 24 patients in the omeprazole group; 14 were *H. pylori*-negative while 10 were *H. pylori*-positive. The mean increase in serum gastrin level was a 1.7-fold increase (range of 1.2- to 3.4-fold) in *H. pylori*-

negative patients. The mean increase in serum gastrin level was a 1.5-fold increase (range of 1.0- to 6.2-fold) in *H. pylori*-positive patients.

In Trial 7, all the treatments showed small increases in gastrin concentrations in the initial healing period with the concentrations returning to normal or near normal (normal range < 40 pmol/L). In Trial 8, the number of patients with gastrin concentrations outside the normal range of less than or equal to 100 pmol/L was examined. Analysis of the data indicates that 24% of patients (20 of 82 total) had gastrin concentrations above the normal range at the end of the omeprazole maintenance period compared to 9% (10 of 108) at baseline and 6% (2 of 34) in the ranitidine maintenance group.

Only 53 post-marketing reports of hypergastrinemia were received through 30-Jun-98, including 9 reports in patients with established or clinically suspected ZES, 18 reports in patients without documented evidence of ZES or pernicious anemia, and 26 reports in patients with limited information for medical assessment. The reports of patients with ZES were remarkable for serum gastrin levels in excess of 400 pg/mL in all cases. Elevations of gastrin levels in reports of patients without documentation of ZES or pernicious anemia were more moderate.

### **9.3.2 Clinical Trial Data Examining ECL Cell Hyperplasia**

In man, uninhibited gastrin release is associated with an increase in the number of ECL cells of the oxyntic mucosa, but progression to ECL cell carcinoids has not been demonstrated solely as an effect of acid suppressive therapy. It is also postulated that in humans the trophic effects of elevated serum gastrin resulting from gastric acid suppression may produce an increase in the proliferation of the more predominant epithelial cells of the stomach and intestine, producing pathologic manifestations such as polyps, or in theory, cancer.

In long-term clinical studies assessing the effects of omeprazole on the development of ECL hyperplasia and gastric carcinoids in patients with GERD or peptic ulcer disease, it was noted that no patients developed dysplasia of ECL cells, or intramucosal or invasive ECL cell carcinoids. In the studies of longer duration, there were numerical increases in the numbers of patients with linear or micronodular ECL cell hyperplasia, but no cases of dysplasia or neoplasia were found.

In two US studies, patients treated with omeprazole for up to 24 months were assessed for ECL cell changes. Simple or linear ECL cell hyperplasia was observed in 8 of 57 patients in Trial 1. Micronodular hyperplasia was rarely observed. In fact, there were no patients with ECL cell micronodular hyperplasia at Last Assessment in Trial 1. In Trial 2, simple or linear ECL cell hyperplasia was observed in 61 of 308 in the omeprazole 10 mg and 20 mg groups versus 4 of 27 in the placebo group. Micronodular hyperplasia was identified in 4 of 170 in the omeprazole 20 mg group and 3 of 138 in the omeprazole 10 mg group after 2 years. No patients developed dysplasia of ECL cells, or intramucosal or invasive ECL cell carcinoid.

Similar results have been seen in two, long-term foreign clinical trials of patients treated with omeprazole for up to 24 months. Simple or linear hyperplasia was observed in only 2 of 155 patients in Trial 3 that assessed changes over 24 months. Micronodular hyperplasia was observed in five patients treated with omeprazole, 4 of whom were positive for *H. pylori* infection and had corpus atrophy of moderate degree. This finding supports observations that atrophy, which can be a manifestation of *H. pylori* infection, can lead to such a clustering of ECL cells that it fulfills

the histologic criterion for micronodular hyperplasia.<sup>67</sup> In a separate foreign study, Trial 4, 8 of 155 patients treated with omeprazole for up to 36 months developed diffuse, linear, or micronodular ECL cell hyperplasia. Again, no patients developed dysplasia of ECL cells, or intramucosal or invasive ECL cell carcinoid in either study.

Additionally, ECL assessments were available from two, very long-term, foreign treatment studies (12 and 14 years). Diffuse, linear, or micronodular ECL cell hyperplasia increased from 21 patients at Baseline to 64 patients at Last Assessment in Trial 5, a 12 year study (262 patients), and from 10 patients at Baseline to 30 patients at Last Assessment in Trial 6, a 14 year study (83 patients). In the 14 year study, two patients developed adenomatoid ECL cell hyperplasia, both associated with severe gastric gland atrophy. No patients developed dysplasia of ECL cells, or intramucosal or invasive ECL cell carcinoid in either study.

In Trial 7, there was no evidence of any change in endocrine cell counts (chromogranin, serotonin, or somatostatin cells) from the gastric biopsies in the three treatment groups during the study. Trial 8 showed slight increases in endocrine cell hyperplasia during four years of treatment with omeprazole.

Of the 21 post-marketing reports of ECL cell hyperplasia received through 30-Jun-98, 12 involved patients with established or clinically suspected ZES. The remaining 9 reports involved patients without documented evidence of ZES or pernicious anemia. Among these latter reports, insufficient information was available to include or exclude the possibility of gastrinoma or pernicious anemia. In several cases, the descriptions of concomitant atrophic gastritis and intestinal metaplasia suggest the possibility of either pernicious anemia or ECL cell clustering (so-called ECL cell pseudohyperplasia) secondary to atrophic gastritis, rather than a manifestation of drug-induced hypergastrinemia.

Of the 32 post-marketing reports of gastric, duodenal, or gastroduodenal carcinoids received through 30-Jun-98, 18 involved patients with established or suspected ZES. The remaining 14 cases involved patients without documented evidence of ZES or pernicious anemia. In the latter group of reports, there was usually insufficient information provided to make a determination of the presence or absence of gastrinoma, but in several cases there was evidence suggesting gastric acid hypersecretion based on the severity of symptoms or findings that were reported. Eight additional cases of carcinoids were also identified, two in the small intestine and six with the GI anatomic site unknown. These cases do not meet the criteria specifically addressed in this category (i.e., carcinoids anatomically situated in the stomach or duodenum), they are mentioned here for completeness.

### **9.3.3 Literature Perspective, Clinical Trial Data, and Post-Marketing Reports Examining Fundic Gland Polyps**

Fundic gland polyps are rare, asymptomatic, and benign lesions that can occur in patients with familial adenomatous polyposis or sporadically in the general population. These polyps may be more common in patients who are treated long-term with omeprazole or other antisecretory medications. But no controlled, prospective studies exist to scientifically assess this. There is no evidence that fundic gland polyps progress to adenomas or gastric malignancy, and they have been observed to regress when therapy with omeprazole is discontinued.

The development of parietal cell hyperplasia, fundic gland polyps, and hyperplastic polyps are potential outcomes associated with long-term treatment with omeprazole and other antisecretory therapies. These entities are asymptomatic and are not associated with other known deleterious tissue effects, nor are they predisposed to gastric malignancy when they arise in association with long-term treatment with omeprazole.

The histology of fundic gland polyps was originally described by Elster in Germany.<sup>68</sup> Their pathology is remarkable for hyperplastic foveolar epithelium and a glandular component that is often cystic. These polyps lack adenomatous change, and thus, have no cancer potential. The use of the nomenclature “fundic gland polyps” reflects the American influence on terminology for the anatomy of the stomach, for which “fundus” refers to the gastric body where these polyps are most commonly found.<sup>69</sup>

Fundic gland polyps were first reported as spontaneous lesions unrelated to drug therapy or associated disease states, but these have also been reported in individuals with the inherited genetic syndrome, familial adenomatous polyposis, otherwise known as Gardner’s syndrome.<sup>70-77</sup> Fundic gland polyps may be multiple in number, and are generally small (less than 10 mm).<sup>74</sup>

The incidence of fundic gland polyps is 0.085% to 1.9% in individuals without familial adenomatous polyposis (23 of 27,000 cases) and 38.7% in those with this syndrome (12 of 31 cases).<sup>72,75</sup> These polyps are reported to be present in approximately 2% of patients having upper endoscopy.<sup>69</sup> The natural history of fundic gland polyps in patients without familial adenomatous polyposis is benign and is characterized by regression, or complete disappearance of the polyps, reduction in the number of polyps present, or spontaneous increases in the number of polyps.<sup>72,76</sup>

A search of the published medical literature has shown that cases of parietal cell hyperplasia and fundic gland polyps occurring with the use of omeprazole have been reported exclusively as selected case series or under inadequately controlled circumstances.<sup>78-99</sup>

Trial 6, an international, open-label, uncontrolled study, looked at the long-term safety of omeprazole treatment in patients with peptic ulcer or reflux esophagitis disease refractory to H2-antagonists and ineligible for surgery. Although the study was not designed *a priori* to specifically study the occurrence of gastric polyps, endoscopic data was available from baseline and at the end of the study. Data on treatment-emergent gastric polyps was collected and recorded for up to 8 years. Although treatment-emergent polyps were noted in a small proportion of patients at variable time points, the lack of a control arm in this study confounds the assessment of the relevance of these findings.

Only 97 post-marketing reports of benign gastric or duodenal polyps were received through 30-Jun-98, including 3 reports of parietal cell hyperplasia, 39 reports of fundic gland polyps, 23 reports of benign gastric hyperplastic polyps, 27 reports of benign gastric polyps not otherwise specified (NOS) histologically, 2 reports of benign gastric adenomatous polyps, and 3 reports of benign duodenal adenomatous polyps.

Parietal cell hyperplasia and fundic gland polyps lack neoplastic elements on histopathologic examination, and are therefore believed to lack the potential to progress to gastric malignancy. Parietal cell hyperplasia can be a manifestation of the trophic effects of elevated serum gastrin



levels, although this was not reported in the 3 spontaneous reports. Parietal cell hyperplasia may progress to fundic gland polyps, and was associated with such polyps in some reports. Fundic gland polyps also can be a manifestation of the trophic effects of elevated serum gastrin levels, although this was documented in only 2 spontaneous reports.

Hyperplastic polyps of the stomach are common and occur sporadically. Several reports of hyperplastic polyps did not include information on the pre-treatment status of the gastric mucosa, and thus polyps may have been present prior to initiation of therapy with omeprazole. It should be noted that fundic gland polyps are composed of both hyperplastic epithelium and cystic glandular structures. Therefore, it is possible that histologic evaluation of biopsies of fundic gland polyps may only reveal hyperplasia, leading to an incorrect diagnosis of hyperplastic polyps. In addition, it is not clear from these spontaneous reports whether the diagnosis of hyperplastic polyps was based on a visual endoscopic examination or on biopsy histology, which is more sensitive and specific than the visual impression.

Adenomatous polyps of the stomach and duodenum have cancer potential. The 5 reports of benign gastric or duodenal adenomatous polyps contain limited information and/or suggest that these lesions may have been present prior to initiation of treatment with omeprazole.

#### **9.3.4 Clinical Trial Information and Post-Marketing Reports Examining Colon Adenomatous Polyps and Adenocarcinoma**

Because gastrin receptors have been detected on plasma membranes of noncancerous and cancerous colon cells, as well as on gastric epithelial cells, concerns have been raised that trophic effects of hypergastrinemia, resulting from PPI use, might increase the proliferation of gastric and colonic epithelial cells. This concern has therefore led to speculation that proton pump inhibition may lead to an increased risk of developing gastric and colonic adenomatous polyps and adenocarcinomas or of acceleration of the growth of such lesions. Available studies do not substantiate this theory in man.

Adenocarcinoma of the colon and rectum is a major cause of morbidity and mortality in the United States, with approximately 56,000 deaths and 150,000 new cases per year.<sup>100</sup> Progression to cancer in the large intestine is a complex, multiple-step pathologic process involving an accumulation of genetic abnormalities associated with alterations in cell growth (cellular proliferation) and biologic invasiveness that characterize cancer. The morphologic evidence of this process is the adenoma-carcinoma sequence, which has been related to specific molecular genetic events, such as allelic loss and/or mutations of the *hMSH2*, *hMLH1*, *APC*, *K-ras*, *DCC*, *p53* genetic loci.

The potential role of gastrin in the pathogenesis of colorectal adenocarcinoma has been reviewed.<sup>101-106</sup> Although gastrin is a known trophic hormone for the gastric mucosa, its effects on the colonic mucosa have been debated. Gastrin can increase proliferation of colonic epithelial cells, but patients with ZES or pernicious anemia with severe hypergastrinemia do not evidence an increased risk for colorectal adenomatous polyps or adenocarcinoma.<sup>107,108</sup> The most recent data indicate that colorectal cancer cells produce incompletely processed forms of gastrin, and a subset of these cancers bear novel gastrin receptors capable of binding these species. These observations, coupled with the lack of association between colorectal neoplasia and hypergastrinemic states, suggest that some colorectal cancers undergo growth stimulation from

incompletely processed gastrin species via autocrine proliferation rather than from increased circulating gastrin produced as a result of acid suppressive therapies.

The published data do not suggest the presence of an increased risk of colorectal adenocarcinoma resulting from hypergastrinemia that is associated with acid suppressive therapy.<sup>109-128</sup> Increased serum gastrin has been reported in subsets of patients with colorectal adenocarcinoma, possibly as a result of elevations of an incompletely processed form of the hormone, coincidental infection with *H. pylori* or other factors. The data suggest that growth of colorectal adenocarcinoma may be in part driven by autocrine stimulation of cells mediated by immature forms of gastrin that bind to novel types of cell receptors. There is no evidence that hypergastrinemic states, including those associated with long-term omeprazole treatment, other antisecretory medications, or primary disease states such as ZES or pernicious anemia, promote colorectal carcinoma formation or growth.

The published data do not support an association between hypergastrinemia and the development of colon cancer in humans. In addition, there is no evidence in humans of any trophic effect by hypergastrinemia on this tumor type following long-term exposure to antisecretory therapy.

Of the long-term clinical trials summarized in this document, Trial 1, a US double-blind study to determine whether long-term therapy with omeprazole or an H<sub>2</sub>RA will alter the natural course of Barrett's esophagus and result in regression on the area of esophageal involvement, was the only study that specifically addressed and studied colon pathology. Safety assessment included colonoscopic evaluation of polyps. There was no significant difference between treatment groups in the development of colon polyps > 3 mm in diameter following 24 months of treatment. For patients participating in the other long-term studies, there were 9 cases of colon carcinoma reported as adverse events. In six of these 9 cases, the carcinoma was either pre-existing (2 cases) or was reported within 6 months of initial omeprazole exposure (4 cases). The remaining 3 cases occurred with a time to onset of six months or greater.

Only 22 post-marketing reports of benign colon polyps were received, through 30-Jun-98 including 12 reports of inflammatory or hyperplastic polyps, benign polyps, or colon polyps not otherwise specified (NOS) histologically, and 10 reports of benign colon adenomatous polyps.

Inflammatory and hyperplastic polyps of the colon do not progress to colon malignancy. The reported benign polyps of the colon may have been so characterized based on endoscopic visual impression or histopathology. Reports of colon polyps NOS contained no further information as to their histologic characteristics and neoplastic potential.

Adenomatous, or villoglandular, polyps of the colon have the potential to progress to malignancy. As previously discussed, the progression of colon adenomatous polyps to malignancy is a complex process. The malignant potential of the adenomatous polyp depends on size, number, architectural type, and degree of atypia. Most adenomas take at least 3 to 7 years to progress to frank malignancy. In general, the prevalence of colon adenomas in a given country parallels the frequency of colon cancer in that country. Age is a major determinant and risk factor of the frequency of occurrence of adenomatous polyps. The prevalence of adenomas increases after 50 years of age with a peak prevalence of 60 years of age. Hereditary factors play a role in the sporadic occurrence of adenomas and a family history increases the risk for their

development. Environmental factors that contribute to the risk of developing adenomas include diet, that is, an increase in fat intake and a decrease in fiber intake (as noted in the US), as well as an increased concentration of bile acids and an increased concentration of fecal bacteria.

Although adenomatous polyps are common and occur sporadically, only 10 spontaneous AE reports of colon adenomatous polyps were received during the 10 years of clinical experience with omeprazole following market approval. In several cases, risk factors for colorectal neoplasia were not reported nor were the results of pre-treatment endoscopy to screen for colon polyps.

Seven individuals had polyps detected within 12 months of initiating omeprazole therapy. It would be unlikely for adenomatous polyps to develop within this time period.

The prevalence of colon adenomatous polyps in individuals greater than 50 years of age is increased compared to that of the general population. In these 10 cases, 8 individuals were over 50 years of age. One patient had a family history of colon cancer; 1 patient had a history of colon adenomas. The chronology of events and available information do not support a drug-event relationship in these cases of colon adenomatous polyps.

Only 41 post-marketing reports of definite or possible colon adenocarcinoma were received through 30-Jun-98. Reports of colon adenocarcinoma developing within 6 months of initiation of treatment with omeprazole were excluded because it is unlikely for this disease to become manifest within such a short time period. There were 9 reports for which a diagnosis of colon adenocarcinoma could not be definitively ruled out upon assessment by the sponsor's medical officer. For 2 of these 9 reports, the time to onset of the event was unknown. For the 32 reports received where definite or possible colon adenocarcinoma were reported, the time to onset of colon adenocarcinoma could not be determined in 18 of these 32 reports.

The development of colon adenocarcinoma is a complex and multifactorial process. Heredity (family history) is the principal feature used to identify risk for developing colon adenocarcinoma. Age is a known risk factor for the occurrence of adenocarcinoma with the prevalence of colon adenocarcinoma increasing after 55 years. The cellular damage from exposure to environmental carcinogens accrues over many years. Environmental risk factors considered to play a role in the progression to this type of malignancy are dietary pattern and alcohol consumption. As previously discussed, the potential role of gastrin in the pathogenesis of colon adenocarcinoma is considered to be controversial.

Although colon adenocarcinomas are common, occur sporadically, only 14 reports with a time to onset greater than 6 months during omeprazole therapy have accumulated from both clinical trials experience and spontaneous post-marketing reports. In several cases, risk factors for colon adenocarcinoma were not reported nor were the results of pre-treatment endoscopy to screen for colon cancer.

Seven of the 14 individuals had colon cancer detected within 12 months of initiating omeprazole therapy. It would be unlikely for colon adenocarcinoma to develop within this time period. The duration of drug exposure does not appear to be a factor influencing the occurrence of colon cancer as for only 4 of the 14 individuals, omeprazole exposure was greater than 24 months. In these 14 reports, 11 individuals were over 50 years of age. The prevalence of colon

adenocarcinoma in individuals greater than 50 years of age is increased compared to that of the general population. The chronology of events and available information do not support a drug-event relationship in these cases.

### **9.3.5 Clinical Trial Data and Post-Marketing Reports Examining Atrophic Gastritis and Potential for Progressive Histologic Alterations**

Atrophic gastritis, a chronic inflammation of the stomach with atrophy of the gastric glands, has occasionally been noted in gastric corpus biopsies of patients treated long-term with omeprazole or ranitidine. It has been suggested that long-term acid suppression with PPI, and the associated decrease in the production of hydrochloric acid, may result in the development of gastric gland atrophy and atrophic gastritis. Although atrophic gastritis has been noted in gastric corpus biopsies of patients treated long-term with omeprazole, this pathology appears to be associated with *H. pylori* infection. Studies have shown that atrophic gastritis is common in *H. pylori*-infected patients who have not been given antisecretory therapy. There has been no conclusive evidence that acid suppression contributes to the development of atrophic gastritis or to the potential for progressive histologic alterations.

Recent publications, appearing in the medical literature, provide information that 1) reinforces the importance of the contribution of *H. pylori* infection and its interplay with other factors in multistep gastric carcinogenesis; 2) describes the continuing difficulties in achieving satisfactory agreement among pathologists on the interpretation of gastric gland atrophy in gastric mucosal biopsies; 3) reveals inconsistent observations regarding the reversibility of gastric mucosal pathology (atrophic gastritis, intestinal metaplasia) following eradication of *H. pylori* infection; and 4) offers limited new information regarding the necessity of eradicating *H. pylori* prior to long-term therapy with PPI, but demonstrates that such therapy does not predispose to the development of precursor lesions of gastric adenocarcinoma, such as Types II or III intestinal metaplasia or gastric dysplasia.

Published controlled and uncontrolled prospective studies of patients receiving long-term therapy with PPI were largely conducted in Europe, varied in the length of follow-up, and were flawed in study design. These studies discussed the possible association between the development of histopathologic abnormalities of the gastric mucosa (atrophic gastritis, intestinal metaplasia) and *H. pylori* infection. However, they do not provide definitive conclusions regarding a causal association with omeprazole or the necessity of eradicating *H. pylori* infection when considering long-term acid inhibitory treatment.

The published medical literature supports and reinforces the conclusion that there is no evidence of the long-term use of omeprazole increasing the risk of the hypothetical sequelae of *H. pylori*-associated atrophic gastritis, Type II or III variants of intestinal metaplasia, gastric dysplasia, or gastric adenocarcinoma.

Trial 1, a double-blind, multicenter, parallel group study, was conducted to determine whether long-term therapy with omeprazole or a histamine-2 receptor antagonist alters the natural course of Barrett's esophagus and results in regression on the area of esophageal involvement during a two-year treatment period.

Very few cases of corpus atrophic gastritis were identified in this study. Four of 73 patients (5.5%) had corpus atrophic gastritis at Baseline. Three of these patients were in the ranitidine

group, while 1 was in the omeprazole group. Only 1 of 39 patients (2.6%) from the omeprazole group had mild grade atrophic gastritis at the end of treatment. No patient developed gastric mucosal dysplasia or adenocarcinoma. Based on Last Assessment biopsy results, there was no significant difference between patients treated with omeprazole and those treated with ranitidine in the development of corpus atrophic gastritis or intestinal metaplasia.

In Trial 2, investigators compared omeprazole vs. placebo in the maintenance treatment of patients with active duodenal ulcers healed by omeprazole. This study was conducted over a two year period.

Atrophic gastritis data was obtained for patients completing 24 months of therapy without ulcer recurrence. Because of treatment failure, many more patients in the placebo arm were unable to complete the study. Analysis of atrophic gastritis data from corpus biopsy specimens revealed that only a very small percentage of patients developed mild/moderate atrophic gastritis at 24 months (5.6% (6 of 108) in omeprazole 20 mg group, 0% in the omeprazole 10 mg group, and 0% in the placebo group). Intestinal metaplasia was observed in 1 patient in the omeprazole 20 mg daily group.

Trial 3 was conducted comparing omeprazole vs. ranitidine in the long-term treatment of patients with Barrett's esophagus. Moderate atrophy of the corpus mucosa was observed in 4 patients (3 patients treated with omeprazole and 1 patient treated with ranitidine) at the end of treatment. One of these patients also had moderate atrophy at Baseline. All patients with atrophy were *H. pylori*-positive. Two of these patients had previously undergone fundoplication and vagotomy. No patient developed gastric mucosal dysplasia or adenocarcinoma.

In addition, Trial 4 was conducted comparing omeprazole vs. anti-reflux surgery in the long-term management of peptic esophagitis. The number of patients in the omeprazole group with atrophy did not change from Baseline to end of treatment (10 of 155 at both time points), but there was some increase in severity across the group. In the surgery group, 4 more patients had atrophy at the end of treatment than at Baseline (14 vs. 10 of 144), but the severity remained similar across the group.

Atrophy was observed mainly in the *H. pylori*-positive patients. However, mild atrophy was present at Baseline in 3 patients with *H. pylori*-negative status in the omeprazole group and in 1 patient in the surgery group. At the end of treatment, mild atrophy was present in 4 patients with *H. pylori*-negative status in the surgery group, but not in the *H. pylori*-negative patients in the omeprazole group. There were 7 of 40 patients with *H. pylori*-positive status from the omeprazole group with some degree of atrophy at Baseline (all mild), and this number increased to 10 of 40 patients by the end of the study (3 patients with mild atrophy, 6 patients with moderate atrophy, and 1 patient with severe atrophy). In the surgical group, the number of patients with *H. pylori*-positive status with atrophy was 9 of 53 at entry (6 patients with mild atrophy, 3 patients with moderate atrophy) and 10 of 53 patients at the end of the study (7 patients with mild atrophy, 2 patients with moderate atrophy, 1 patient with severe atrophy).

The occurrence of intestinal metaplasia was rare in both the omeprazole (3 of 155) and surgery (4 of 144) groups at Baseline and did not increase during the course of the study. Intestinal metaplasia was found to be present at the end of the study only in *H. pylori*-positive patients. No patient developed gastric dysplasia or adenocarcinoma.

Extended long-term studies have also been conducted to assess the safety and efficacy of omeprazole. Trial 5, an open-label study lasting twelve years involved patients with peptic ulcer and esophageal reflux disease. Patients treated continuously with omeprazole for at least 5 years were assessed. The *H. pylori* status of some patients appeared to change from Baseline to end of treatment. A total of 9/142 patients with *H. pylori*-negative status became positive and 41/114 patients with *H. pylori*-positive status became negative. The change to negative *H. pylori* status may have been a result of eradication (accidental or intentional), or to atrophy development, while changes to positive *H. pylori* status may have been the result of infection being acquired during the study.

Among patients for whom gastric biopsies were available, the development of mild, moderate, or severe atrophic gastritis was greater in patients with *H. pylori* infection. In 89 *H. pylori*-positive patients, 11 had atrophic gastritis at Baseline compared to 35 at end of treatment. In 132 *H. pylori*-negative patients, 2 had atrophic gastritis at Baseline compared to 8 at end of treatment. One omeprazole patient developed gastric adenocarcinoma 21 months after initiation of omeprazole therapy.

Similarly, Trial 6, an open-label, prospective study was conducted in patients with peptic ulcer or reflux esophagitis disease refractory to histamine-2 antagonists and ineligible for surgery who were treated with omeprazole for up to 14 years.

Among patients for whom gastric biopsies were available, the development of mild, moderate or severe atrophic gastritis was greater in patients with *H. pylori* infection. In 55 *H. pylori*-positive patients, 4 had atrophic gastritis at Baseline compared to 15 at end of treatment. In 27 *H. pylori*-negative patients, none had atrophic gastritis at Baseline compared to 2 at end of treatment. One patient developed gastric adenocarcinoma 14 months after initiation of omeprazole therapy.

In Trial 7, there was no evidence of any change in histologic variables including frequency of acute inflammation, frequency and severity of chronic inflammation, frequency and severity of metaplasia, or frequency of atrophy. In Trial 8, there was no evidence of any significant change in the number of patients with gastritis.

If progression of atrophic gastritis to pre-cancerous gastric lesions and gastric adenocarcinoma occurred with the use of omeprazole, the extent and duration of drug exposure occurring in clinical studies and in marketed use should be sufficient to allow their recognition. This is particularly true among those patients who were chronically treated with this drug. Although the latency period between the initial exposure of omeprazole and the evolution of a gastric cancer may be considerably longer than the 10 years that this drug has been commercially available for use by patients, the development of potential histopathologic precursors of gastric adenocarcinoma (atrophic gastritis, intestinal metaplasia, dysplasia) would be expected to be detected if there is a causal link between omeprazole and neoplastic progression in the stomach.

Only 6 post-marketing reports of atrophic gastritis were identified through 30-Jun-98. Four reports did not include results of gastric mucosal biopsies and contained limited information. One report was an atypical case of achlorhydria in a patient with ZES. The *H. pylori* status was positive in 1 case, negative in 1 case, and not reported in 4 cases.

Only 5 post-marketing reports of intestinal metaplasia were identified through 31-Dec-98. Other diseases are implicated in 4 of the 5 cases, such as *H. pylori* infection or primary atrophic gastritis not associated with acid suppressive therapy.

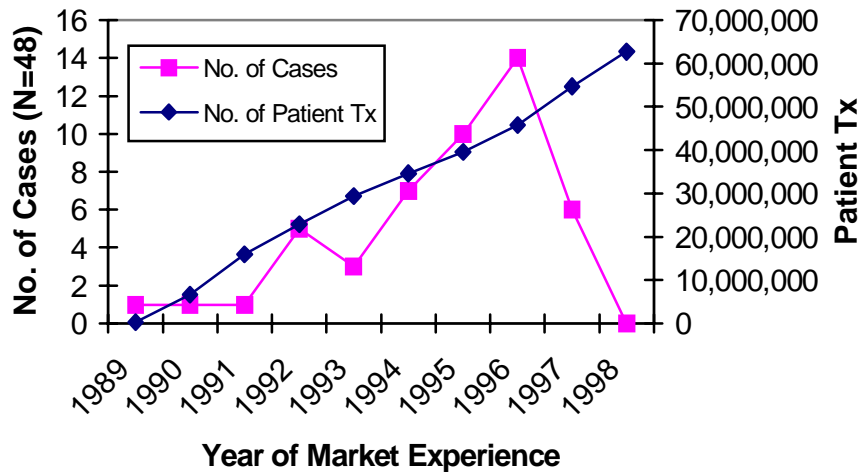
Only 1 post-marketing case of gastric dysplasia was identified through 31-Dec-98. The patient received omeprazole for treatment of a bleeding gastric ulcer. Subsequently, the ulcer tested positive for *H. pylori*.

A search of the AE database was conducted to identify reports of gastric adenocarcinoma and omeprazole. Reports were then assessed for cases for which there was an interval of at least 6 months between the initial omeprazole exposure and the diagnosis of gastric adenocarcinoma. This interval was taken into consideration because it is highly unlikely for gastric adenocarcinoma to develop within 6 months of initial exposure. A total of 49 reports were identified.

Over the last 10 years of patient use, the number of events of gastric adenocarcinoma has occurred in a nonlinear time trend with a peak number of cases noted in 1996 because of reports received from New Zealand as part of a post-marketing surveillance study. Not only did the number of reports not increase proportionally over time, there was also no proportional increase in the number of reports as contrasted with the yearly number of patient treatments, as noted in the figure below. If a drug-event relationship existed, a proportionate increase in the number of cases of gastric adenocarcinoma would be expected. This time-trend analysis supports the lack of a causal relationship between omeprazole and gastric adenocarcinoma.

**FIGURE 9.1**

**REPORTS OF GASTRIC ADENOCARCINOMA CONTRASTED WITH PATIENT TREATMENTS**



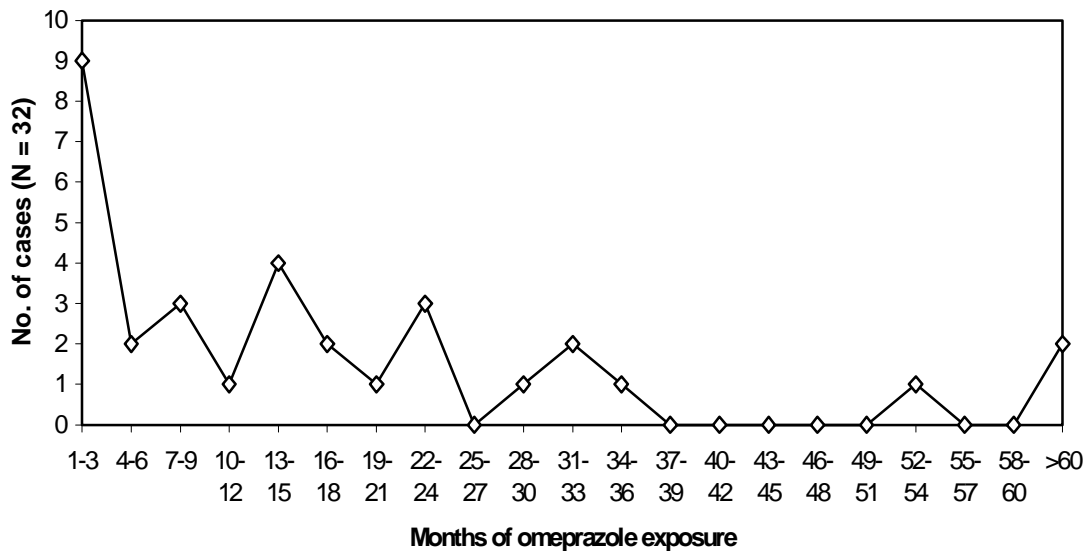
The y-axis variables reflect yearly totals. A patient treatment (Tx) is defined as an individual prescription calculated by IMS MIDAS Database (1/89-12/98) to be an average of 38.54 counting units. One case report is not included in the total number of cases as the event did not occur during market experience.

When contrasting the number of cases of gastric adenocarcinoma with the duration of omeprazole exposure as noted in the figure below, a nonlinear (disproportionate) trend is observed. If a causal relationship between gastric adenocarcinoma and omeprazole existed, an increasing linear time-trend would be observed as the drug exposure time increased. This time-trend analysis supports the lack of a causal relationship between omeprazole and gastric adenocarcinoma. In fact, the number of cases of gastric adenocarcinoma appears to decrease with increasing duration of omeprazole exposure. This suggests that these cancers were already present in most patients when omeprazole treatment was initiated.



**FIGURE 9.2**  
**GASTRIC ADENOCARCINOMA AND DURATION OF OMEPRAZOLE EXPOSURE**

**Figure 2. Gastric Adenocarcinoma and Duration of Omeprazole Exposure**



Duration of omeprazole exposure is defined as the time from first dose to last dose. For 17 of the 49 AE patient reports, the duration of exposure was not reported.

Of the 49 cases, 71% occurred outside of the US. It is well known that the incidence of gastric adenocarcinoma is higher in several non-US countries than in the US. Forty-one percent of cases occurred in patients more than or equal to the age of 65 years. The risk of gastric adenocarcinoma increases with age. In 96% of cases, the *H. pylori* status was not reported. The risk of gastric adenocarcinoma is higher in patients infected with *H. pylori*.

**9.4 Conclusions**

Based on long-term Rx studies, continuous use of omeprazole up to 80 mg/day for 2 or more years does not lead to clinically significant abnormalities in gastrointestinal mucosa, such as gastric ECL cell carcinoids or gastric or colonic malignancies.