180/ M. WALSH

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**OPDRA POSTMARKETING SAFETY REVIEW**	
TO: Lilia Talarico, M.D., Director Division of Gastrointestinal and Coagulation Drug Products HFD-180	**FROM:** Ann Corken, RPh, MPH, Safety Evaluator Mary Willy, PhD, Epidemiologist Ron Wassel, Pharm.D, Safety Evaluator Division of Drug Risk Evaluation I I (DDREII) HFD-440	OPDRA PID # D000223

DATE REQUESTED:
March 15, 2000

AUG 1 4 2000

NDA #19-810 SPONSOR: **MERCK**

DRUG :
OMEPRAZOLE (PRILOSEC)

EVENT:
EVALUATION OF SAFETY PROFILE FOR OTC SWITCH CONSIDERATION

Executive Summary: This consult was prepared in response to a request from Lilia Talarico of HFD-180 dated March 15, 2000 to review selected adverse events for omeprazole as the sponsor has submitted an NDA for a change to nonprescription status. The Adverse Event Reporting System (AERS) was searched for adverse event reports received for omeprazole up to March 31, 2000; 10,005 reports were identified in the database. Both domestic and foreign experience is addressed in this document, however, the focus is on the domestic experience.

The following issues have been reviewed in this consult: cases with an outcome of death, pediatric experience, drug interactions, serious hematologic events, serious liver events, serious skin disorders, vertricular arrhythmias, pancreatitis, ophthalmologic events, hearing disorders, cancer reports, and delay in diagnosis. For many of these adverse events, analysis of cases did not support significant safety concerns with general use of omeprazole; many patients had underlying conditions or were taking concomitant medications which could have contributed to the events. Summary of these issues appears at the end of each section. The most compelling issue reviewed was serious liver events, which were temporally related to omeprazole use and included serious outcomes such as liver transplants, deaths, and encephalopathy. Serious liver events are included in the current labeling for omeprazole. The pediatric cases reviewed tended to mirror events seen in adults; these typically were not healthy children prior to omeprazole use.

A review of AERS reports for gastrointestinal neoplasms (this body site had the most cancer-related reports in the AERS database) found that there was a trend for larger numbers of reports with a longer duration of omeprazole use, however, conclusions cannot be made because the data was derived from small numbers of spontaneous reports in the system. A review of the literature for omeprazole-related cancer revealed that the studies had limited numbers of patients exposed for short time periods with limited follow-ups. A review of the studies and case reports in the literature for delays in GI cancer diagnosis due to patient self-medication revealed that both prescription and OTC use of antacid drugs may delay diagnosis; additional studies are needed. Data regarding congenital anomalies will be addressed in a separate document.

Given the number of years that omeprazole has been on the market (11 years) and its extensive use (prescriptions), AERS report data suggest that the frequency of serious adverse events associated with omeprazole is low, however, with any evaluation of spontaneous reports, underreporting must be considered.

Reason for Request/Review:
Omeprazole (Prilosec) is indicated to treat duodenal ulcer and gastric ulcer, symptomatic GERD, erosive esophagitis, pathological hypersecretory conditions, and for maintanence of healing of erosive esophagitis. It is marketed by Astra Merck and was approved on September 14, 1989. Division HFD-180 has requested a review of selected adverse events for omeprazole because Astra Merck has petitioned for an Rx to OTC switch.

Reviewers' Signatures / Date:	Team Leader's Signature / Date:
Ann Corken Mary Willy Ann Corken, RPh, M.P.H. Mary Willy, Ph.D. Ron Wassel Ron Wassel, Pharm.D.	Toni Piazza-Hepp 8/11/2000 Toni Piazza-Hepp, Pharm.D.

Division Director Signature / Date: 8/14/2000

Kathleen Uhl MD for

Evelyn Rodriguez, M.D., M.P.H.

Cc: NDA # 19-810
HFD-180 Division File/Div Dir / MO / SMO / Project Manager
HFD-560 Division File/Div Dir / MO / SMO / Project Manager
HFD-440 Rodriguez/Willy/Corken/Wassel/Piazza-Hepp/Chron/Drug
HFD-400 Honig

TABLE OF CONTENTS

1.0 LABELING

The current Prilosec labeling contains the following events in the ADVERSE REACTIONS section relating to the corresponding body systems discussed in this review:

Hematologic—Rare instances of pancytopenia, agranulocytosis (some fatal)

Hepatic—Mild and rarely, marked elevations of liver function tests (ALT [SGPT], AST [SGOT], γ-glutamyl transpepridase, alkaline phosphatase, and bilirubin [jaundice]). In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy

Gastrointestinal—Pancreatitis (some fatal)

Skin—Rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe)

Special senses—Tinnitus

Under PRECAUTIONS:

Drug Interactions—Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

Pediatrics - Safety and effectiveness in pediatric patients have not been established.

Pregnancy Category C - Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Carcinogenesis - The labeling refers to studies in rats, at daily doses approximately 4 to 352 times the human dose, which produced gastric ECL cell carcinoids in a dose-related manner (incidence higher in female rats, which had higher blood levels of omeprazole). Gastric carcinoids seldom occurred in the untreated rat.

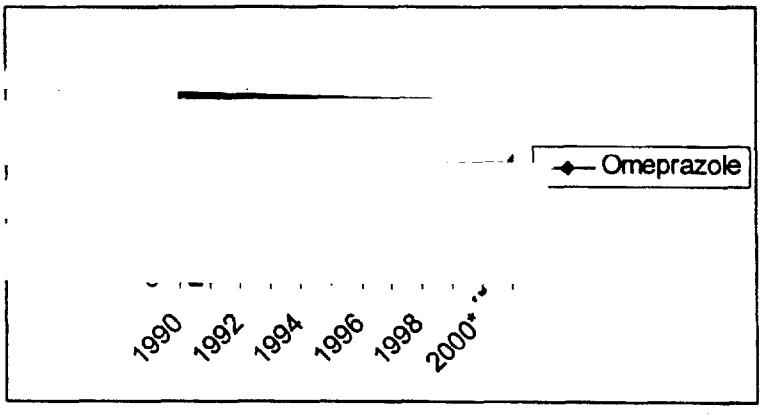
2.0 INTERNATIONAL EXPERIENCE

To date, Sweden is the only country that has granted nonprescription status to omeprazole. The MUPS dosage form (10 and 20 mg) of omeprazole was approved in April 2000 for the prevention and treatment of heartburn. Since the switch was recent, there are no data regarding nonprescription use in Sweden.

3.0 DRUG USE

The chart below summarizes projected total prescriptions of omeprazole dispensed by retail pharmacies (chain, independent, food store, and mail order) in the U.S. from January 1, 1990 through March 31, 2000. A total of prescriptions have been filled in the specified time period.

*Jan-Mar



The table below represents projected estimated proportion of omeprazole use by gender from January 1, 1989 through March 31, 2000.

Total % Use by Gender	
Female	
Male	
Unspec	
Total	100%

The table below shows projected estimated proportion of omeprazole use by age category from January 1, 1989 through March 31, 2000.

Total% Use by Age Bracket (in years)	
00 to 10	
11 to 20	
21 to 30	
31 to 40	
41 to 50	
51 to 60	
61 to 70	
71 to 80	
81 to 90	
91 to 100	
101-110	
Unspec	
Total	100%

This information is from IMS Health National Prescription Audit Plus (on-line) and National Disease and Therapeutic Index and is not to be used outside of the FDA without prior clearance by IMS Health.

4.0 ADVERSE EVENTS OVERVIEW

There are a total of 10,005 adverse reaction reports of any nature for omeprazole from time of marketing through March 31, 2000 in the Adverse Event Reporting System (AERS). A total of 579 reports with a death outcome will be further discussed in this document. More than half (5431) of the reports were received from the U.S.; 533 of the reports were received from France, 298 of the reports were received from the United Kingdom, 203 of the reports were received from Germany, and 180 of the reports were received from Japan. Attachment A is a listing of MEDDRA Preferred terms (PT) by decreasing order of frequency where there were 10 or more cases per event in AERS. Since these are raw figures from AERS, some of the numbers may represent duplicates.

5.0 DEATH OUTCOME CASES

AERS was searched for reports involving omeprazole that were received by the FDA up through and including March 31, 2000 and resulted in an outcome of death. A total of 579 reports were retrieved. From these results, a search was conducted to separate the data into domestic and foreign reports, which resulted in the identification of 184 domestic reports. The remaining 395 foreign reports is a raw number and does not reflect the actual number of cases (no attempt was made to review these reports). Reviewing these 184 domestic reports identified 98 unduplicated cases. Of the 98 cases, 52 were excluded from further review for the following reasons: 3 cases that were actually foreign reports, 3 cases that were incorrectly entered into AERS as having a death outcome, 1 case in which the adverse event that led to the patient's death (bone marrow depression) was present prior to omeprazole therapy, and the remainder in which the patient's death was not related to the use of omeprazole but rather their underlying disease such as sepsis or carcinoma. The remaining 46 cases were analyzed for cause of death and are discussed below.

5.1 Gastric carcinoma (n = 3)

Three cases, although probably not omeprazole–related deaths, are of interest to report here in that they involved the use of omeprazole for stomach pain in which the patients eventually died due to gastric carcinoma. Two of these cases (one unknown demographics; one 46-year-old male) involved short–term omeprazole use with no relief of pain and were eventually diagnosed with the malignancy. One case (unknown demographics) was described as the "patient died from stomach cancer after two and a half years of therapy with omeprazole."

Another case involved an 80-year-old male who took omeprazole 20 mg daily for seven years for the treatment of gastroesophageal reflux disease. The patient was eventually diagnosed with "abdominal carcinomatosis" with a biopsy revealing "adeno-carcinoid carcinoma." The patient had a history of pancreatic cancer treated with four courses of chemotherapy and had documented "carcinomatosis of the peritoneal cavity." Two years after the original diagnosis of abdominal carcinomatosis, biopsies of the gastric body and antrum revealed "mild to moderate chronic gastritis with no malignancies, no metastatic disease, no intestinal metaplasia, no helicobacter and no mention of enterochromaffin cell hyperplasia or carcinoid." The reporter indicated the patient died from "probable poorly differentiated neuroendocrine carcinoma of unknown primary."

5.2 Complications of pregnancy (n = 4)

There were four cases involving the death of a fetus or infant in which the women took omeprazole during their pregnancy. Two of the cases were stillbirths, one case involved a child born with hydranencephaly who died on day 1, and one case of a child born with a hypoplastic heart who eventually died on day 74 following numerous open heart procedures.

5.3 Drug interactions (n = 9)

There were nine cases in which the death outcome may have been due to a drug interaction. Each of the offending drugs is involved in the cytochrome P-450 metabolic pathway. Six of the cases reported the cause of death as cardiac arrest or sudden death. In these six cases, four involved cisapride, one involved amitriptyline, and one involved nicardipine. The other three cases in which the cause of death was not reported involved one case each of the use of omeprazole with fluconazole, clarithromycin, and cisapride.

5.4 Hepatic failure (n = 8)

Demographic data

AGE (years) (n = 7):	Range—48 to 83 years; Median—66 years; Mean—66
SEX:	Female—4; Male—4
REPORTING YEAR:	1990—2; 1992, 1996, 1997—1 each; Unknown—3
REACTION ONSET (DAYS) (n=5):	Range—7 to 150 (approx.) days; Median—13 days; Mean—48 days (approx.)
DOSE PER DAY (n = 7):	20 mg—6; 40 mg—1

In six of the eight cases there were possible confounding factors including a history of alcohol abuse (two cases), a history of liver disease (two cases), and concomitant drug therapy that has been associated with liver dysfunction (one case with pravastatin and one case with quinapril).

Representative Case of Hepatic Failure Death

Case# 5336663 (Mfr.# 19951100203) A 62-year-old male with a history of intermittent epigastric and right upper quadrant pain associated with reflux symptoms unsuccessfully treated with ranitidine, erosive esophagitis, hypertension, and coronary artery disease was placed on therapy with omeprazole 20 mg daily. Other medication, which the patient had been taking for over one year, included atenolol, diltiazem, and aspirin. Seventeen days after starting omeprazole, the patient was hospitalized with a four day history of worsening epigastric pain, anorexia, nausea and vomiting, and one day of weakness and dizziness. The patient denied any history of hepatitis, blood transfusions, toxin exposures, alcohol or acetaminophen use. He was alert with a mild slowing of mentation and a slight flapping tremor. By the next morning he was obtunded. His ammonia had reached 238 micromol/L and his asterixis was much more marked. He was transferred to another hospital for a possible liver transplant, but no liver donor was available. Hepatitis serologies were all negative. His hospital course was complicated by respiratory failure, oliguric renal failure, and seizures and he died five days after initial presentation. Autopsy revealed severe hepatic necrosis and special stains for other causes were negative. This was reported in the published article Jochem V, Kirkpatrick R, Greenson J, et al. Fulminant hepatic failure related to omeprazole. Am J Gastroenterology 1992; 87: 523-5.

5.5 Pancytopenia / Bone marrow depression (n = 3)

Demographic data

AGE (years):	Range—60 to 85 years; Median—66 years; Mean—70.3
SEX:	Female—1; Male—2
REPORTING YEAR:	1990—1; 1993—1; Unknown—1
REACTION ONSET (DAYS):	Range—6 to 11 (approx.) days; Median—7 days; Mean—8 days (approx.)
DOSE PER DAY:	20 mg—1; 40 mg—1; 80 mg—1

Two of the cases had potentially confounding drug therapy with known adverse hematologic effects including the use of nortriptyline and ranitidine in one case, and multiple drug therapy with several antibiotics in the other.

Representative Case of Bone Marrow Depression Death

Case# 5512622 (Mfr.# 19961100176) An 85-year-old male with upper gastrointestinal bleeding secondary to gastric ulcer disease with gastritis and positive Helicobacter pylori was placed on therapy with omeprazole 20 mg twice a day along with clarithromycin 500 mg three times a day and metronidazole 500 mg three times a day. Six days later the patient was admitted to the hospital because of the following reported lab values: WBC 900 (25% seg), platelets 26,000, bilirubin 7.7, AST 6 times normal, ALT 2.5 times normal, and alkaline phosphatase 3 times normal. The patient's bone marrow showed almost complete bone marrow failure and subsequently he died secondary to severe sepsis.

5.6 Congestive heart failure (n = 3)

Demographic data

AGE (years) (n = 2):	54 and 56
SEX:	Female—2; Male—1
REPORTING YEAR:	1990—1; 1994—1; Unknown—1
REACTION ONSET:	6 days; 3 months; 4 years
DOSE PER DAY:	20 mg—1; 40 mg—1; 120 mg—1

In two of the cases the patients had a history of CHF prior to omeprazole therapy, but developed worsening heart failure and eventually died. In the case in which the patient had been taking omeprazole for four years, he had a severe myocardial infarction complicated by several cardiac arrests, which led to poor myocardial function and eventual death from heart failure. Whether omeprazole contributed to diminished cardiac function in any of these cases is unknown.

5.6 Miscellaneous Death Outcome Cases
There was one case of **toxic epidermal necrolysis** in a 77-year-old male after 15 days of omeprazole therapy 20 mg daily.

In another case, a male of unknown age developed an ileus and subsequent **pancreatitis** within one week after initiation of omeprazole therapy. Concomitant therapy included Augmentin, furosemide and an unspecified steroid for what was believed to be an immune-related thrombocytopenia. He was hospitalized, underwent surgery and died post-operatively.

There were two cases of deaths following **gastrointestinal hemorrhage** in patients of unknown age and gender. In one case omeprazole was given after intravenous cimetidine was used to treat the hemorrhage, but the patient subsequently experienced another hemorrhage and died. In the other case it is unclear whether the patient bled while on omeprazole or was being treated for the bleeding with omeprazole and eventually died.

An 87-year-old male treated with omeprazole 20 mg daily for approximately 8 months died from a "**gastric outlet obstruction and prolonged complications.**"

One patient committed **suicide** soon after starting omeprazole.

A case of **lymphoma** occurred in a male patient treated with omeprazole 20 mg daily for approximately 2 years for the treatment of reflux esophagitis.

There were eight poorly documented cases that were generally reported as death occurring while taking omeprazole or shortly after initiating omeprazole therapy. Three of these cases

may have been related to a cardiac arrest or arrhythmia, one case was reported as possibly related to the liver or the kidneys, and one case was noted to have a pain in the leg with subsequent chest pain prior to the patient's death.

5.7 Summary of Death Cases

Of the 46 cases that were reviewed, the most compelling cases had causes of death due to hepatic failure and bone marrow depression. The product labeling for omeprazole includes hepatic failure, pancytopenia/agranulocytosis, toxic epidermal necrolysis and pancreatitis as events with reports of fatalities. Deaths attributed to drug interactions and complications of pregnancy are also noteworthy. The one case of suicide may be of note in that depression is listed in the product labeling. It is difficult to make any kind of determination in the cases of congestive heart failure, gastrointestinal hemorrhage, gastric outlet obstruction, and lymphoma.

In the drug interaction section, mention is made that patients should be monitored to determine the necessity of adjusting the dosage of drugs metabolized by the cytochrome P-450 system when taken concurrently with omeprazole, although few drugs are given as examples (none of which are those that are mentioned above). In regard to pregnancy, the product labeling lists omeprazole as Pregnancy Category C and discusses sporadic reports of congenital abnormalities in humans and embryo/fetal toxicity in animals.

6.0 PEDIATRIC EXPERIENCE

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and age criteria of 0 to 16 years. The search produced 182 reports. These 182 cases were separated into serious (i.e., hospitalization, death, life threatening, disability) and nonserious outcomes; the cases with serious outcomes were separated into domestic and foreign and then checked for duplicates. Among these were 19 cases of congenital anomalies; an assessment of these cases along with other available epidemiologic data on this topic will be provided in a separate document. There were 20 other domestic pediatric cases and 28 foreign cases of a serious nature for review.

6.1 Deaths (n = 8)

There were a total of eight reports of deaths in children receiving omeprazole; seven of these reports were from foreign sources. Three patients died of cardiac arrhythmias; all three patients also were receiving cisapride concomitantly. Two patients died of hematologic events (thrombocytopenia and aplastic anemia); both patients had other serious medical conditions and were taking numerous concomitant medications. Two patients with end-stage renal failure received omeprazole; both patients received other medications that were considered suspect by the reporters. One patient experienced sepsis and died of cardiac arrest. One of the patients described above had received the IV form of omeprazole. These reports also are described below under their respective categories.

6.2 Carcinoma or neoplasms (n = 3)
U.S. experience- There were two cases. A 16-year-old boy developed a gastrin-producing chromafin-cell hyperplasia after taking 40 mg of omeprazole a day for an unknown duration; no other information was available. A 14-year-old boy was thought to have developed gastric carcinoma after taking 20 mg of omeprazole a day for an unknown duration; subsequent tests did not indicate carcinoma.

Foreign experience-One case of a testicular cyst was received through AERS.

6.3 Cardiac events (n = 5)
U.S. experience- A single case was identified of a 7-year-old boy who developed ventricular fibrillation and torsades de pointes and died after receiving 40 mg of omeprazole a day for 2.5 years; he had a history of congenital heart disease and was receiving numerous concomitant medications including cisapride.

Foreign experience-There were two cases of tachycardia, one case of QT prolongation/ asystole/cardiac arrest leading to death; both patients were receiving cisapride. There was one case of cardiac arrest leading to death.

6.4 Gastrointestinal events (n = 6)
U.S. experience-No cases of serious gastrointestinal events were received through AERS.

Foreign experience-There was one case of rectal hemorrhage, one case of severe epigastric pain and nausea, one case of epigastric pain and colic, one case of severe bloating and cramping, one case of hematemesis, and one case of GI hemorrhage reported through AERS; all patients had to be hospitalized because of the event.

6.5 Hematologic events (n = 5)
U.S. experience-There were two cases. A 15-year-old girl experienced thrombocytopenia (platelet count = 80,000) after taking 20 mg of omeprazole a day for two to three weeks; the event abated when omeprazole was discontinued. Her medical history included dyspepsia and Evans Syndrome; concomitant medication included prednisone. A 13-year-old girl experienced anemia, hematuria, lupus-like syndrome, and possible autoimmune syndrome after taking 20 mg of omeprazole a day for approximately three months; her symptoms worsened when omeprazole was replaced with ranitidine. Omeprazole therapy was reinitiated; the patient's outcome was not reported.

Foreign experience-There was one case of thrombocytopenia/leukocytosis, one case of thrombocytopenia, and one case of thrombocytopenia/aplastic anemia received through AERS. Two of these patients died.

Hepatic disorders (n = 2)
U.S. experience-A 15-year-old boy developed hepatitis after taking 20 mg of omeprazole a day for two months; the event abated when omeprazole was discontinued. The report provided very little information regarding the patient's medical history and concomitant medications.

Foreign experience-One case of increased liver enzymes was received through AERS.

6.6 Neurological events (n = 9)
U.S. experience-There were six cases. A 2-year-old boy developed ataxia, gait abnormalities, and coordination problems after taking 7 to 9 mg of omeprazole a day (duration unknown); the events resolved when omeprazole was discontinued and reappeared when omeprazole was reintroduced. Concomitant medications included cisapride, Benadryl, Intal, and Atrovent. The dose was titrated down and the patient continued on therapy without incident. A 12-year-old girl developed breakthrough seizures when omeprazole was added to her medication regimen that included phenytoin; her phenytoin levels were stable, but began fluctuating when omeprazole was introduced. The patient had a history of seizures, encephalopathy, attention-deficit disorder, possible hypothyroidism, and porphyria. She continued on omeprazole; her outcome was not reported. A 3-year-old girl with brain damage developed multiple seizures after taking 20 mg of omeprazole a day (duration not specified); concomitant medication included Depakote. The outcome was not specified; very little information was provided. A 10-year-old boy experienced a change in carbamazepine levels after taking 10 mg of omeprazole a day (duration unknown); his outcome was not reported. He had a history of seizures and was physically disabled; concomitant medications included carbamazepine, terbinafine, and diazepam. A 5-year-old girl experienced seizures (both focal and general) after receiving 20 mg of omeprazole a day (duration unknown); an EEG indicated a diagnosis of benign rolandic epilepsy. Concomitant medication included amoxicillin and Biaxin. Omeprazole was discontinued; the reporter stated that a lowered seizure threshold triggered seizures which is consistent with benign rolandic epilepsy. A 13-year-old girl experienced one seizure among other medical events (consumer report).

Foreign experience-One patient experienced an exacerbation of her movement disorder, one patient experienced extreme vertigo, and another patient experienced an increase in seizure activity.

6.7 Pancreatic events (n = 5)
U.S. experience-There were three cases. An 8-year-old boy with leukemia developed pancreatitis after taking 20 mg of omeprazole a day for six months; concomitant medications and outcome were not reported. A 3-year-old boy developed pancreatitis after taking 20 mg of cisapride a day (duration unknown); his outcome was not reported. His medical history included cerebral palsy, convulsions, and esophageal reflux; concomitant medications included cisapride, valproic acid, and multivitamins. A 14-year-old girl experienced elevated amylase and lipase after taking 40 mg of omeprazole a day for 3 days; she continued to take omeprazole and was diagnosed with pancreatitis 12 days later. The event was beginning to resolve when omeprazole was discontinued. Concomitant medications included acyclovir, Mag-Ox, prednisone, Procardia, Ativan, Zantac, and Lo/Ovral; her medical history included reflux esophagitis and aplastic anemia for which she was receiving a bone marrow transplant at the time of the report.

Foreign experience: There were two cases of pancreatitis received through AERS. One patient was receiving IV omeprazole; both patients had extensive medical histories and were taking numerous concomitant medications.

6.8 Renal events (n = 5)
U.S. experience-There were two cases. A 12-year-old boy developed an increase in creatinine (from 0.5 to 1.7) and an increase in blood urea nitrogen (BUN) (to 24 [baseline not reported]) after taking 20 mg of omeprazole a day for one week; the patient had Sanfilippi's syndrome, diabetes insipidus, hyponatremia, and acute urinary retention. Omeprazole therapy continued and his BUN and creatinine returned to normal. A 10-month-old boy developed nephrotic syndrome after taking 20 mg of omeprazole a day for one month; little information was provided other than the history of cystic fibrosis.

Foreign experience-One case of a patient with acute renal failure with hematuria and interstitial nephritis was received through AERS. Two patients in end stage renal failure received omeprazole and eventually died; both both patients received concomitant medications that were considered suspect by the reporter. One of those patients was receiving IV omeprazole.

6.9 Special senses (n = 4)
U.S. experience- A 6-year-old boy developed tinnitus and hearing loss soon after taking 5 mg of omeprazole a day to treat a stomach ulcer; eight months later the patient underwent an audiogram which revealed a significant drop in the high frequency range.

Foreign experience-There were two cases of blindness (one patient had optic neuritis and the other patient was receiving IV omeprazole) and one case of blurred vision received through AERS. The patient receiving IV omeprazole died (note that this case has been discussed under renal events as well).

6.10 Miscellaneous pediatric events (n = 5)
U.S. experience-There were two cases. A 12-year-old girl experienced diarrhea, rash, headache, backache, stomachache, tightening of the throat, and wheezing after taking 20 mg of omeprazole a day for 16 days. The patient had developed stridor and "noisy breathing" following an influenza-like illness. Omeprazole was stopped and the patient was reported as doing very well. Her medical history included GERD and depressive disorder; concomitant medications were not reported. A 7-year-old boy experienced metabolic acidosis after receiving 20 mg of omeprazole a day (duration unknown); his outcome was not reported. His medical history included partial epilepsy and changes in mental status; concomitant medication included phenytoin.

Foreign experience-There was one case of a polymyositis-like reaction, one case of a dermatomyositis-type reaction, and one case of angioedema and oral thrush reported through AERS.

6.11 Summary of pediatric events
The omeprazole labeling states that safety and effectiveness in children has not been established. The use of omeprazole in children represents less that 3% of total use. None of the pediatric reports received through AERS were particularly compelling. In general, most the pediatric patients described in this section had underlying conditions or were receiving concomitant medications making it difficult relate their outcome to omeprazole use. Further, the types of notable events were consistent with those of concern in adults (i.e. pancreatitis, liver events, hematologic events, drug interactions). Neurological events was the most frequent adverse reaction group; it appears that four patients had an interaction between omeprazole and their seizure medication and one patient was diagnosed with rolandic epilepsy.

7.0 DRUG INTERACTIONS

Omeprazole is metabolized by the cytochrome P-450 system. It is a substrate for isoenzymes 2C8, 2C18, and 2C19; an inhibitor of isoenzymes 2C8, 2C19, and 3A4; and an inducer for isoenzyme 1A2 (American College of Clinical Pharmacy [website=www.accp.com]). Therefore, omeprazole has the potential to interact with other medications also affected by these systems. The labeling states that omeprazole can prolong elimination of diazepam, warfarin, and phenytoin and that clinical reports have been received regarding interactions with cyclosporine, disulfiram, and benzodiazepines.

The Adverse Event Reporting System (AERS) was searched as of March 31, 2000 using omeprazole as suspect and concomitant drug and *Drug interactions* as the MEDDRA PT term. The search produced a total of 209 reports. The individual cases were reviewed for those drugs that had five or more reports (i.e., digoxin, sertraline, divalproex sodium, conjugated estrogens, and fluconazole). Warfarin and cisapride had more than five reports, but they were excluded from this review because an interaction with warfarin is listed in the omeprazole labeling and cisapride has been withdrawn from the market.

A hands-on review of the reports for the drugs mentioned above found a signal of an interaction involving decreased effectiveness of conjugated estrogens (eight cases) when given concomitantly with omeprazole. There were eight cases of a return of menopausal symptoms (e.g., breast tenderness, hot flashes, breakthrough bleeding, uterine bleeding, and increased night sweats) when omeprazole and conjugated estrogens were given concomitantly. Eight reports, however, may not be enough to indicate a definite interaction. Additionally, a possible interaction involving decreased effectiveness of sertraline and divalproex sodium was noted when given concomitantly with omeprazole (three cases reported for each drug).

8.0 SERIOUS HEMATOLOGIC EVENTS

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and *Marrow depression and hypoplastic anemias* and *agranulocytosis* as the MedDRA HLT and PT terms, respectively. The search produced 172 cases. These 172 cases were separated into domestic and foreign and checked for duplicates; only severe hematologic events (i.e., agranulocytosis, aplastic anemia, bone marrow suppression, pancytopenia, severe neutropenia [neutrophil count < 500]) were included for discussion. A total of 16 cases (5 domestic and 11 foreign) were excluded because they were nonserious hematologic events; the remaining 21 reports were duplicates. Thus, there were 47 domestic cases and 88 foreign cases available for review.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 47)

AGE (YEARS):	RANGE 17 to 85, MEAN 62 (n = 38)
SEX:	M (22), F (18), UK (7)
REPORTING YEAR:	1989 (1), 1990 (6), 1991 (4), 1992 (1), 1993 (8), 1994 (3), 1995 (2), 1996 (11), 1997 (2), 1998 (5), 1999 (3), UK (1)
REACTION ONSET (DAYS):	RANGE 4 to 1440, MEAN 142, MEDIAN 30 (n = 21)
DOSE PER DAY (MG):	20 MWF (1), 20 (28), 40 (4), 80 (1), 120 (1), UK (12)
DECHALLENGE POSITIVE:	17
RECHALLENGE POSITIVE:	1
OUTCOME*:	DIED(4), HOSP(25), LIFE-THREATENING(8), NONSERIOUS (4), OTHER (3), UK (9)
EVENT DESCRIPTION:	AGRANULOCYTOSIS (11), PANCYTOPENIA (24), APLASTIC ANEMIA (1), BONE MARROW SUPRESSION (6), MULTIPLE HEMATOLOGIC EVENTS (5)
PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE HEMATOL. EVENTS†	27

* Some patients had multiple outcomes.

† Concomitant medications including allopurinol, amitryptyline, atenolol, captopril, carbamazepine, ceftazidine, cyclosporin, diclofenac, diltiazem, fluconazole, furosemide, isorsorbide, mesalamine, metoclopramide, metoprolol, metronidazole, nortriptyline, prochlorperazine, ranitidine, tobramycin, and vancomycin.

In addition to the Domestic cases that were individually reviewed, there were 88 foreign cases of serious hematologic events in AERS (agranulocytosis [37], pancytopenia [24], aplastic anemia [8], bone marrow supression [8], multiple hematologic events [11]).

Representative Case of Serious Hematologic Event

Case# 4735645 (direct report) 1990) A 69-year-old female developed pancytopenia and eventually died after taking 20 mg of omeprazole a day for 16 days to treat reflux esophagitis unresponsive to ranitidine. The patient had been admitted to the hospital for inflammatory bowel disease; her medical history included surgery for lower GI bleeding and adult respiratory distress syndrome. Her lab values after 14 days of omeprazole therapy were reported as follows: WBC 400; Hgb/Hct 10.1/30.1 mg%; and platelets 80,000/mm^3. She developed cellulitis with generalized septicemia and died of bacterial endocarditis 33 days after omeprazole was discontinued. Concomitant medications included corticosteroids, Flagyl, Pamelor, Rowasa, and TPN; she also received a blood transfusion. The reporter stated that her WBC did increase after omeprazole was discontinued.

8.1 Summary of Serious Hematologic Events

This section describes cases of serious hematologic events associated with the use of omeprazole. Pancytopenia (rare) and agranulocytosis (some fatal) are labeled events. Of the four domestic deaths, three patients were receiving medications known to cause hematologic events (one of those patients was taking an 80-mg dose of omeprazole per day) and the fourth patient had a history of bone marrow suppression while taking indomethacin. Overall, more than half (27 out of 47) of the patients were receiving medications know to cause hematologic events. Many reports described in this section lacked specific information (e.g., concomitant medications, lab values) making it difficult to determine causality or severity.

9.0 SERIOUS LIVER EVENTS

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and *Hepatic disorders (exc neoplasms)* and *Liver transplant* as the MedDRA HLGT and PT terms, respectively. Domestic and foreign cases were searched separately. The search produced 208 domestic cases. These 208 cases were separated and checked for duplicates; only unduplicated cases with a serious outcome (i.e., death, life threatening, hospitalization, and disability) were included in this discussion (a total of 57 unduplicated domestic cases).

DEMOGRAPHIC DATA OF SERIOUS DOMESTIC CASES (n = 57)

AGE (YEARS):	RANGE 21 to 90, MEAN 59 (n = 45)
SEX:	M (23), F (28), UK (6)
REPORTING YEAR:	1989 (2), 1990 (10), 1991 (4), 1992 (9), 1993 (3), 1994 (6), 1995 (7), 1996 (5), 1997 (3), 1998 (6), 1999 (2)
REACTION ONSET (DAYS):	RANGE 1 to 730, MEAN 47, MEDIAN 15.5 (n = 36)
DOSE PER DAY (MG):	20 MG (35), 40 mg (5), 60 mg (1), 20-40 MG QOD (1), 20 INC. TO 40 MG (1), 20 mg QOD (1), UK (12)
DECHALLENGE POSITIVE:	25
RECHALLENGE POSITIVE:	1
OUTCOME:	DIED (8), LIFE-THREATENING (8), HOSP (40)*, DISABILITY (1)
EVENT DESCRIPTION:	HEPATITIS (14), HEPATIC FAILURE (16), JAUNDICE (14), MIXED EVENTS (HEPATOCELLULAR AND CHOLESTATIC) (13)
HISTORY OF ALCOHOL ABUSE	4
PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE HEPATIC EVENTS†	24

* Two patients required liver transplants.

† Concomitant medications included acetaminophen, allopurinol, amitriptyline, ciprofloxacin, cisapride, clonidine, conjugated estrogen, Darvocet N, Diflucan, Dyazide, diltiazem, enalapril, famotidine, halogenated anesthesia, Hyzaar, Naprosyn, nifedipine, Noroxin, Pravachol, quinapril, ranitidine, steroids, thorazine, Vasotec, verapamil.

In addition to the domestic cases that were individually reviewed, there were 199 foreign cases. A hands-on review and a check for duplicates of the foreign cases was not performed; a report of MEDDRA SOC and PT terms was printed and reviewed. The following counts of serious events were noted: hepatic failure (25), hepatic necrosis (11), hepatitis (all types) (41), cholestatic jaundice (25), and jaundice (33).

Representative Case of Liver Failure

Case# 3387227 (Mfr# 199910200349) 1999) A 42-year-old female experienced acute liver failure requiring a liver transplant after taking 20 of omeprazole a day for approximately 3 months to treat GERD. The patient had had prior exposure to omeprazole (dose and duration unknown). She developed pruritus, anorexia, and jaundice with elevated SGOT (2165 Units/L), billirubin (10 mg/dL), and alkaline phosphatase (292 Units/L); an HIDA scan of the liver revealed poor uptake and a biopsy indicated massive hepatic necrosis with proliferation of cholangioles. There was no indication of autoimmune hepatitis; hepatitis A and B and herpes virus screens were negative. Her condition deteriorated; she developed Grade I-II hepatic encephalopathy and asterixis. The patient underwent a liver transplant and made an uneventful recovery. Her medical history included hypothyroidism; concomitant medication included Synthroid.

9.1 Summary of Serious Liver Events

This section describes cases of hepatic events possibly associated with the use of omeprazole. The hepatic events discussed in this section are labeled events. The categories in Event Description section above are mutually exclusive (e.g., a case of hepatitis leading to liver failure would be recorded as liver failure). Overall, these cases are more compelling (regarding severity and association with omeprazole) than the cases for other events described in this document. Of the eight deaths, five of the patients were receiving medications known to cause liver events and/or had underlying conditions (including alcohol abuse) that were more likely the cause of death. Two patients required a liver transplant; one case is described above and the other case did not provide much information, but the reporter did state that there was no cause for the patient's hepatitis other than omeprazole use. Four patients developed encephalopathy and four patients had hepatic necrosis. Overall, 24 patients (out of a total of 57 patients) were receiving medications also known to cause liver events; 4 patients had a history of alcohol abuse.

10.0 STEVENS-JOHNSON SYNDROME / TOXIC EPIDERMAL NECROLYSIS

Previously, HFD-180 received a Monitored Adverse Reaction Report concerning severe skin reactions associated with omeprazole dated October 19, 1992, which presented two cases of Stevens-Johnson Syndrome (SJS) and three cases of toxic epidermal necrolysis (TEN) (Attachment B). This section updates that previous information.

AERS was searched for reports of SJS or TEN (MedDRA preferred terms [PT] STEVENS JOHNSON SYNDROME and EPIDERMAL NECROLYSIS) involving omeprazole that were received by the FDA from October 1, 1992 up through and including March 31, 2000. A total of 84 reports were retrieved, which represented 49 unduplicated cases. Forty-two of these cases were from foreign sources, primarily Germany (25), which is performing an extensive epidemiological study regarding severe skin reactions and maintains a registry of patients.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 7)

AGE (YEARS) (n = 6):	Range—47 to 72 years; Median—53 years; Mean—55.7
SEX (n = 6):	Female—2; Male—4
EVENT DATE:	1993, 1995, 1996—1 each; 1997—2; 1998—1; Unknown—1
REACTION ONSET (DAYS) (n=4):	Range—1.5 to 120 (approx.) days; Median—23.5 days; Mean—42.1 days (approx.)
DOSE PER DAY (n = 6):	20 mg—5; 40 mg—1
DECHALLANGE:	Positive—5; Negative—1; Unknown—1
OUTCOME:	Hospitalized—2; Non-serious—4; Unknown—1
REACTION (n = 6):	SJS—4; TEN—1; SJS/TEN—1

Two of the cases had very minimal information; one noting that the patient was admitted to the hospital with "Stevens-Johnson like syndrome," and the other, from a physician reporter, stating the patient came to his office saying "a combination of Prilosec and Dilantin caused Steven-Johnson syndrome." One case had a negative dechallenge in that the patient's rash continued to wax and wane for several weeks following discontinuation of the drug. Also in this case, a confirmed diagnosis was never made; the patient claimed he possibly had a mild case of TEN. There was a well-documented case of TEN, but it's possible that ranitidine, which lists erythema multiforme in its labeling, may have contributed to the reaction. In that case, the patient originally developed a rash while on omeprazole, which was then discontinued and replaced with ranitidine. The rash initially improved, but then progressed after about three weeks of ranitidine therapy, eventually developing into TEN.

Representative case of Stevens Johnson Syndrome

Case# 3300119 (Mfr.# 19980900019) A 47-year-old female with reflux esophagitis, esophageal stricture and hiatal hernia was placed on omeprazole 20 mg twice a day on August 14, 1998 for the treatment of gastroesophageal reflux disease. Concomitant therapy included loratidine and levothyroxine. Five days later, the patient experienced pruritis, which was worse on the hands. Four days after that, the rash had worsened and the patient discontinued omeprazole. Two days later, her physician noted that there were multiple wheel-like bulls-eye lesions on the posterior and anterior aspect of the trunk. There was involvement, to a lesser extent. on the patient's extremities. Additionally, there were several superficially ulcerated areas on her tongue. There was some ecchymotic involvement on the soft palate and some erythematous areas on the posterior pharynx. The patient was diagnosed with probable Stevens-Johnson syndrome. The patient was treated with hydroxyzine, prednisone, and triazolam. Ranitidine was also started for the treatment of reflux. The patient had improved five days after beginning treatment. The rash changed from primarily papular and vesicular to macular, especially on her back and chest, and these areas had begun to scale. There was no further involvement of the oral mucosa and her lips were less swollen.

10.1 Summary of SJS and TEN Cases

One or two domestic cases per year have been reported since the previous document was issued. Of the seven updated domestic cases, three could be considered compelling for an association between the events and omeprazole. None of these cases were fatal. Additionally, there does not appear to be an increase in the reporting of this event since the last consult. The current labeling includes TEN and SJS, noting that some reactions have been severe and fatal.

11.0 VENTRICULAR ARRHYTHMIAS

AERS was searched for reports of ventricular arrhythmias associated with the use of omeprazole that were received by the FDA up through and including March 31, 2000 using the OPDRA Reaction Group VENT ARRHYTHMIAS. This grouping includes the terms VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST (HLGT), ELECTROCARDIOGRAM QT PROLONGED (PT), ELECTROCARDIOGRAM QT CORRECTED INTERVAL PROLONGED (PT), and ELECTROCARDIOGRAM QRS COMPLEX PROLONGED (PT). A total of 92 reports were retrieved, which represented 76 unduplicated cases. From these 76 cases, 1 was excluded because it involved a report of a medication error in which the patient received Prozac instead of Prilosec. An additional 16 cases were excluded after reviewing them as the association with omeprazole was poor (negative dechallenge, poor temporal relationship, other causes). Three cases, all of them deaths, were not included in the demographics as ventricular arrhythmias per se were not documented, although the deaths were stated as due to cardiac arrest or possible cardiac arrest. Two of those cases involved the use of cisapride and the other one involved the use of amitriptyline, which are all metabolized through the cytochrome P450 system. There were 32 foreign cases in the AERS database. The remaining 24 domestic cases are summarized below.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 24)

AGE (n = 18):	Range—7 to 71 years; Median—49.5 years; Mean—48.1 years
SEX (n = 20):	Female—11; Male—9
EVENT DATE:	1990, 92, 93, 94, 95—1 each; 1996—4; 1997—4; 1998—4; 1999—1; Unknown—6
REACTION ONSET (n=9):	Range- 1-60 days; Median-9; Mean 19
DOSE PER DAY (n = 15):	20 mg—12; 40 mg—2; 60mg—1
DECHALLANGE:	Positive—7; Unknown—17
OUTCOME:	Death—5; Hospitalized (or prolonged)—8; Non-serious—7; Unknown—4
REACTION:	Prolonged QT interval—8 PVCs—5 Torsade de pointes—4 Ventricular tachycardia—4 Ventricular fibrillation—4 Palpitations—3 Paroxysmal atrial tachycardia—1 Ventricular bigeminy—1

he reaction total is greater than 24 as some cases listed more than one event.

Regarding onset of event, five of the nine cases involved a potential drug interaction; onset was calculated in relationship to omeprazole initiation. In one of the cases, the patient had been on the drug for 13 months, but experienced the event 4 days after the dose was increased from 20 mg once to 20 mg twice daily. At the same time, the cisapride dose was increased from 30 mg to 40 mg daily (in this case onset was counted as 4 days). In another case, the patient had been taking the drug for 49 days when symptoms appeared (palpitations/syncope); at day 62 of therapy an ECG showed PVCs (in this case onset was counted as 49 days).

Eleven of the 24 cases were potentially due to a drug interaction. Cisapride was involved in six of these cases. Of the four torsade de pointes cases, three included the concomitant use of cisapride. Other potential drug interactions included amiodarone, terfenadine, nelfinavir, clarithromycin, and nicardipine.

Representative Case: Prolongation of QT interval

Case# 3152050 USA
A 55-year-old male with a history of a kidney transplant and CAD, was admitted to the hospital on 9/25/98 already on cisapride 10 mg four times a day for chest pain. On 9/26 the patient was started on omeprazole 20 mg once a day for symptoms of GERD. Baseline ECG on 9/25 showed a QT interval of 400 msec. After receiving three doses of omeprazole the QT interval on 9/28 was 500 msec. Omeprazole was stopped and replaced with famotidine. On 9/30 the QT interval was back to baseline at 380 msec.

11.1 Summary of Ventricular Arrhythmia Cases

Of the 16 cases involving a serious arrhythmia (increased QT interval, torsade de pointes, ventricular fibrillation, ventricular tachycardia), 11 were potentially due to a drug interaction, principally with cisapride (6). Of the 13 cases in which there was no interacting drug mentioned, 8 were non-serious arrhythmias including PVCs, palpitations, ventricular bigeminy, and paroxysmal atrial tachycardia. It appears omeprazole has the potential for causing certain arrhythmias (tachycardia, bradycardia, and palpitation are listed in the product labeling). The risk for serious arrhythmias may be increased when used with interacting drugs that are known to produce such arrhythmias (e.g., cisapride). However, the data from AERS is not supportive of a clear relationship of omeprazole independently to cause such serious ventricular arrhythmias, and cisapride is no longer available on the general market.

12.0 PANCREATITIS

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and *Pancreatitis* and *Digestive enzymes* as the MedDRA HLT terms. The search produced 126 cases. These 126 cases were separated into domestic and foreign and checked for duplicates. A total of 3 cases were excluded because they were miscoded and 34 reports were duplicates. Thus, there were 62 unduplicated domestic cases and 27 unduplicated foreign cases for review.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 62)

AGE (YEARS):	RANGE 3 TO 85, MEAN 52 (n = 46)
SEX:	M (29), F (26), UK (7)
REPORTING YEAR:	1989 (1), 1991 (5), 1992 (2), 1994 (1), 1995 (6), 1996 (11), 1997 (15), 1998 (14), 1999 (3), 2000 (1), UK (3)
REACTION ONSET (DAYS):	RANGE 2 TO 540, MEAN 131, MEDIAN 51
DOSE PER DAY (MG):	10 (1), 20 (47), 40 (1), 60 (1), 20 QOD (1), UK (11)
DECHALLENGE POSITIVE:	24
RECHALLENGE POSITIVE:	2
OUTCOME*:	DIED (2), HOSP (41), NONSERIOUS (12), LIFE-THREATENING (3), RECOVERED (1), UK (5)
EVENT DESCRIPTION:	PANREATITIS (58), ELEVATED AMYLASE AND/OR LIPASE (4)†
PTS WITH HISTORY OF ALCOHOL ABUSE	3
PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE PANCREATIC EVENTS‡	13

* Several patients had multiple outcomes.
† Two of these patients had clinical symptoms of pancreatitis as well as elevated amylase and/or lipase, but reporter did not specify that the patient had pancreatitis.
‡ Concomitant medications including furosemide, lisinopril, prednisone, divalprox, estrogens, Prozac, Voltaren XR, Zestril, valproic acid, and Procardia.

In addition to the Domestic cases that were individually reviewed, there were 27 foreign cases of pancreatitis in AERS; 7 of those cases resulted in death from other causes. (Note that four patients were receiving IV omeprazole.)

Representative Case of Pancreatitis

Case# 4733766 (Mfr# WAES 90070191) 1990) A male (age unknown) developed an ileus one week after taking an unknown dose of omeprazole to treat duodenal ulcer; he subsequently developed pancreatitis, underwent surgery, and eventually died. His medical history included thrombocytopenia; concomitant medications included Augmentin, Lasix, and unspecified steroids.

12.1 Summary of Pancreatitis Cases

This section describes 62 cases of pancreatitis possibly associated with the use of omeprazole. Pancreatitis (some fatal) is a labeled event. Two domestic deaths were reported; one case is described above and the other case provided even less information. Eight patients were reported to have acute pancreatitis (including one of the patients that died) and one patient was reported to have hemorrhagic pancreatitis. Of these nine cases, three patients were receiving concomitant medications known to cause pancreatitis, two patients had a history of pancreatic problems, one patient had a history of alcohol abuse, and one patient's pancreatitis was attributed (by the physician) to gallstones. Overall, 13 of the 62 patients were receiving medications known to cause pancreatitis, 3 patients had a history of alcohol abuse, and 4 patients had a history of pancreatic problems. Many reports described in this section lacked relevant information (e.g., concomitant medications, lab values) making it difficult to assess causality or severity.

13.0 OPHTHALMOLOGIC EVENTS

This section also responds to a consult dated February 17, 2000 from HFD-180 for a search of the AERS database for cases of visual disturbances associated with the use of omeprazole. The purpose of that request was to provide documentation for the addition of "blurred vision" and "eye irritation" to the Adverse Reactions section of the omeprazole labeling, as requested by the manufacturer.

Note that three previous consults have been completed at HFD-180's request regarding this issue (see Attachments C, D, and E). The case inclusion date for the most recent consult (Attachment E) was April 28, 1998. The reader is encouraged to review these previous documents.

To update the previous consults, AERS was searched using omeprazole as suspect drug and *Eye Disorders* as the MedDRA System Organ Class (SOC) term. This search produced a total of 351 reports. A listing of the eye events with 10 or more cases is presented below (some of these numbers may represent duplicate reporting). In order to evaluate the most severe outcome of an ophthalmic event, a second search using omeprazole as suspect drug and *Blindness HLT* as the MedDRA High Level Term (HLT) was performed from the time of marketing to March 31, 2000. This search produced a total of 31 reports. There were 11 domestic blindness cases; a hands-on review of these was conducted.

SOC EYE DISORDERS: EVENTS WITH 10 OR MORE CASES (U.S. PLUS FOREIGN)

Vision abnormal NEC	63
Vision blurred	40
Dry eye NEC	28
Eye disorder NOS	20
Visual distrubance	20
Visual acuity reduced	17
Eye pain	15
Diplopia	15
Papilledema	14
Optic atrophy	13

DEMOGRAPHIC DATA FOR U.S. BLINDNESS CASES (n = 11)

AGE (YEARS):	66 MEAN (RANGE 39 to 81)
SEX:	M (2), F (9)
YEAR OF EVENT:	1989 (1), 1993 (1), 1994 (2), 1997 (5), 1998 (2)
REACTION ONSET:	1 DOSE (2), 2 DAYS (1), 8 DAYS (1), 38 DAYS (1), >1.5 YEARS (3), UK (3)
ORAL DOSE PER DAY:	20 MG (7), 20-40MG (1), 40MG (1), UK (2)
DECHALLENGE:	POSITIVE (1), NEGATIVE (1)
RECHALLENGE:	POSITIVE (1)

SERIOUS OUTCOME RELATED TO OPHTHAL. EVENT: HOSPITALIZED (2), DISABLED (4)

The following three blindness cases are domestic cases received since the last consult of April 23, 1998

Case# 3300292 (Mfr# 19980600094) (U.S. [consumer], 1998) A 61-year-old female was driving and became unable to see out of her left eye after taking omeprazole 20 mg for one day to treat "reflux." She also experienced dizziness. Her blindness abated (timeframe unknown); she continued omeprazole therapy. Her concomitant medications and medical conditions were not reported.

Case# 3130343 (Mfr# 19980500646) 1997) A 68-year-old female experienced temporary loss of vision lasting for several minutes after taking one dose of omeprazole 20 mg to treat GERD and *Helicobacter pylori*. Omeprazole was discontinued and the event abated. Concomitant medications included Lasix, Zestril, Coumadin, and Lanoxin; she also received Biaxin and Tritec, but temporal relationship to omeprazole therapy was not specified. Her medical history included chronic atrial fibrillation, hypertension, other disorders of the esophagus, and allergy to Naprosyn (caused rash).

Case# 3295045 (Mfr# 19980300172) eported 1998) An 81-year-old female developed blindness after taking omeprazole 20 mg every 2 to 3 days for "several years" to treat GERD. The event abated after omeprazole was discontinued. Her medical history included macular degeneration; muscle spasm reaction to cimetidine; visual difficulties from lansoprazole, cisapride, and famotidine; and allergies to sulfa, penicillin, neosporin, and novacaine. Concomitant medications included Prevacid, Propulsid, and Pepcid.

13.1 Summary of Ophthalmologic Events

This information updates three previous consults regarding omeprazole and ophthalmic events. OPDRA was asked specifically about AERS cases of blurred vision and eye irritation, as these relate to a manufacturer's request for labeling change. In addition, we looked at cases of blindness received through AERS since the time of marketing. From the recent printout of all visual disturbances associated with omeprazole use, there are a total of 40 reports of *Vision blurred*. There are a total of 5 reports of *Eye irritation NOS* in AERS. Note that eye irritation also could include other PT terms such as *Eye Pain* (15 cases), *Eye inflammation* (1 case), *Dry eye NEC* (28 cases), *Conjunctivitis NEC* (18 cases), as well as other terms. It appears that we continue to receive AERS reports of blurred vision, eye irritation and other ophthalmologic events associated with the use of omeprazole. However, it is difficult to establish a clear relationship between omeprazole use and these events, particularly because of the extensive use of omeprazole in the U.S. as well as the prevalence of general vision disorders.

It would appear reasonable to allow the sponsor to include blurred vision and eye irritation in the omeprazole labeling, although the relationship appears inconclusive. A general term, such as "visual distrubance" or "abnormal vision" might also be considered to reflect the reporting of such cases (Vision abnormal NEC: 63 cases, Visual distrubance: 20 cases, Visual acuity reduced: 17 cases). Although blindness cases have been reported, analysis of these do not support a relationship to omeprazole; no labeling recommendation regarding blindness can be made at this time.

14.0 HEARING DISORDERS

AERS was searched for reports of hearing disorders associated with the use of omeprazole that were received by the FDA up through and including March 31, 2000. Terms used for the search were HEARING DISORDERS (HLGT), INNER EAR & VIIIth CRANIAL NERVE DISORDERS (HLGT), and MISCELLANEOUS EAR DISORDERS (HLGT). A total of 167 reports were retrieved, which represented 158 unduplicated cases. Twenty-six cases were excluded after reviewing them as the association with omeprazole was poor (poor temporal relationship, other causes [e.g., salicylate intoxication, acoustic neuroma, earwax]). There were 22 foreign cases in the AERS database. The remaining 110 domestic cases are summarized below.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 110)

AGE (n = 83):	Range—6 to 89 years; Median—54 years; Mean—54.6 years
SEX (n = 100):	Female—64; Male—36
EVENT DATE (n = 76):	1989—2 1990—5 1991—4 1992—1 1993—10 1994—2 1995—9 1996—9 1997—15 1998—17 1999—2
REACTION ONSET (n = 57):	Range—1 day to approx. 3.5 years; Median—approx. 6 days; Mean—approx. 100.6 days
DOSE PER DAY (n = 70):	5 mg—1; 20 mg—54; 40 mg—15
DECHALLANGE/RECHALLENGE:	Dechallenge positive—49 Dechallenge negative—16 Rechallenge positive—6 Rechallenge negative—1
OUTCOME:	Non-serious—100; Disability—5; Hospitalized—1; Unknown—4
REACTION:	Tinnitus—68 Vertigo—21 Hearing loss—17 Dizziness—14 Ear pain—10 "Ototoxicity" (undefined)—2

The reaction total is greater than 110 as some cases listed more than one event.

A review of the cases of ***hearing loss*** (n = 17) showed the following demographics:

AGE (n = 15):	Range—6 to 74 years; Median—49 years; Mean—47.3 years
SEX (n = 17):	Female—8; Male—9

REACTION ONSET (n = 11):	Range—1 day to approx. 6.5 months; Median—approx. 5 days; Mean—approx. 25.4 days
DOSE PER DAY (n = 10):	5 mg—1; 20 mg—7; 40 mg—2
DECHALLENGE:	Dechallenge positive—11 Dechallenge negative—3
OUTCOME (n = 15):	Non-serious—11; Disability—3; Required intervention (Rx)—1

Representative Case of Hearing Loss

Case# 5499583; Mfr.# 19950900131 (USA, 1995) A 42-year-old male physician with no known allergies was placed on omeprazole 20 mg daily for the treatment of GERD on 09/09/95. There were no concomitant medications reported. On 09/16/95 the patient experienced decreased auditory acuity. Audiometric exam revealed a unilateral sensory deficit, and an MRI was negative. Omeprazole was discontinued on 09/16/95 and since that time his hearing has improved slightly.

There did not appear to be an appreciable difference in the characteristics of the patients who developed HL compared to the group as a whole, although they tended to be younger in age. The majority of HL cases (65%) exhibited a positive dechallenge with the patient either returning to baseline or showing an improvement in symptoms.

An attempt was made to determine from all cases with a negative dechallenge (n = 16), which might indicate a permanent hearing disorder, if they could be associated with a longer duration of therapy. In those negative dechallenge cases in which a reaction onset could be determined (n = 7), the median time to onset was 72 days with a mean of 108.4 days, which could imply that a longer duration of therapy may lead to permanent damage, although additional follow-up in those patients might prove otherwise. On the other hand, in the four patients who had a reaction after years of therapy (two cases of tinnitus, one case each of vertigo and ear pain), three had a positive dechallenge (unknown for one case of tinnitus). In the three patients with HL who had a negative dechallenge, there was not enough information to make a determination regarding length of therapy and permanent HL. Two of these patients were considered to have a permanent disability, which occurred after approximately six weeks and six and a half months of therapy, respectively. The third patient's condition was described as persisting 10 days following discontinuation of omeprazole, which he had taken for approximately 9 days. In those HL patients with a positive dechallenge, reaction onset ranged from one to seven days following initiation of therapy. Therefore, in cases of hearing loss, it might appear that a longer duration of therapy may lead to permanent damage, but this is a tenuous assumption based on only two cases.

14.1 Summary of Hearing Disorder Events

Regarding the 110 domestic cases, the vast majority (91%) had a non-serious outcome and in 45% of the cases there was documentation of improvement in the hearing disorder after omeprazole was discontinued (positive dechallenge). Tinnitus and vertigo represented the most frequently submitted reports and both are listed in the product labeling along with dizziness. Hearing loss (HL) and ear pain are not specifically listed in the product labeling and accounted for 17 and 10 reports, respectively. The 17 hearing loss cases were mainly reversible; there was not a strong signal for hearing loss association with omeprazole. Further, an attempt was made to relate duration of omeprazole use to nonreversible hearing disorders by reviewing 17 cases with negative dechallenge. Although a trend was seen with the nonserious cases, only two hearing loss cases seemed to bear this relationship.

15.0 CANCER

A July 30, 1999 memorandum summarized a review of the medical literature and worldwide post-marketing reports for tumors associated with proton pump inhibitors including omeprazole. The medical literature review included a discussion of toxicological studies in rats, mice and dogs that showed generalized hyperplasia of the gastric mucosa. No human studies were identified in the search that proved carcinogenesis. This document also described 362 AERS reports of neoplasms, benign and malignant as of 7/13/99[1]. Among these domestic and foreign cases, age and gender information was available in 276; 45% were female and 39% were considered elderly. The 85 case report forms of domestic and foreign GI neoplasms were retrieved and 54 unduplicated U.S. cases were analyzed; neoplasms reported included gastric polyps (19), gastric cancer (14) and gastric carcinoids (9). This document is included as Attachment F.

15.1 CANCER REPORTS IN AERS

Two updated AERS searches (data as of 3/31/2000) were performed relating to cases of cancer. The first search included the SOC Neoplasms benign and malignant (including cysts and polyps). This broad search revealed a total of 456 cases. Two hundred fifteen (215) were domestic, 236 were foreign and in 77 reporter country was unknown. Neoplasm events of any nature among the 456 cases which had counts of 5 or more are presented below (some may be duplicates):

Neoplasm NOS	54
Gastrointestinal tract cancer NOS	40
Carcinoma NOS	20
Gastric polyps	16
Gastrointestinal neoplasm NOS	12
Carcinoid tumor of the stomach	10
Lymphoma NOS	8
Carcinoid tumor NOS	6
Cyst NOS	5

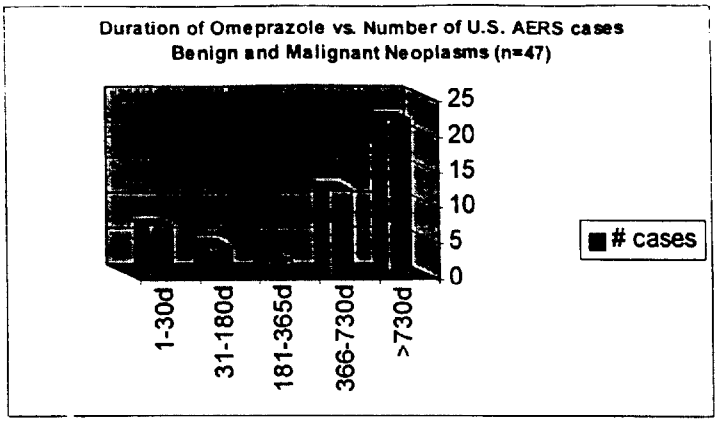
The second search utilized the HLGT Gastrointestinal neoplasms malignant and unspecified, which revealed 171 cases, 78 of which were from the U.S. (domestic). The domestic cases of all cancers and gastrointestinal cancers were further analyzed to relate duration of use to numbers of reported cases of cancer. Duration was a computer-based calculation, which used the following algorithm:

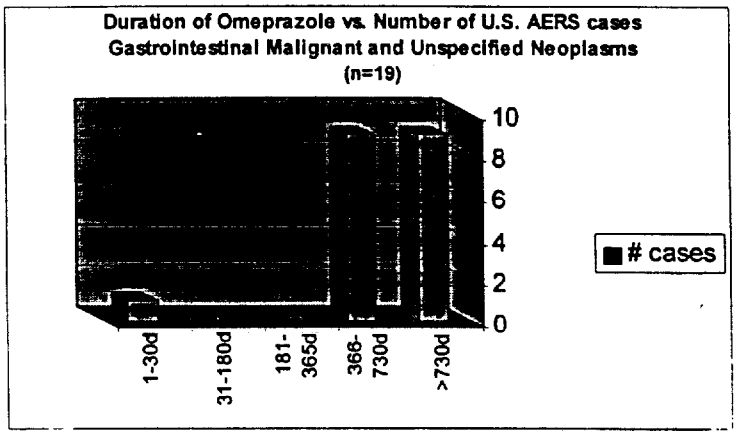
Number of days duration = Start Date of omeprazole to End Date of omeprazole (if no End Date was present, Event Start Date was utilized).

Since this calculation depended on the specific data fields being populated in the reports, this did not result in a large data set. Of the 215 total domestic cases, 47 had sufficient data; of the 78 total GI cases, only 19 had sufficient data to perform the duration calculation. The results are presented graphically below. There is a general trend for larger numbers of reports with a longer duration of use, however, conclusions would be difficult to draw as this data is derived from small numbers from a spontaneous reporting system, which is subject to various reporting biases.

---

[1] Correction of previous document information: total number of AERS reports for omeprazole as of 7/13/99 was approximately 8400; number of U.S. cases of neoplasms (all types) was approximately 180. These numbers may include duplicate reporting.





15.2 CANCER DATA IN THE LITERATURE

An updated review of the literature was obtained June 2000 to look for case reports of cancer or incidence studies of Omeprazole-related cancer. The following databases were searched: MEDLINE, Embase, Derwent Drug File, IPA, Biosis, Life Sciences, and CANCERLIT. A few possible cases of omeprazole-related cancers were identified in the literature review. A 31-year-old man who had received four courses of antiulcer drugs (famotidine, omeprazole, and lansoprazole) over 38 months developed an argyrophil-positive carcinoid tumor (1). Three patients with severe exudative distal esophagitis were diagnosed with invasive adenocarcinoma within one year of continuous omeprazole treatment (2).

A recent comprehensive review article by Laine et al summarizing animal studies and short- and long-term human studies asserts that omeprazole rarely produces adverse events (3). Since most cancers generally have long latency periods, with gastric cancer reported to have a latency period greater than 15 years (4), a special search for long-term studies was completed to look for cancer incidence. Five long-term (> 12 months of treatment) studies of omeprazole were reviewed (Table 1) (5-9). These studies were conducted outside the United States and may have overlapping patient populations (the methods sections provide limited patient population descriptions). Most of the investigators of these studies also received funding from the sponsor. The longest period of treatment for any study group was 11 years - short of the time needed to study omeprazole-related cancers. No histologically proven gastric cancer cases were reported in any of these studies. Two possible cases of cancers were reported by Lloyd-Davies et al.- one patient diagnosed with primary pancreatic and duodenal tumor after an

undefined period of drug exposure and another patient diagnosed with lymph node metastasis without an identified primary tumor and an undefined drug exposure (8). Klinkenberg-Knol et al reported a case of Barrett's carcinoma diagnosed in a 75-year-old man who had a Barrett's ulcer at study entry (9). Six other carcinomas, none of them gastric, were reported in this same study(9).

The long-term studies of omeprazole-related cancer that have been published are limited by three important factors – study size, exposure time, and duration of follow-up. A study of omeprazole-related cancer requires a large number of patients and an extended period of follow-up since gastric cancer is not common, only 22,000 cases of gastric cancer occur in the United States each year (10), and has a long latency period. The studies reviewed have limited number of patients exposed for short time periods and limited follow-ups. The study of omeprazole-related cancer requires extended cohort or nested case control designs that include adjustments for potential confounders, such as underlying disease and smoking. None of the studies in the literature meet this criteria.

Table 1. Summary of Long-term Studies of Omeprazole Cancer Outcomes

Study	No. of Patients	Patient Population	Range of Treatment (No. Range)	Dose	No. of Cancer Cases
Lloyd-Davies KA et al 1988*	80	Zollinger-Ellison	< 1 month – 4 yrs; mean 19 months	260 - 360 mg (median 60 – 70 mg)	1 - Pancreatic and duodenal carcinoma 1 – lymph node metastasis
Joelson S et al 1992*	859	Poorly responsive peptic ulcer or oesphagitis	Up to 6 years	NL	0
Solcia E et al 1992*	448	Peptic ulcer, anastomotic ulcer, or reflux oesophagitis	Up to 4 years	20 - 40 mg	0
Lamberts R et al 1993	74	Chronic esophageal, gastric, or duodenal ulcerations resistant to other treatment	6 months – 7 yrs; median 48 months	40 - 60 mg	0
Klinkenberg -Knol EC et al 2000*	230	Persistent reflux esophagitis	Up to 11 years; mean 6.5 years	10 – 120 mg	1 - Barrett's ca and 6 - non-gastric carcinomas

* Astra Hässle AB either listed as an author or source of funding for the study

16.0 DELAYS IN DIAGNOSIS

Concerns about possible delays in diagnosis exist because the symptoms of gastric cancer can be similar to those of peptic ulcer and thus attempts at medical treatment may be initiated without diagnostic work-ups (11, 12). Diagnostic delays related to cimetidine have been reported in the literature in the past and can be instructive when considering diagnostic delays related to omeprazole. Stoddard et al reviewed the cases of adenocarcinoma of the stomach diagnosed in their unit from August 1979 to May 1980. Investigators identified 12 of 29 patients with delays between 2 and 12 months; 8 of the 12 patients had been treated with cimetidine and antacids for up to 12 months before surgical referral (13). Another group of investigators from the United Kingdom searched the Cambridge Cancer Registration Bureau to identify patients with gastric carcinoma presenting to their hospital between 1978 and 1980 (12). Medical records were reviewed and general practitioners interviewed patients (if necessary) to obtain information about the 100 cases identified. Sixteen patients received cimetidine before diagnosis (duration of therapy varied from 1 to 13 months). Five of the 16 received cimetidine without an upper gastrointestinal barium study or endoscopy.

Mikulin et al more recently interviewed all patients identified with gastric cancer in Nottingham from October 1981 and September 1982 (14). Eighty-three patients (mean age 71 years) were asked about their symptoms and management histories. Fifty-three (64%) of the patients received medication prior to diagnosis, 24 of whom had no investigation prior to drug therapy, 17 of whom received cimetidine. There was no difference in the median days of delay to treatment among those receiving cimetidine (6 weeks) and those receiving antacids (5 weeks).

Of special concern related to drugs used to treat dyspepsia are the case reports of patients who show improvement with drug treatment, delay further diagnostic work-up, and later are identified as patients with gastric cancer. Mikulin et al describes 3 patients who had benign gastric ulcers diagnosed, were treated with cimetidine, and showed improvement of their symptoms (14) All three patients relapsed and were found to have gastric cancer. Wayman et al reports a case series of 7 patients who participated in a special endoscopy protocol (15). Patients in this study had an initial endoscopy, were then started on proton pump inhibitors, and underwent a second endoscopy to ensure resolution of any biopsied ulcer. The 7 patients were found to have ulcerating early gastric cancer when the second endoscopy was performed, but only after inadvertently receiving a short course of a proton pump inhibitor that produced an asymptomatic state. Given the resulting asymptomatic state these patients might have experienced further diagnostic delays if they had not been participated in this study, but instead just initiated medical therapy.

All these papers were conducted by English authors and may not be generalizable to the United States where medical manangement may differ. These papers emphasize, though, that even medical experts have delayed the diagnosis or mis-diagnosed gastric cancer and used a variety of drugs in lieu of or despite a diagnostic work-up. At least one study suggests that the delays in diagnosis were not different for over the counter treatments (antacids) versus prescription treatments (cimetidine) (14). Future studies of delays in diagnosis related to over the counter omeprazole should be done and could use similar methods to these referenced studies.

18.0 DISCUSSION/CONCLUSION

This consult was prepared in response to a request from Lilia Talarico of HFD-180 dated March 15, 2000 to review selected adverse events for omeprazole as the sponsor has submitted an NDA for a change to nonprescription status. The Adverse Event Reporting System (AERS) was searched for adverse event reports received for omeprazole up to March 31, 2000; 10,005 reports were identified in the database. Both domestic and foreign experience is addressed in this document, however, the focus is on the domestic experience. The following issues have been reviewed in this consult: cases with an outcome of death, pediatric experience, drug interactions, serious hematologic events, serious liver events, serious skin disorders, vertricular arrhythmias, pancreatitis, ophthalmologic events, hearing disorders, cancer reports, and delay in diagnosis. For many of these adverse events, analysis of cases did not support significant safety concerns with general use of omeprazole; many patients had underlying conditions or were taking concomitant medications which could have contributed to the events. Summary of these issues appears at the end of each section. The most compelling issue reviewed was serious liver events, which were temporally related to omeprazole use and included serious outcomes such as liver transplants, deaths, and encephalopathy. Serious liver events are included in the current labeling for omeprazole. The pediatric cases reviewed tended to mirror events seen in adults; these typically were not healthy children prior to omeprazole use.

A review of AERS reports for gastrointestinal neoplasms (this body site had the most cancer-related reports in the AERS database) found that there was a trend for larger numbers of reports with a longer duration of omeprazole use, however, conclusions cannot be made because the data was derived from small numbers of spontaneous reports in the system. A review of the studies and case reports in the literature for omeprazole-related cancer revealed that the studies had limited numbers of patients exposed for short time periods with limited follow-ups. A review of the literature for delays in GI cancer diagnosis due to patient self-medication revealed that both prescription and OTC use of antacid drugs may delay diagnosis; additional studies are needed. Data regarding congenital anomalies will be addressed in a separate document.

Given the number of years that omeprazole has been on the market (11 years) and its extensive use prescriptions), AERS report data suggest that the frequency of serious adverse events associated with omeprazole is low, however, with any evaluation of spontaneous reports, underreporting must be considered.

REFERENCES

1. Haga Y, Nakatsura T, Shibata Y, Sameshima H, Nakamura Y, Tanimura M, Ogawa M. Human gastric carcinoid detected during long-term antiulcer therapy of H_2 receptor antagonist and proton pump inhibitor. Digestive Disease and Science 1998; 43: 253-257.
2. Farivar M. Omeprazole may promote cancer development in patients with severe exudative Barrett's esophagitis. AJG 1997; 92: 1590.
3. Laine L, Ahnen D, McClain C, Solcia E, Walsh JH. Review article: Potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. Aliment Pharmacol Ther 2000; 14: 651-668.
4. Møller H, Toftgaard C. Cancer occurrence in a cohort of patients surgically treated for peptic ulcer. Gut 1991; 32:740-744.
5. Solcia E, Fiocca R, Havu N, Dalväg A, Carlsson R. Gastric endocrine cells and gastritis in patients receiving long-term omeprazole treatment. Digestion 1992; 51 (suppl 1): 82-92.
6. Lamberts R, Creutzfeldt W, Strüber HG, Brunner G, Solcia E. Long-term omeprazole therapy in peptic ulcer disease: gastrin, endocrine cell growth, and gastritis. Gastroenterology 1993; 104: 1356-1370.
7. Joelson S. Joelson IB, Lundborg P, Walan A, Wallander MA. Safety experience from long-term treatment with omeprazole. Digestion 1992; 51 (suppl 1): 93-101.
8. Lloyd-Davies KA, Rutgersson K, Sölvell. Omeprazole in the treatment of Zollinger-Ellison syndrome: a 4-year international study. Aliment Pharmacol Therap 1988; 2: 13-32.
9. Klinkenberg-Knol E, Nelis F, Dent J, Snel P, Nitchell B, Prichard P, Lloyd D, Havu N, Frame M, Roman J, Walan A, Long-Term Study Group. Gastroenterology 2000; 118: 661-669.
10. Neugut AI, Hayek M, Howe G. Epidemiology of gastric cancer. Seminars in Oncology 1996; 23: 281-291.
11. Elder JB, Ganguli PC, Gillespie IE. Cimetidine and gastric cancer. Lancet 1979; 1: 1005-1006.
12. Scotcher S, Sikora K, Freedman L. Gastric cancer and cimetidine: does delay in diagnosis matter? Lancer 1981; 2: 630-631.
13. Stoddard CJ, Smith JAR, Johnson AG. Cimetidine, delay in diagnosis, and carcinoma of the stomach. Lancet 1980; 1: 199-200.
14. Mikulin T, Hardcastle JD. Gastric cancer – delay in diagnosis and its causes. Eur J Cancer Clin Oncol. 1987; 23: 1683-1690.
15. Wayman J, Hayes N, Raimes SA, Griffin SM. Prescription of proton pump inhibitors before endoscopy. Arch Fam Med 2000; 9: 385-388.

Attachment A

PT	Count of PTs	Percent of Total	Labeled
Drug Ineffective	692	6.92	U
Abdominal Pain Nos	536	5.36	U
Diarrhoea Nos	491	4.91	U
Headache Nos	489	4.89	U
Dermatitis Nos	450	4.50	U
Nausea	406	4.06	U
Dizziness (Exc Vertigo)	334	3.34	U
Pruritus	323	3.23	U
Drug Interaction Nos	288	2.88	U
Pyrexia	269	2.69	U
Alopecia	249	2.49	U
Condition Aggravated	249	2.49	U
Vomiting Nos	232	2.32	U
Thrombocytopenia	227	2.27	U
Chest Pain	224	2.24	U
Pain Nos	215	2.15	U
Dyspepsia	211	2.11	U
Arthralgia	197	1.97	U
Dyspnoea Nos	194	1.94	U
Urticaria Nos	192	1.92	U
Confusion	189	1.89	U
Constipation	188	1.88	U
Back Pain	185	1.85	U
Asthenia	179	1.79	U
Leucopenia Nos	175	1.75	U
Flatulence	170	1.70	U
Myalgia	166	1.66	U
Abdominal Pain Upper	161	1.61	U
Paraesthesia Nec	159	1.59	U
Dry Mouth	153	1.53	U
Hepatic Function Abnormal Nos	150	1.50	U
Taste Disturbance	139	1.39	U
Abdominal Distension	137	1.37	U
Insomnia Nec	137	1.37	U
Blood Creatinine Increased	132	1.32	U
Fatigue	128	1.28	U
Malaise	128	1.28	U
Depression Nec	126	1.26	U

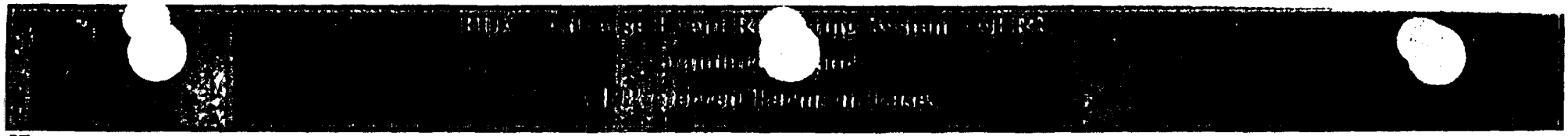
PT	Count of PTs	Percent of Total	Labeled
Cough	120	1.20	U
Weight Increased	120	1.20	U
Gastrointestinal Disorder Nos	117	1.17	U
Liver Function Tests Nos Abnormal	115	1.15	U
Oedema Peripheral	106	1.06	U
Weakness	103	1.03	U
Anaemia Nos	101	1.01	U
Palpitations	100	1.00	U
Tremor Nec	99	0.99	U
Gastrointestinal Tract Cancer Nos	98	0.98	U
Hepatitis Nos	98	0.98	U
Renal Failure Acute	98	0.98	U
Weight Decreased	97	0.97	U
Sedation	93	0.93	U
Dysphagia	92	0.92	U
Pancreatitis Nos	91	0.91	U
Nervousness	90	0.90	U
Tinnitus	90	0.90	U
Hypoaesthesia	88	0.88	U
Muscle Cramps	87	0.87	U
Sepsis Nos	87	0.87	U
Hypertension Nos	85	0.85	U
Anxiety Nec	84	0.84	U
Jaundice Nos	84	0.84	U
Blood Bilirubin Increased	83	0.83	U
Gastrointestinal Haemorrhage Nos	81	0.81	U
Neoplasm Nos	80	0.80	U
Hyponatraemia	78	0.78	U
Urinary Frequency	77	0.77	U
Face Oedema	76	0.76	U
Hallucination Nos	76	0.76	U
Syncope	76	0.76	U
Tachycardia Nos	76	0.76	U
Blood Urea Increased	75	0.75	U
Drug Effect Decreased	74	0.74	U
Hypersensitivity Nos	74	0.74	U
Sweating Increased	74	0.74	U
Pain In Limb	72	0.72	U

PT	Count of PTs	Percent of Total	Labeled
Eructation	71	0.71	U
Pancytopenia	71	0.71	U
Oedema Nos	69	0.69	U
Acute Circulatory Failure	67	0.67	U
Hypoglycaemia Nos	66	0.66	U
Myocardial Infarction	66	0.66	U
Laboratory Test Abnormal Nos	64	0.64	U
Haematuria Present	63	0.63	U
Rash Maculo-Papular	63	0.63	U
Vision Abnormal Nec	63	0.63	U
Agitation	62	0.62	U
Angioneurotic Oedema	62	0.62	U
Agranulocytosis	61	0.61	U
Convulsions Nos	60	0.60	U
Nephritis Nos	60	0.60	U
Pneumonia Nos	60	0.60	U
Oedema Lower Limb	59	0.59	U
Rash Erythematous	58	0.58	U
Coma Nec	57	0.57	U
Epidermal Necrolysis	57	0.57	U
Renal Failure Nos	57	0.57	U
Stevens Johnson Syndrome	57	0.57	U
Haemoglobin Decreased	56	0.56	U
Neutropenia	54	0.54	U
Stomatitis	54	0.54	U
Blister	53	0.53	U
Drug Maladministration	53	0.53	U
Oesophagitis	53	0.53	U
Amnesia Nec	52	0.52	U
Burning Sensation Nos	52	0.52	U
Impotence	52	0.52	U
Blood Alkaline Phosphatase Nos Increased	51	0.51	U
Blood Creatine Phosphokinase Increased	49	0.49	U
Hypotension	49	0.49	U
Iron Deficiency Anaemia	48	0.48	U
Renal Impairment Nos	48	0.48	U
Cerebrovascular Accident Nos	47	0.47	U
Faeces Discoloured	47	0.47	U

PT	Count of PTs	Percent of Total	Labeled
Peripheral Neuropathy Nec	47	0.47	U
Prothrombin Level Decreased	47	0.47	U
Sore Throat Nos	47	0.47	U
Anorexia	46	0.46	U
Aspartate Aminotransferase Increased	46	0.46	U
Hyperglycaemia Nos	46	0.46	U
Gastritis Nos	45	0.45	U
Tongue Oedema	45	0.45	U
Haemolytic Anaemia Nos	44	0.44	U
Jaundice Cholestatic	44	0.44	U
Pharyngitis Nos	44	0.44	U
Alanine Aminotransferase Increased	43	0.43	U
Gastro-Oesophageal Reflux Disease	43	0.43	U
Carcinoma Nos	42	0.42	U
Drug Level Nos Above Therapeutic	42	0.42	U
Erythrocyte Sedimentation Rate Increased	42	0.42	U
Urinary Tract Infection Nos	42	0.42	U
Appetite Decreased	41	0.41	U
Dermatitis Bullous	41	0.41	U
Gynaecomastia	41	0.41	U
Hepatic Failure	41	0.41	U
Cardiac Failure Nos	40	0.40	U
Infection Nos	40	0.40	U
Vision Blurred	40	0.40	U
Ecchymosis	39	0.39	U
Asthma Nos	38	0.38	U
Cardiac Arrest	38	0.38	U
Dehydration	38	0.38	U
Eosinophilia (Exc Pulmonary)	38	0.38	U
Arrhythmia Nos	37	0.37	U
Psychotic Disorder Nos	37	0.37	U
Unevaluable Reaction	37	0.37	U
Hypokalaemia	36	0.36	U
Mouth Ulceration	36	0.36	U
Platelet Count Decreased	36	0.36	U
Vasodilatation	36	0.36	U
Bone Marrow Depression Nos	35	0.35	U
Haematemesis	35	0.35	U

PT	Count of PTs	Percent of Total	Labeled
Haemorrhage Nos	35	0.35	U
Hypertonia	35	0.35	U
Thinking Abnormal Nec	35	0.35	U
Dry Skin	34	0.34	U
Gait Abnormal Nos	34	0.34	U
Urine Abnormal Nos	34	0.34	U
Vertigo Nec	34	0.34	U
Abnormal Dreams	33	0.33	U
Delirium	33	0.33	U
Disorientation	33	0.33	U
Gamma-Glutamyltransferase Increased	33	0.33	U
Photosensitivity Reaction Nos	33	0.33	U
Rigors	33	0.33	U
Bradycardia Nos	32	0.32	U
Hyperkalaemia	32	0.32	U
Leucocytosis Nos	32	0.32	U
Myasthenic Syndrome	32	0.32	U
Deafness Nos	31	0.31	U
Feeling Abnormal	31	0.31	U
Hepatocellular Damage	31	0.31	U
Epistaxis	30	0.30	U
Glossodynia	30	0.30	U
Oral Candidiasis	30	0.30	U
Dermatitis Exfoliative Nos	29	0.29	U
Flushing	29	0.29	U
Purpura Nos	29	0.29	U
Urine Discolouration	29	0.29	U
Acidosis Nos	28	0.28	U
Blood Gastrin Increased	28	0.28	U
Blood Pressure Increased	28	0.28	U
Cholelithiasis	28	0.28	U
Dry Eye Nec	28	0.28	U
Glossitis	28	0.28	U
Throat Irritation	28	0.28	U
Amblyopia Nos	27	0.27	U
Angina Pectoris	27	0.27	U
Antinuclear Factor Positive	27	0.27	U
Aplastic Anaemia	27	0.27	U

PT	Count of PTs	Percent of Total	Labeled
Atrial Fibrillation	27	0.27	U
Dysuria	27	0.27	U
Melaena	27	0.27	U
Nephritis Interstitial	27	0.27	U
Rash Pruritic	27	0.27	U
Urinary Retention	27	0.27	U
Arthritis Nos	26	0.26	U
Blindness Nec	26	0.26	U
Gastric Polyps	26	0.26	U
Muscle Weakness	26	0.26	U
Oesophageal Reflux	26	0.26	U
Vasculitis Nos	26	0.26	U
White Blood Cell Count Decreased	25	0.25	U
Anaphylactic Reaction	24	0.24	U
Blood Lactate Dehydrogenase Increased	24	0.24	U
Encephalopathy Nos	24	0.24	U
Hostility	24	0.24	U
Personality Disorder Nos	24	0.24	U
Apnoea	23	0.23	U
Ataxia Nec	23	0.23	U
Blood Cholesterol Increased	23	0.23	U
Breast Pain	23	0.23	U
Emotional Disturbance Nos	23	0.23	U
Inappropriate Adh Secretion	23	0.23	U
Migraine Nos	23	0.23	U
Muscle Spasms	23	0.23	U
Neck Pain	23	0.23	U
Petechiae	23	0.23	U
Heart Rate Increased	22	0.22	U
Multi-Organ Failure	22	0.22	U
Sleep Disorder Nos	22	0.22	U
Tongue Disorder Nos	22	0.22	U
Death	21	0.21	U
Faecal Abnormality Nos	21	0.21	U
Gastric Ulcer	21	0.21	U
Liver Fatty	21	0.21	U
Muscle Twitching	21	0.21	U
Oral Pain	21	0.21	U



PT	Count of PTs	Percent of Total	Labeled
Paranoia	21	0.21	U
Parosmia	21	0.21	U
Pulmonary Embolism	21	0.21	U
Respiratory Disorder Nos	21	0.21	U
Swelling Nos	21	0.21	U
Systemic Lupus Erythematosus	21	0.21	U
Blood Amylase Increased	20	0.20	U
Erythema Multiforme	20	0.20	U
Eye Disorder Nos	20	0.20	U
Fall	20	0.20	U
Hepatic Necrosis	20	0.20	U
Hypercholesterolaemia	20	0.20	U
Influenza Like Illness	20	0.20	U
Lung Disorder Nos	20	0.20	U
Lymphoma Nos	20	0.20	U
Speech Disorder Nec	20	0.20	U
Visual Disturbance Nos	20	0.20	U
Balance Impaired Nos	19	0.19	U
Blood In Stool	19	0.19	U
Bone Pain	19	0.19	U
Cardiovascular Disorder Nos	19	0.19	U
Hoarseness	19	0.19	U
Libido Decreased	19	0.19	U
Phlebitis Nos	19	0.19	U
Abdominal Pain Lower	18	0.18	U
Conjunctivitis Nec	18	0.18	U
Dyspepsia Aggravated	18	0.18	U
Mania	18	0.18	U
Oedema Upper Limb	18	0.18	U
Oesophageal Ulcer	18	0.18	U
Rash Generalised	18	0.18	U
Rhabdomyolysis	18	0.18	U
Skin Disorder Nos	18	0.18	U
Anuria	17	0.17	U
Congenital Abnormality Nos	17	0.17	U
Dysphonia	17	0.17	U
Haematocrit Decreased	17	0.17	U
Haemoptysis	17	0.17	U

PT	Count of PTs	Percent of Total	Labeled
Hepatomegaly	17	0.17	U
Idiopathic Thrombocytopenic Purpura	17	0.17	U
International Normalised Ratio Increased	17	0.17	U
Prostatic Disorder Nos	17	0.17	U
Rectal Bleeding	17	0.17	U
Taste Loss	17	0.17	U
Tongue Discolouration Nos	17	0.17	U
Unexpected Therapeutic Effect	17	0.17	U
Ventricular Extrasystoles	17	0.17	U
Visual Acuity Reduced	17	0.17	U
Bronchospasm Nos	16	0.16	U
Cholestasis	16	0.16	U
Colitis Nos	16	0.16	U
Diabetes Mellitus Nos	16	0.16	U
Disseminated Intravascular Coagulation	16	0.16	U
Drug Hypersensitivity	16	0.16	U
Intestinal Obstruction Nos	16	0.16	U
Nail Disorder Nos	16	0.16	U
Overdose Nos	16	0.16	U
Salivary Hypersecretion	16	0.16	U
Suicide Attempt	16	0.16	U
Appetite Increased	15	0.15	U
Blood Glucose Increased	15	0.15	U
C-Reactive Protein Increased	15	0.15	U
Coordination Abnormal Nos	15	0.15	U
Diplopia	15	0.15	U
Extrapyramidal Disorder Nec	15	0.15	U
Eye Pain	15	0.15	U
Faecal Incontinence	15	0.15	U
Gastroenteritis Helicobacter	15	0.15	U
Gastrointestinal Neoplasm Nos	15	0.15	U
Haematoma Nos	15	0.15	U
Hepatic Encephalopathy	15	0.15	U
Hyperlipidaemia Nos	15	0.15	U
Lethargy	15	0.15	U
Lipase Increased	15	0.15	U
Loose Stools	15	0.15	U
Mucous Membrane Disorder Nos	15	0.15	U

PT	Count of PTs	Percent of Total	Labeled
Nasopharyngitis	15	0.15	U
Prothrombin Time Prolonged	15	0.15	U
Rebound Effect	15	0.15	U
Splenomegaly	15	0.15	U
Thirst	15	0.15	U
Throat Tightness	15	0.15	U
Albuminuria Present	14	0.14	U
Candida Nos	14	0.14	U
Colitis Pseudomembranous	14	0.14	U
Electrocardiogram Abnormal Nos	14	0.14	U
Electrocardiogram Qt Prolonged	14	0.14	U
Feeling Hot	14	0.14	U
Hair Disorder Nos	14	0.14	U
Hypovitaminosis Nos	14	0.14	U
Movement Disorder Nos	14	0.14	U
Neurological Disorder Nos	14	0.14	U
Oral Discomfort	14	0.14	U
Papilloedema	14	0.14	U
Pelvic Pain Nos	14	0.14	U
Pulmonary Fibrosis	14	0.14	U
Pulmonary Oedema Nos	14	0.14	U
Sinusitis Nos	14	0.14	U
Vaginal Candidiasis	14	0.14	U
Ventricular Fibrillation	14	0.14	U
Ventricular Tachycardia	14	0.14	U
Vitamin B12 Deficiency	14	0.14	U
Ascites	13	0.13	U
Calculus Renal Nos	13	0.13	U
Coagulation Disorder Nos	13	0.13	U
Discomfort Nos	13	0.13	U
Disturbance In Attention Nec	13	0.13	U
Drug Level Nos Below Therapeutic	13	0.13	U
Feeling Cold	13	0.13	U
Frequent Bowel Movements	13	0.13	U
Joint Stiffness	13	0.13	U
Mental Impairment Nos	13	0.13	U
Mucosal Erosion Nos	13	0.13	U
Nightmare	13	0.13	U

PT	Count of PTs	Percent of Total	Labeled
Oesophageal Disorder Nc.	13	0.13	U
Optic Atrophy	13	0.13	U
Polyuria	13	0.13	U
Rhinitis Nos	13	0.13	U
Torsade De Pointes	13	0.13	U
Urinary Incontinence	13	0.13	U
Visual Field Defect Nos	13	0.13	U
Accident Nos	12	0.12	U
Accidental Overdose (Therapeutic Agent)	12	0.12	U
Bacterial Infection Nos	12	0.12	U
Cataract Nec	12	0.12	U
Cerebral Ischaemia	12	0.12	U
Cholecystitis Nos	12	0.12	U
Collapse	12	0.12	U
Facial Palsy	12	0.12	U
Gingival Bleeding	12	0.12	U
Haemolysis Nos	12	0.12	U
Hiatus Hernia	12	0.12	U
Hypoproteinaemia	12	0.12	U
Irritability	12	0.12	U
Joint Disorder Nos	12	0.12	U
Joint Swelling	12	0.12	U
Laryngospasm	12	0.12	U
Loss Of Consciousness Nec	12	0.12	U
Memory Impairment	12	0.12	U
Non-Accidental Overdose	12	0.12	U
Polyp Nos	12	0.12	U
Red Blood Cell Count Decreased	12	0.12	U
Restlessness	12	0.12	U
Thrombocythaemia	12	0.12	U
Vaginal Haemorrhage	12	0.12	U
Viral Infection Nos	12	0.12	U
Abnormal Behaviour Nos	11	0.11	U
Apathy	11	0.11	U
Breast Enlargement	11	0.11	U
Carcinoid Tumour Of The Stomach	11	0.11	U
Corneal Erosion	11	0.11	U
Cystitis Nos	11	0.11	U

PT	Count of PTs	Percent of Total	Labeled
Dementia Nos	11	0.11	U
Dialysis Nos	11	0.11	U
Difficulty In Walking	11	0.11	U
Dyskinesia Nec	11	0.11	U
Fungal Infection Nos	11	0.11	U
Gastric Ulcer Haemorrhage	11	0.11	U
Hair Colour Changes	11	0.11	U
Hyperkinetic Syndrome	11	0.11	U
Hyperplasia Nos	11	0.11	U
Hypocalcaemia	11	0.11	U
Hypoxia	11	0.11	U
Inflammation Nos	11	0.11	U
Metabolic Acidosis Nos	11	0.11	U
Micturition Urgency	11	0.11	U
Myoclonic Jerks	11	0.11	U
Myopathy	11	0.11	U
Oesophageal Pain	11	0.11	U
Oliguria	11	0.11	U
Osteoporosis Nos	11	0.11	U
Peripheral Vascular Disease Nos	11	0.11	U
Pharyngeal Disorder Nos	11	0.11	U
Skin Discolouration	11	0.11	U
Testicular Pain	11	0.11	U
Vaginitis	11	0.11	U
White Blood Cell Count Increased	11	0.11	U
Acne Nos	10	0.10	U
Atrioventricular Block Complete	10	0.10	U
Blood Iron Decreased	10	0.10	U
Blood Potassium Decreased	10	0.10	U
Cardiac Disorder Nos	10	0.10	U
Chest Pressure Sensation	10	0.10	U
Choking	10	0.10	U
Cyanosis Nos	10	0.10	U
Cyst Nos	10	0.10	U
Depersonalisation	10	0.10	U
Drug Withdrawal Syndrome	10	0.10	U
Earache	10	0.10	U
Epidermolysis Bullosa	10	0.10	U

PT	Count of PTs	Percent of Total	Labeled
Eyelid Oedema	10	0.10	U
Grand Mal Convulsion	10	0.10	U
Hepatic Neoplasm Malignant Nos	10	0.10	U
Hypercalcaemia	10	0.10	U
Irritable Bowel Syndrome	10	0.10	U
Pleural Effusion	10	0.10	U
Rash Papular	10	0.10	U
Red Blood Cell Abnormality Nos	10	0.10	U
Renal Colic	10	0.10	U
Respiratory Failure (Exc Neonatal)	10	0.10	U
Sexual Dysfunction Nos	10	0.10	U
Skin Odour Abnormal	10	0.10	U
Skin Ulcer Nos	10	0.10	U
Sputum Increased	10	0.10	U
Stupor	10	0.10	U
Transaminase Nos Increased	10	0.10	U