

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA: 21-229

Sponsor: Astra-Zeneca LP  
Wayne, PA

Date Submitted: January 27, 2000

Drug: Omeprazole Magnesium (Prilosec 1™) for OTC use

Pharmacological Category: PPI inhibitor; inhibitor of gastric acid secretion

Formulation: 20 mg tablets

Administration: The sponsor proposes that one over-the-counter oral tablet be administered for the relief of heartburn, acid indigestion and sour stomach or for the prevention of these symptoms brought on by consuming food and beverages or associated with events such as stress, hectic life style, lying down for exercise, once every 24 hours for no more than 10 days in a row, unless directed by a doctor.

Material Reviewed: Application, clinical sections, labeling, summary, safety update report, case report tabulations, case report forms, other pertinent information and literature references

Reviewer: Mark Avigan, M.D., C.M.

## **Executive Summary of Safety Profile for Omeprazole-Mg**

The sponsor has requested OTC approval for omeprazole mg 20.6 mg, 1 tablet per day, for both the relief and prevention of heartburn. The proposed labeling includes the following instructions:

- Do not use for more than 10 days in a row unless directed by a doctor
- Do not use if you are allergic to omeprazole
- Do not use with if you have difficulty swallowing
- Do not use with acid reducers
- Stop use and ask a doctor if stomach pain continues for 10 days
- Ask a doctor or pharmacist before use if you are taking ketoconazole or itraconazole – both antifungal medicines
- If pregnant or breast-feeding, ask a health professional before use. May cause damage to your unborn or nursing child
- Children under 12 years of age: ask a doctor

### **Clinical Study Safety Results Primary Safety Data Base**

In the submission, adverse event information has been provided from the following sources:

- 10 US clinical trials involving 11,299 subjects to study Omeprazole-magnesium (Ome-Mg) tablets for OTC use. These studies form the core of the current NDA submission and were a significant component of the safety database. A total of 8,179 subjects in these studies were exposed to Ome-Mg from one dose to multiple doses given over a 4 week period. In the database, 5,040 subjects were exposed to 20 mg doses of Ome-Mg and 3,039 subjects to 10 mg doses of Ome-Mg. In addition, 3,120 subjects were exposed to placebo.
- A database of previous clinical trials to study the prescription formulation of omeprazole for the treatment of GERD, erosive esophagitis and dyspepsia. 6 US trials, 29 non-US trials consisting of over 7,500 patients (5,757 unique patients) treated with omeprazole comprised this database. In these clinical trials patients were treated with doses of 10 mg, 20mg or 40 mg with a duration of exposure ranging from one day to 12 weeks (short-term studies) and up to one year (long-term studies; 1,235 patients).
- A database of voluntary reports at AstraZeneca LP (SafeTnet) of serious adverse events (SAEs), during the 300 million courses of prescription treatment and nonserious adverse events (AEs) in the US from a background of 90 million courses of treatment since 1989. The database includes 15,385 AE reports from 7,344 patient cases and includes 287 outcomes of death. It also contains 1,750 cases of nonfatal SAEs.

Determination of the safety profile of this drug can conveniently be divided into 2 categories:

- An analysis of adverse events related to short-term drug administration (less than 4 weeks) characterized by a single course of treatment without chronic or intermittent use
- An analysis of adverse events related to long-term drug administration (more than 4 weeks) characterized by chronic or intermittent use

The sponsor has made a presentation to support the claim that omeprazole-mg has a benign safety profile in the context of short-term use (10 day limit). Despite this assumption, a thorough safety analysis must take the following points into consideration:

- The proposed labeling does not specifically warn against long-term intermittent use
- Actual Use studies of the product indicate that a significant percentage of test subjects who were self-medicated to prevent heartburn, did not follow instructions in the label and continued to treat themselves beyond 10 days
- The pharmacodynamic/pharmacokinetic characteristics of omeprazole include the points that maximal acid suppression does not occur after a single 20 mg dose, but only occurs after 2-3 days with daily dosaging. Moreover, the effects, even of a single dose, last for up to 5 days. These properties are consistent with a high degree of efficacy for the prevention of chronic heartburn rather than occasional episodes of heartburn that, in the absence of an ongoing treatment course, require immediate relief by the administration of a single tablet
- A significant percentage of subjects who were recruited into the OTC studies had chronic heartburn consistent with GERD. The natural course of GERD is characterized by a high percentage of individuals who develop recurrence of symptoms when treatment to suppress gastric acid is stopped

For these reasons, it is likely that many consumers will use the OTC product, either chronically or intermittently. Safety issues that are related to short-term and long-term omeprazole-mg exposure, as defined above, will be addressed separately (Parts A and B, respectively), followed by conclusions (Part C).

## **A. Adverse events associated with short-term administration of omeprazole (less than 4 weeks total use)**

### **OTC Ome-Mg Clinical Trial Adverse Events**

A total of 10 US studies involving 11,299 subjects have contributed to the safety database. 8,179 subjects were exposed to Ome-Mg from a single dose to 4 weeks of active treatment. Of these, 5,040 were treated

with 20 mg doses and 3,039 subjects were treated with 10 mg doses. The composite number of individuals treated with placebo alone was 3,120.

- In all studies AEs were scored during the active phase of treatment. In some they were also recorded during a brief placebo run-in period and/or a brief post-treatment followup period. AEs were recorded during the indicated study phases.
- It is apparent that the entire safety analysis presented represents very short-term exposure to the drug as well as short-term monitoring of AEs. A second limitation for the detection of rare AEs is the limited number of patients who have been entered into the OTC studies.

In a composite of the OTC studies the most commonly reported AEs were headache (5%), infection (2%) and diarrhea (2%). These rates do not appear to be significantly higher than the rates observed in individuals treated with placebo. Similarly, in a 465 patient US clinical trial of the prescription delayed-release capsule formulation of omeprazole, headache and diarrhea were considered to be possibly/probably/definitely related to the drug in 2.4% and 1.9% of study patients, respectively (Ref. PDR). In conjunction with skin rash which was observed in 1.1% of patients in the clinical study population, these side-effects were generally mild and self-limiting.

The assessment of omeprazole related side-effects in adolescents is limited by the following:

- In the composite of OTC studies only 105 subjects were in this age group. This small number precludes detection of side-effects that may be age-related.
- Currently the prescription formulation of omeprazole is only approved by the FDA for adult use. This reflects absence of adequate studies to determine efficacy/safety profiles in pediatric individuals, including adolescents (see below).
- World-wide post-marketing surveillance of both SAEs and non-serious AEs in children ages 12-16 captured in SafeTNet (see below) contains a total of 92 AEs experienced by 39 unique patients. This small number precludes an assessment of the repertoire of side-effects that may be associated with omeprazole in adolescents, particularly those that are uncommon.

In the composite of OTC studies a total of 961 Blacks, 361 Hispanics and 171 others complemented the 6,686 Caucasians who made up the subject population. It should be noted that representation by Asians, particularly of Japanese, Chinese and Korean extraction was minimal. From the data, there is no evidence that common side effects are predisposed to occur in particular racial groups. Because of the relatively high representation of 'slow-metabolizers' of omeprazole in people of Asian origin compared to Caucasians (15% vs 3%) a definitive assessment of AE rates in Asians is currently not possible.

The profile of Ome-Mg 20 mg daily doses is similar to the profile of 10 mg doses. This finding is consistent with the sponsor's interpretation that there are no dose-related differences of AEs in this dose range. However, it should be emphasized that within the set of the 6 clinical controlled OTC studies numbers of study subjects were too small to assess dose-related risks of rare/very rare AEs. Furthermore, long-term exposure to varying doses to Ome-Mg was not performed.

A total of 59 subjects, 41 on Ome-Mg and 18 on placebo discontinued study participation due to an AE. The most commonly reported AEs experienced by Ome-Mg treated subjects were headache (10 subjects), nausea (10 subjects) and vomiting (8 subjects). These were distinct from the most commonly reported AEs for placebo treated subjects which were diarrhea (5 subjects), abdominal pain (4 subjects) and nausea (3 subjects). Of the 41 Ome-Mg treated subjects 28 were treated with 20 mg doses and 13 were treated with 10 mg doses. Of the 28 cases in the 20 mg dose group, in 16 cases the medication was considered 'possibly causative' and in 5 cases 'probably causative'. Causes for discontinuation of Ome-Mg also included rash (3 cases), fever (2 cases), and 1 death. The only fatality which occurred during all of the OTC studies is not ascribable to Ome-Mg since it occurred in an individual with polydrug intoxication who had stopped taking the study medication 10 days earlier. Overlapping with these cases of drug discontinuation were 24 cases of SAEs in individuals who received Ome-Mg in the OTC studies. In one case the study subject who received Ome-Mg 10 mg doses developed serum sickness which was considered 'probably related' to administration of the test drug. In a comprehensive composite of all AEs for the 8,179 subjects who were administered Ome-Mg and the 3,120 subjects who were administered placebo 11 cases of liver function

abnormalities (6 cases of SGOT elevation, 7 cases of SGPT elevation), 4 cases of urticaria, 3 cases of eye disorders and 1 case of vision abnormality occurred .

### **Prescription formulation of Omeprazole – Clinical Trial Adverse Events**

To gain a full appreciation of the range of side-effects that are associated with the administration of omeprazole the sponsor has presented a review of AEs observed in all clinical trials that have been performed previously to study the prescription formulation of omeprazole in the treatment of GERD, erosive esophagitis and dyspepsia. Patient populations that have been excluded from this composite analysis include those with peptic ulcer disease and severe hypersecretory conditions (eg Zollinger-Ellison Syndrome). In the analysis 6 US trials conducted by Astra Merck and Merck & Co, Inc. and 29 non-US clinical trials conducted by Astra Hassle were evaluated. The analysis encompassed over 7,500 patients, including a total of 5,757 unique patients who were exposed to omeprazole

Despite the fact that the trials were characterized by a number of different study designs the sponsor has presented an overall safety profile of omeprazole for daily doses ranging from 10 mgs to 40 mgs, with duration of exposure from 1 day to 12 weeks in the 'short-term' trials and from above 12 weeks to 1 year for 'long-term' trials (Long-term drug exposure for periods longer than 1 year has been presented separately by the sponsor and will be discussed below).

Although these groupings are useful for the purpose of distinguishing AEs associated with the US vs the non-US study subjects as well as differences in short and long-term treatment, a major limitation of the analysis flows from the fact that only 1,086 unique omeprazole-treated patients are represented in both the US short and long-term trials and only 4,671 unique omeprazole-treated patients are represented in the non-US trials. Therefore, rare and very rare AEs including SAEs that have been linked to omeprazole may not be detected in this analysis. For example, in the case of the US studies, a predicted event rate less than 1 per 333 unique patients would not inevitably occur in the population size that has been analyzed. Likewise, the non-US population and event rate less than 1 per 1,200 unique patients exposed to omeprazole would not necessarily be detected. Therefore, it needs to be emphasized that compilation of a comprehensive list of rare SAEs associated with omeprazole mostly is derived from the post-marketing voluntary reporting system of the prescription formulations (SafeTNet) that has been provided. This will be discussed below. A second limitation of an analysis of the AEs linked to the clinical trials is the diminishing numbers of patients exposed to omeprazole over increasing durations of treatment.

In the case of US short-term studies, beyond 20 days of treatment, patient numbers diminished rapidly. In the case of US long-term studies, the group exposed to omeprazole for more than 180 days was characterized by dramatically diminishing patient numbers.

A third limitation in the analysis of AEs associated with the clinical studies is the negligible representation of certain demographic groups. By age, representation of adolescents (12-17 years) was absent. In addition, with regards to race representation of Asians was negligible. As discussed above, because of the potential for different susceptibilities to side-effects based on differences in CYP2C19 activity, full elucidation of the safety profile of omeprazole in Asians and others with a significantly higher incidence of genetic polymorphisms is an important goal in the completion of a comprehensive analysis. Similar deficiencies in demographic representation were observed in the composite of long-term studies performed in the US.

Upon examination of demographic groupings no substantial differences were observed between various races or groups including geriatric individuals vs younger subjects. With regards to gender, differences in adverse event reporting were observed in the US short-term controlled and uncontrolled trials. These include omeprazole-linked monoliasis in 0.8% in female study subjects treated with omeprazole vs 0% treated with placebo and gastroenteritis in 1% of females treated with omeprazole vs 0% treated with placebo. These side-effects were absent/negligible in males. Conversely, elevation of transaminases including SGOT and SGPT were more frequent in omeprazole-treated males compared to females (2.0% vs 0.5%). With the exception of monoliasis it is not possible to distinguish whether the rates of these adverse

events are meaningfully different from background rates of placebo users or between genders, due to the small numbers of study subjects.

Interestingly, rates of elevation of transaminases do not appear to have been affected by the daily doses of omeprazole (10-40 mg range). In the short-term controlled and uncontrolled US clinical trials the most common AEs which led to discontinuation of omeprazole usage were diarrhea, nausea and vomiting. Rates of discontinuation in these categories were no different than discontinuation rates in those treated with placebo. It should be pointed out that in these studies, elevation of liver transaminases, episodes of acute gastroenteritis and of visual blurring were each responsible for the cessation of omeprazole in single individuals. The association of these side-effects with omeprazole will be discussed below. In the non-US long-term trials, angioedema and rash were both causes of cessation of omeprazole in single individuals.

### **SAEs/fatalities associated with clinical trials of the prescription formulation of omeprazole**

In the non-US trials fatalities which occurred do not appear to be related to the study drug. In the short-term controlled and uncontrolled non-US trials there were 3 nonfatal SAEs which appeared to be related to the drug. These included drug-associated arthralgia/enterocolitis, bronchospasm, and interstitial nephritis. Importantly, common side-effects associated with omeprazole such as nausea, vomiting and diarrhea were occasionally listed as SAEs, inferring that in some cases such symptoms caused significant morbidity in study patients. This is demonstrated in US short-term controlled and uncontrolled trial tabulations in which nausea and vomiting each accounted for a 0.5% rate of SAEs. In addition, SAEs marked by body ache, chest pain and fever were recorded as SAEs in 2 patients each. In the placebo arm of these studies the rate of SAEs was negligible, supporting an association of the aforementioned symptoms (when described as SAEs) and omeprazole. Other drug-related SAEs in the US short-term studies included pancytopenia (1 case), pancreatitis (1 case), thrombocytopenia (1 case), bacterial infection (1 case) and acute gastroenteritis (1 case). Consistent with these findings, in the non-US long-term controlled and uncontrolled trials the administration of omeprazole was linked to 2 cases of pancreatitis, 1 case of angioedema and 1 case of gastroenteritis. In contrast, SAEs in the placebo arm of these studies were negligible. Despite the fact that SAEs were mostly recorded in the active treatment group who were administered omeprazole and not in those administered placebo the total number of patients in each group were discrepant, as there were more subjects who were treated with the PPI. Because of this difference in numbers of study subjects it is possible that some of the SAEs linked to omeprazole in these studies are manifestations of background rather than drug-related events.

Based on the data from the clinical trials previously conducted on the prescription formulation of omeprazole in the disease states of GERD and Dyspepsia that have been described above, the sponsor has made the following conclusions:

- In general, the short-term trials demonstrate that diarrhea and headaches are the most frequently recorded AEs associated both with the omeprazole and the placebo groups.
- For trials less than 12 weeks in duration, omeprazole has a safety profile which is similar to placebo.
- Based on the long-term clinical trials, the adverse event profiles were similar for omeprazole and placebo.
- There were no meaningful differences in the adverse event profiles for omeprazole when evaluations were performed according to age, race, gender, dose or duration of use.
- The rates of discontinuation from the clinical trials due to AEs were lower in the omeprazole groups than the placebo groups.
- Fatalities that occurred in the clinical trials were unlikely to be due to trial medication.
- SAEs that were reported in the clinical trials were not considered to be related to omeprazole, in most instances.
- Based on the data presented, it is suggested that omeprazole is safe for OTC use.

Because of the limitations in study design and patient numbers that this reviewer has enumerated above definitive conclusions concerning the linkage between omeprazole and rare or very rare adverse events cannot be drawn. In fact, postmarketing experience with omeprazole has demonstrated that certain

uncommon AEs that were detected in the clinical trials are indeed linked to treatment with omeprazole. AEs, such as liver toxicity, pancreatitis, agranulocytosis, toxic epidermal necrolysis can present with a spectrum of severity. In some instances, these AEs have led to death. The specific side-effects will be more extensively discussed below. It is noteworthy that even common side effects of the drugs such as headache, diarrhea, nausea and vomiting have occasionally been listed as SAEs by patients and/or their physicians, inferring that occasionally they may be associated with significant morbidity. Finally, certain demographics subsets including adolescents 12 years of age or older and Asian individuals have not been adequately studied to determine whether they manifest differential vulnerabilities to toxicity by omeprazole.

### **Prescription formulation of Omeprazole - Postmarketing Surveillance Data**

The sponsor Astra-Zenica LP maintains a database of drug experience reports related to the patient usage of omeprazole which is called SafeTnet. This database contains both domestic and foreign serious postmarketing AEs and domestic nonserious post-marketing AEs. In addition, safeTnet contains the SAEs from clinical trials world-wide. In the database, adverse events in a single individual which are associated medically and/or temporally are grouped together in a single case which can be identified by a unique product safety and epidemiology (PSE) ID number. In the submission, the SafeTnet database was searched for reports accumulated and verified on or before June 30, 1998 that were linked to oral omeprazole as the suspected medication causing the side effects. A total of 7,344 cases that encompassed 15,385 adverse events were retrieved. The database, which has been generated through the voluntary reporting of physicians, healthcare professional and patients reflects widespread usage of omeprazole in 103 countries for various acid-related gastrointestinal disorders. The sponsor has estimated that approximately 300 million courses of omeprazole patient treatments worldwide encompassing approximately 90 million in the US comprise this database. Each single patient treatment is defined as the number of capsules in an average prescription.

Although varying from year to year, the numbers of these events year to year have not followed a trend of substantial change. As is the case of the clinical trials discussed above, the most commonly reported adverse events were diarrhea, headache, nausea, abdominal pain and rash. In the database there were a total of 287 deaths, 142 of which were coded as an adverse event. The database also contains 108 cases of urticaria, 97 cases of hepatitis, 74 cases of hepatic function abnormality, 72 cases of leukopenia, 74 cases of interstitial nephritis, 67 cases of pancreatitis, 67 cases of vision abnormalities and 65 cases of pancytopenia. Each of these side effects will be discussed below in a section devoted to topics of concern related to the safety profile of omeprazole. It should be emphasized that the absolute numbers of patient counts that have been tabulated cannot be extrapolated to the true incidence in the US of omeprazole users. This limitation flows from the voluntary nature of the reporting system and the absence of a comprehensive system of detecting and reporting side effects in the omeprazole-treated population. Thus, the main value of these reports is that they form a basis to identify "signals" of side-effects that are linked to omeprazole.

The fatalities associated with hepatic failure agranulocytosis, pancytopenia, marrow depression, leukopenia, hepatic function abnormalities, pancreatitis, hepatic necrosis, and epidermal necrolysis underlines the important point that although these omeprazole-linked SAEs are uncommon they can lead to death. This must be taken into account in the formulation of a risk/benefit equation for the OTC use of omeprazole.

The sponsor has requested approval for omeprazole OTC marketing in patients 12 years of age and older. A profile of the 190 worldwide serious and US nonserious adverse events in adolescence has been performed for individuals age 12 to 16 years. This safety analysis is severely limited by the relatively small number of adolescent subjects entered into the database. Most likely, the paucity of data reflects both less usage and possibly a reduced reporting rate in this age group, compared to adult individuals. That the repertoire of side effects in this age group is qualitatively and or quantitatively different than in adult patients is unlikely. However, significant age related side effects cannot be ruled out.

Significant differences in commonly reported AEs in individuals 65 years or older, compared to younger adults, were not noted.

## **Special Topics of Safety (including rare adverse events) that are related to the short-term use of Omeprazole**

The following adverse effects have been observed in individuals, even after short-term use of omeprazole.

- hepatic dysfunction
- cardiac function
- acute pancreatitis
- toxic epidermal necrolysis (TEN)
- Agranulocytosis
- Angioedema/anaphylaxis
- Visual disturbances
- Drug - drug interactions

An analysis of postmarketing reports, clinical trial data and a review worldwide literature has been provided. In addition, safety issues in special patient populations and alterations of metabolism and dosage requirements have been discussed. Special populations addressed are:

- Subjects with hepatic impairment
- Subjects with renal impairment
- geriatric subjects
- pediatric subjects
- 'slow' omeprazole metabolizers
- pregnant subjects

### **Omeprazole Related Liver Injury**

The spectrum of liver toxicity associated with omeprazole treatment ranges from asymptomatic transient elevations of liver enzymes to occasional cases of fulminant hepatic failure. Mild increases of serum transaminases of approximately twice the upper limit of normal occur in less than 1% of patients and apparently do not increase with long-term use. In most cases, ALT levels tend to return to normal during treatment with the drug. However, rare cases of severe liver toxicity have occurred as a result of omeprazole treatment.

In non-clinical toxicology studies omeprazole has demonstrated a low potential for hepatotoxicity. In a clinical setting, drug induced liver abnormalities can be divided into a number of categories. These are reflected by the pattern of perturbations of liver function tests, the presence or absence of hepatocellular necrosis, the mechanism of toxicity (eg. immunologically mediated hypersensitivity responses, metabolic toxicity, etc.), the rate of onset and the severity of necrosis and the presence or absence of fibrosis). Typically, liver functions test abnormalities indicate one of the following groups of pathological perturbations which can often be confirmed by liver biopsy.

- Hepatocellular toxicity (elevated serum transaminases)
- Cholestasis (elevated alkaline phosphatase and/or total bilirubin; minimal elevation of transaminases)
- Hepatocellular necrosis (significant elevation of serum transaminases greater than 3 times the upper limit of normal)
- Mixed hepatocellular cholestatic injury (elevation of both transaminases and alkaline phosphatase/total bilirubin)

The sponsor presented data obtained from 4 US (853 patients) and 5 non-US (556 patients) clinical omeprazole trials. The duration of treatment ranged from 4 weeks to 15 months. After initial screening, the advent of elevated liver function tests did not appear to be dependent on dosage regimens. Therefore, AEs in subjects treated with omeprazole 20 mg and 40 mg doses were combined. Toxic events were scored only once on a per patient basis with the highest laboratory value and the peak levels of elevated liver function tests being recorded.

Of 556 patients, 9 manifested a hepatocellular toxicity pattern; 1 developed elevated transaminases over a 3-fold increase above the upper limit of normal consistent with significant hepatocellular necrosis. In

addition, 31 patients developed a cholestatic picture with elevated alkaline phosphatase; another 14 developed isolated hyperbilirubinemia. Although 177 of the 556 patients in the non-US clinical studies had an abnormal liver function test while on omeprazole treatment, significant hepatocellular necrosis can only be ascribed to 10 patients, or less. Similarly, in the US studies, among 853 omeprazole-treated patients, 253 developed an abnormal liver function test while on treatment. Mildly elevated transaminases were noted in 31 patients and 5 patients had transaminase elevations of more than 3 times above the upper limit of normal. Assuming that this cutoff is a marker of significant hepatocellular necrosis, these numbers suggest an incidence of approximately 6 per thousand omeprazole users that develop this condition. It should be emphasized that a majority of patients who developed abnormalities of liver function tests manifested isolated elevations of alkaline phosphatase (35) or bilirubin (17) or isolated elevations of transaminases (SGOT, 10; SGPT, 66). Thus, most of the liver function test abnormalities appear to be mild and there is no consistent pattern of perturbation of liver function. In addition, there is no apparent association of these abnormalities with either the dose or duration of omeprazole therapy. Nonetheless, there appears to be a small percentage of patients who develop more significant hepatocellular necrosis with elevations of transaminases above 3 times the upper limit of normal. The incidence of this phenomenon in these studies ranges between approximately 1 and 500 and 3 through 500 patients treated with omeprazole.

To further analyze the hepatotoxic potential of omeprazole, the postmarketing surveillance database (safeTnet) was analyzed. The events that were analyzed included:

- All non-serious postmarketing adverse events in the US
- All serious postmarketing adverse events worldwide
- All serious clinical trial adverse events reported worldwide

The thorough search of adverse event terms were reviewed in the screen of all serious clinical and postmarketing adverse events. This search revealed 261 serious adverse events consistent with hepatic dysfunction. These events were rated by a sponsor-designated physician to assign a probability of causal association with omeprazole treatment. There were 4 rating categories that are listed below:

- Category A: Defined as a well documented case with no other explanation for toxicity.
- Category B: Defined as a well documented case with more than one possible explanation or suggestive contributing factor for toxicity.
- Category C: Defined as a case with evidence of the reported adverse event but insufficient information available to determine causality.
- Category D: Defined as a case with no documented evidence of the reported adverse event.

Using these criteria, the following numbers of fatal and non-fatal cases were identified according to their case rating.

Of the total 33 fatal cases, 2 were assigned an 'A' rating; in at least one of these cases, the patient was dechallenged successfully with resolution of liver function tests. Upon rechallenge with omeprazole, liver enzymes again rose. In a list of a total of 227 involving hepatic dysfunction as SAEs not associated with death, 4 were assigned an 'A' rating. In at least 2 of the 4 cases, the patients were successfully dechallenged and upon repeat challenge with omeprazole either symptoms and/or the transaminase elevations recurred. In one of these cases, the appearance of omeprazole related jaundice, an elevated alkaline phosphatase was not specifically related to an elevation of transaminases. However, in the other, omeprazole induced elevations of the ALT to over one thousand units per liter. In another 'A' case rated patient, the patient, who was treated with omeprazole and no other medications, developed hepatitis with jaundice and possible hepatic failure. Omeprazole was discontinued and the patient recovered within a month. These cases illustrate the potential that omeprazole has to induce severe hepatocellular necrosis and, rarely, liver failure. From the voluntary reporting system it is not possible to assess the incidence of these events.

A review of the literature by the sponsor demonstrates that in a small series of patients, significant omeprazole related hepatotoxicity is unusual. Based on an investigation of medical records from the General Practitioners Research Database that included 108,981 patients who received an H-2 blocker or



omeprazole (Insert Reference 20), the sponsor has concluded that the risk of acute injury using cimetidine which was estimated to be approximately 1 per 5,000 patients exposed to the drug is qualitatively similar to the risk to develop acute liver injury associated with the use of omeprazole. The sponsor has concluded that this low risk is compatible with the over-the-counter use of these agents. Nonetheless, it should be pointed out that at the severe end of the spectrum of relatively rare omeprazole induced hepatotoxic events are cases of hepatocellular necrosis associated with liver failure and even death. The incidence of these events appears to be similar to those associated with the use of cimetidine and possibly some other H-2 blockers that have been approved previously for OTC marketing in the United States. In the current labeling of OTC cimetidine, no mention is made of the potential for liver toxicity, how it should be recognized and acted upon by the consumer. Similarly, in the proposed labeling for OTC omeprazole, the sponsor has not made mention of the potential of liver toxicity by this agent. This reflects a minimalist approach to labeling for rare SAEs that are predicted to occur in an undifferentiated OTC population.

### **Changes in Cardiac Function Associated with Omeprazole**

Nonclinical pharmacodynamic toxicological studies reveal that omeprazole has negligible effects on cardiac conduction. After oral or intraduodenal administration to dogs, specific effects of the drug on the heart have not been observed. In humans, omeprazole does not affect cardiac performance, heart rate or blood pressure. ECG's from pharmacokinetic studies performed in healthy male volunteers were evaluated. In these studies, omeprazole was either administered by oral suspension in doses ranging from 0.5 to 100 mg, or by intravenous infusion ranging between 1 and 20 mg. ECGs were performed at pre-baseline, baseline, peak plasma concentration and post-peak plasma concentration timepoints. ECG tracing evaluation by an independent cardiologist was performed in a blinded fashion. In this study, omeprazole did not induce abnormalities of cardiac repolarization. In a survey of cardiac conduction AEs reported in patients administered omeprazole that encompassed serious clinical and serious post-marketing events worldwide through June 30, 1998, the sponsor identified 148 cases of ventricular, supraventricular, or general conduction irregularities of the heart. These were rated on a scale that was identical with that used for the rating of liver toxicity described above (See above).

Of the 148 serious fatal/nonfatal conduction disorders that have been reported worldwide, there is only one case that was assigned an "A" rating. This case represented an episode of persistent bradycardia that developed after bolus IV infusion of omeprazole in a patient with multiple medical problems who was being simultaneously treated with a number of pharmaceutical agents. The sponsor has provided a literature review to demonstrate that omeprazole does not significantly inhibit CYP3A4, an enzyme which metabolizes cisapride and a number of other drugs that have significant effects on cardiac repolarization. Based on the information that has been provided, the sponsor has concluded that there is no clear association between the use of omeprazole and cardiac function or arrhythmic activity, including effects on supraventricular, ventricular and/or general conduction.

### **Acute Pancreatitis**

In a series of pharmacodynamic non-clinical studies, it has been observed that omeprazole induces a decrease in pancreatic fluid volume flow and bicarbonate secretion. These effects may be secondary to a reduction in gastric acid delivery to the duodenum. No toxic effects of omeprazole have been observed on the pancreas in animal models. In the SafeTNet database, a total of 12 fatal and 69 non-fatal serious adverse event cases were recorded.

None of these cases were rated as "A" category cases (well documented cases with no other explanations identified). Because of their complex nature, it is not possible to ascribe causality of the described episodes of pancreatitis to omeprazole. It has been suggested that omeprazole contributes to the risk of developing acute pancreatitis in certain medical settings. In a study of acute pancreatitis in bone marrow transplant patients, omeprazole was not found to be an independent risk factor. However, when examined as an indicator variable in a univariable analysis, the use of omeprazole approached significance (P=0.12). A recently completed epidemiologic trial evaluated the risk of developing acute pancreatitis upon use of H-2 receptor antagonists or PPIs. Data were obtained from a cohort of 337 practitioners in the United Kingdom (Insert Reference 10). Those patients with a history of known risk factors other than drug exposure were

excluded. A total of 88 cases of idiopathic acute pancreatitis possible related to drug exposure were identified.

Marginal increases in the relative risk to develop acute pancreatitis were noted in patients treated with ranitidine, cimetidine or omeprazole. This risk was greater in the first month of therapy; a dose response relationship was not observed. An interpretation of this comprehensive study is that exposure to omeprazole poses a negligible risk in most individuals to develop acute pancreatitis.

### **Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS)**

In many cases, it is difficult to ascribe causality to a single drug because of the clinical context in which patients receive multiple medications. In addition, time intervals between exposure and dermatologic symptoms is often variable, although most reactions occur between 1 and 3 weeks after initial exposure.

The SafeTnet database was searched for the reports of significant toxic skin reactions in patients exposed to omeprazole. A total of 49 cases were identified.

Based on the aforementioned rating system defining the likelihood of causality, of the 49 cases, 2 were given an 'A' rating (1 fatal, 1 non-fatal). In the non-fatal case, after successful dechallenge with omeprazole, upon reinitiation of therapy, the patient redeveloped the skin lesions. It appears that TEN and SJS are rare but important clinical complications that can occur as a consequence of omeprazole therapy. The incidence of this complication seems to be comparable to that associated with other classes of drugs.

### **Agranulocytosis and other related white blood cell disorders**

The safeTNet database was screened for serious adverse events of agranulocytosis and other related white blood cell disorders reported through June 30, 1998.

Of 122 unique omeprazole-treated patients who developed agranulocytosis, granulocytopenia, or leukopenia, 26 died. Case ratings concerning the likelihood of omeprazole-linked toxicity as described previously were assigned to characterize all of the serious cases. Operational definitions included:

- Agranulocytosis - granulocyte count less than or equal to  $0.5 \times 10^9$  per liter
- Granulocytopenia - granulocyte count less than  $1.5 \times 10^9$  per liter
- Leukopenia - granulocyte count less than  $3.0 \times 10^9$  per liter
- Thrombocytopenia - platelet count less than  $100 \times 10^9$  per liter

Of the 26 fatal cases, 5 were attributable with high certainty to omeprazole exposure and were assigned an 'A' rating. Of the total 96 non-fatal cases, 35 were attributable to omeprazole and were assigned an 'A' rating. Although the true incidence of these side-effects cannot be gleaned from the SafeTNet database because it is predicated on a system of voluntary reporting, it is clear from the clinical trial database which was previously discussed that granulocytopenia and leukopenia occurred at rates of 0.2 % and 0.9% respectively in the US short-term controlled and uncontrolled trials (duration of omeprazole treatment was 12 weeks or less). In the long-term US controlled and uncontrolled trials (duration of omeprazole treatment was 12 weeks or more), the incidence of these side-effects was even higher (granulocytopenia and leukopenia occurred at rates of 0.7% and 1.5% of omeprazole-treated subjects, respectively. This was compared to 0% and 0.8% of placebo-treated subjects, respectively. It can be inferred that mild to moderate suppression of white blood cell numbers in the circulation as a consequence of omeprazole treatment is not exceedingly rare. This effect may be influenced by duration of exposure to the drug. It should be emphasized that an accurate assessment of the incidence of agranulocytosis associated with omeprazole cannot be made from these data. Nonetheless, it is likely that omeprazole-induced agranulocytosis is a relatively rare event. From the Intensive Medicines Monitoring Program (IMMP) that has been established in New Zealand to comprehensively research side-effects of certain drugs in their early post-marketing period, after approval of the prescription formulation of omeprazole, treated individuals were monitored. In a cohort study of 9,260 patients exposed to the PPI. In this cohort, 17 hematologic events were recorded. Of those that appeared to be causally related to omeprazole treatment, there were 3 cases of neutropenia and 1 aplastic anemia. In a study by the French Ministry of Health (refs 14 and 15) a spectrum of hematologic effects related to omeprazole were noted. These

included pancytopenia, thrombocytopenia, leukopenia and hemolytic anemia. All cases occurred after a mean period of 15 days following initiation of PPI therapy. The rapid onset of these effects suggested to the investigators that toxicity resulted from an immunologic mechanism. From the above, it is clear that severe leukocyte suppression or agranulocytosis caused by omeprazole is a relatively rare event. The post-marketing databank and literature also support a linkage between the PPI and these side-effects. Currently, it is not possible to define accurately the incidence of these events. Based on clinical trial data they may occur as frequently as 1/5,000 omeprazole treated patients.

### **Anaphylaxis and Angioedema**

Anaphylaxis and angioedema are associated with exposure to a number of pharmacological agents. The clinical entities are both manifestations of immediate hypersensitivity reactions which are often mediated by IgE antibodies and can be associated with stridor, circulatory collapse and even death. Agents linked to anaphylaxis and angioedema include nonsteroidal antiinflammatory drugs, muscle relaxants, anaesthetics, narcotics and penicillins. Preclinical testing of in guinea pigs has shown that omeprazole has the potential to cause contact hypersensitivity. In human subjects, occupational exposure to the drug has been associated with a positive lymphocyte transformation test. This finding was not linked with evidence of systemic or passive cutaneous anaphylaxis. Post-marketing surveillance for anaphylaxis/angioedema, including both post-marketing and serious clinical trial AEs identified 134 cases.

Importantly, 48 of these cases were from clinical trials, suggesting that these events are not exceedingly rare. 7 of the 134 cases were fatal, 3 of which were observed in clinical trials. Of the 134 cases, 9 were rated as consistent with a category 'A' classification using the same criteria that have been listed above to designate the probability of causality with omeprazole exposure. They point to a number of important features. First, symptoms of swelling, wheezing, urticaria, rash, etc. occurred within a short time after the beginning of omeprazole treatment. Second, the symptoms disappeared after dechallenge and reappeared after rechallenge confirming the linkage between omeprazole and the side-effects. Third, the onset of anaphylaxis/angioedema was idiosyncratic and not predictable prior to drug exposure. Although rare, the fact that few cases of anaphylaxis/angioedema have occurred during clinical trials to study omeprazole suggest that this side effect is not exceedingly rare. A number of publications confirm the observation that omeprazole induces immediate hypersensitivity responses in patients. Nonetheless, the empiric experience that has been reported in the literature suggests that severe angioedema/urticaria linked to omeprazole is quite rare. In the Intensive Medicines Monitoring Program (IMMP) in New Zealand, out of 17,365 patients treated with omeprazole there were 8 confirmed reports of angioedema/urticaria. Based upon this study the AE rate for angioedema/urticaria was estimated to be approximately 0.5 per 1,000 patients. Exposure to H-2 receptor antagonists has also been associated with the advent of immediate hypersensitivity reactions.

### **Visual Disturbances**

Based on a preclinical model that links omeprazole with anterior ischemic optic neuropathy and the accumulation of several cases of severe visual disturbances, including blindness, reported in severely ill patients receiving an intravenous formulation of omeprazole, the Bundesgesundheitsamt (BGA), the drug authority of Germany, decided to suspend the registration of the injectable bolus form of omeprazole. In the US post-marketing reports of blurred vision, eye irritation and other ophthalmologic events have been received. A full analysis of this subject will be performed by Dr. Sheldon Kress, Medical Officer in the DGCDP.

### **Drug-drug interactions**

There is a potential for drug-drug interactions between the PPI and other agents metabolized by CYP2C19 since it is the major cytochrome P450 isoform which is responsible for oxidation of omeprazole in the liver. Like omeprazole, reduced clearance of diazepam has been observed in 'rapid-metabolizers' of omeprazole (patients who produce significant levels of wild-type CYP2C19 activity). In individuals on long-term oral diazepam therapy at steady state drug plasma levels would be expected to be elevated due to corresponding decreased clearance of the tranquilizer. Other drugs whose metabolism is inhibited by omeprazole include phenytoin, R-warfarin and tolbutamide. The effect of omeprazole on plasma levels of phenytoin has been

investigated in four different studies. Omeprazole 40 mgs daily causes a 15%-20% increase in plasma levels of phenytoin in healthy volunteers. In contrast, 20 mg doses in patients continuously treated with phenytoin did not significant changes in plasma levels of the anti-epileptic agent. In contrast to S-warfarin, R-warfarin plasma levels are increased by approximately 10% during coadministration of omeprazole. In most clinical contexts in which other drugs are not being administered the effects of coadministration of omeprazole with warfarin are predicted to be small. Likewise, effects on the sulphonylurea antidiabetic medication tolbutamide by omeprazole 40 mg doses are slight (approximately 10%). Other studies have demonstrated little interaction between omeprazole and clarithromycin, cyclosporine, erythromycin, estradiol, lidocaine, nifedipine and quinidine. These drugs are mainly metabolized by CYP3A4. After administration of 20 mg doses of the PPI in 'slow-metabolizers' who have negligible levels of CYP2C19 activity, plasma omeprazole levels are two-fold higher, compared to 'rapid-metabolizers'. This modest rise does not imply that 'slow-metabolizers' are not especially susceptible to drug-drug interactions, since the saturability of other cytochrome P450 isoforms may be significantly less than that of CYP2C19 in 'rapid-metabolizers' of omeprazole. As alluded to above, approximately 3% of Caucasians and 15% of Asians are 'slow-metabolizers'. The vulnerabilities that these individuals have to drug-drug interactions can only be tested empirically. Currently, there is a paucity of information about the implications of CYP2C19 polymorphisms on drug-drug interactions.

A separate mechanism of drug-drug interactions between omeprazole and other agents is related to the effect of changing luminal pH on drug absorption. Both digoxin and nifedipine absorption are increased when omeprazole is coadministered in daily doses of 20 mg or 40 mg. The differences in absorption are modest and generally not clinically meaningful. However, there are some individuals, particularly those who have renal impairment or are especially susceptible to digoxin toxicity in whom subtle changes in digoxin blood may have an undesirable effect. Other drugs such as ketoconazole or itraconazole are poorly absorbed when the luminal pH of the stomach is elevated. In the case of ketoconazole, a decrease in absorption of 80% has been observed after administration of a 60 mg dose of omeprazole (ref 26). It is predicted that patients who are being treated for fungal infections with ketoconazole/itraconazole will be vulnerable to loss of the therapeutic effect, if omeprazole is coadministered. Appropriated labeling to instruct patients of this effects may be necessary to avoid this problem.

### **Alterations of metabolism/clearance of omeprazole in special patient populations**

The metabolism of omeprazole primarily occurs in hepatocytes. In young healthy subjects the half-life of omeprazole is approximately 0.5 - 1hr. It has been determined that in even in the face of significant hepatic cirrhosis the elimination half-life of the drug is less than 3 hours. Because it is predicted that when single daily doses of omeprazole are administered further accumulation of the parent drug of the parent drug during steady state will be negligible and dose adjustment is unnecessary. In a study of 8 patients with varying severity of liver disease the metabolism of 40 mg oral and 20 mg IV doses of omeprazole were studied. Liver disease did not reduce the bioavailability of the oral formulation of the drug. However, the area under the plasma concentration vs time curve (AUC) was seven-fold higher and the plasma elimination half-life was approximately 4 times longer in hepatically impaired patients than in healthy subjects (2.8 hrs vs 0.7hrs). Because the typical dosing interval of omeprazole is 24 hours, lengthening of the elimination half-life of omeprazole in patients with hepatic cirrhosis to a duration less than 3 hours does not lead to significant increased accumulation of the drug during steady state conditions. Based on this pharmacokinetic prediction it is unlikely that patients with significant liver disease (eg cirrhosis, hepatitis, portal hypertension, portal vein thrombosis, fatty liver, etc.) would be at increased risk for the development of omeprazole-linked AEs compared to normal individuals. The sponsor has presented a summary table of a compassionate use study designed to evaluate the efficacy/safety of the long-term treatment with omeprazole in patients with peptic ulcer disease or severe ulcerative esophagitis resistant to high doses of ranitidine. In the study 41 patients had significant liver disease. Irrespective of the time interval, 80.5% of the subjects reported 1 or more AEs, a similar percentage that has been reported to occur in normal healthy subjects. Although the sponsor has quoted this finding to support the contention that patients with significant liver disease are not predisposed to develop AEs, more complete information is necessary to determine whether this assertion is correct. In particular, different side-effects may occur by distinct mechanisms, some which may be related to drug dosage/serum levels. A comprehensive comparison of

specific side-effects is necessary to draw any firm conclusions. Theoretically the presence of significant liver disease may alter the extent of drug-drug interactions that occur between omeprazole and other drugs or their metabolites which are cleared by the liver. For example, clearance of diazepam is decreased independently by the presence of liver disease and the coadministration of omeprazole. Therefore it is likely that omeprazole will accentuate diazepam-linked effects in patients who are hepatically impaired. The sponsor has not provided information to assess scenarios in which drug-drug interactions occur in hepatically impaired individuals.

### **Renally Impaired Subjects**

Although the renal excretion of inactive omeprazole metabolites is decreased in patients with renal impairment, there is a compensatory increase in the capacity to eliminate these products through alternative routes, such as in the bile. Because omeprazole is completely metabolized by the liver before being excreted in the urine, it is predicted that the pharmacokinetics of the parent compound will remain substantially unaltered in the face of renal impairment. This has been born out empirically in patient studies. Theoretically, renal impairment could play a role in the clearance of other drugs or their metabolites which participate in drug-drug interactions with omeprazole.

### **Elderly Subjects**

As part of the physiologic effects of aging both hepatic and renal functions diminish. High clearance drugs are subject to more profound changes in elimination rates compared to low clearance drugs. Based on the observation is categorized as a low-medium clearance drug, the sponsor has predicted that the physiologic effects of aging on hepatic clearance of omeprazole will be modest. This has been confirmed in studies of the pharmacokinetic properties of the drug in the elderly. In healthy geriatric volunteers (average age of 76) the mean plasma elimination half-life of omeprazole was 1 hour, compared to 0.7 hours in young healthy subjects. In addition the mean AUC was two-fold higher in the elderly. These results have suggested to the sponsor that dose adjustments in geriatric patients are unnecessary both for the prescription and OTC formulations of omeprazole. An analysis of the common AEs listed in the SafeTNet database has shown that the profiles and rates of omeprazole related side-effects are comparable between the elderly and younger patients. Similarly, both profiles and incidence rates of side-effects in the safety database from the 34 clinical trials that have been conducted worldwide to study the prescription formulation of omeprazole are comparable between age groups.

### **'Slow-metabolizers' of omeprazole**

As discussed above, the cytochrome P450 isoform which is predominately responsible for the metabolism of omeprazole is CYP2C19. This isoform is polymorphically expressed in the human population. Amongst 3% of Caucasians and 15% of Asians CYP2C19 levels are negligible. These 'slow-metabolizers' (SM) manifest plasma elimination half-lives of omeprazole which are longer than in individuals who are rapid or 'extensive-metabolizers' (EM). The consequence of this difference is that the former group of individuals manifest a higher 24 hour median intragastric pH and longer intervals per 24 hours in which intragastric pH is greater than 4. Importantly, among EM/SM heterozygotes (30% of the Caucasian population), both the median intragastric pH (5.5 pH units) and intervals during which intragastric pH is higher than 4 (72.4% of a 24 hour period) are longer than in EM/EM homozygotes (3.1 pH units and 37.1% of a 24 hour period, respectively). Moreover, in SM/EM heterozygotes treated with omeprazole once daily, who are *H. Pylori* positive, plasma gastrin levels are more pronounced than in infected EM/EM homozygotes. This finding raises the spectre that pharmacodynamic and serum gastrin responses to standard doses of omeprazole are genetically determined and are significantly heterogeneous. The sponsor has argued that because the dosing interval is longer than the elimination half-life in SM/SM individuals accumulation of drug would be negligible. However, the sponsor has not fully addressed the diversity of response phenomenon that is based on empirical pharmacodynamic measurements. The sponsor has argued that in individuals who are SM/SM homozygotes, the potential of drug-drug interactions between omeprazole and other agents which are metabolized by CYP2C19 is negligible. For example, the clearance of diazepam, which in 'rapid-metabolizers' is decreased by approximately 25%

during treatment with 20 mg omeprazole once daily, is not altered in 'slow-metabolizers'. However, CYP1A2, another cytochrome P450 isoform, may play a significant role in the metabolism of caffeine, phenacetin and theophylline in these individuals. The activity of this isoform is differentially induced by omeprazole treatment in 'slow-metabolizers'. It has been observed that administration of 40mg omeprazole enhances the metabolism of caffeine by 30%. Currently, there is no data to support concerns about the potential for significant interactions between omeprazole and theophylline, a drug with a narrow therapeutic index whose blood levels must be carefully regulated in the treatment of asthma and chronic obstructive lung disease. Despite the absence of data to support the presence of drug-drug interactions between omeprazole and other agents, it is conceivable that subsets of genetically susceptible individuals who express distinct combinations of cytochrome P450 isoforms may be identified in future studies. The absence of a learned intermediary in an OTC setting is expected to blunt recognition of such drug-drug interactions.

## **Pediatric Subjects**

Currently, omeprazole is not indicated for prescription use in pediatric patients in the US. Despite the non-approved status in this age group the prescription formulation the sponsor is seeking approval for OTC use in children 12 years of age or older. Based on an IMS Health national prescription audit, of the total number of prescriptions of omeprazole dispensed in the US, the projected use in the 11 year old to 20 year old age range is 2%. Compared to the adult population, this usage is relatively small. However, in absolute terms, there is a substantial number of adolescent patients who have been exposed to omeprazole. Currently, there is a relative paucity of safety information about omeprazole exposure in this age group. In the past, almost all the clinical studies of the prescription formulation have excluded pediatric patients, including adolescents under the age of 18 years. As an exception, only 2 studies have been performed by the sponsor which included 74 pediatric patients, mostly small children and infants, with GERD. In the OTC arena, 100 adolescent subjects were administered doses of 20 mg omeprazole in an 'actual use' studies in which the labeling indicated not to exceed 10 continuous days of dosing. In these studies, amongst those individuals who self-medicated with omeprazole in order to prevent heartburn anytime, 58% exceeded the 10 day limit of drug administration. In the post-marketing database of world-wide serious and US non-serious AE reports submitted by the sponsor information from a total number of 39 adolescent patients with 1 or more AEs was presented. This represents an extremely small databank of information from which to analyze the safety profile and detect 'signals' of omeprazole-linked toxicity in this age group. Because there may be age-related susceptibility to toxicity caused by long-standing hypergastrinemic responses to chronic administration of the drug (see below), it is apparent that the safety database is inadequate to draw firm conclusions about the relative safety of omeprazole in adolescents.

## **Use in Pregnancy**

Currently, omeprazole is listed as a Pregnancy Category 'C' drug. The rationale for this assignment has been based on the observation that the drug induces embryofetal lethality in rabbits and post-natal body weight gain in rats. Reproductive toxicology studies, however, have indicated that omeprazole does not affect fertility and is not teratogenic. In the clinical arena, omeprazole has been used off-label to treat heartburn associated with pregnancy. Currently, in the US approximately 14% of omeprazole prescriptions are for females of childbearing age (15-45 years old). For combined years 1996 thru August 1999 the estimated prescription use in this subset of the population is 11,478,000. A search of the MedWatch spontaneous reporting databank for all congenital abnormalities associated with omeprazole yielded 18 unduplicated congenital anomalies. These included 5 cases of anencephaly worldwide, of which one was in the US. Based on the number of new prescriptions among women between 15 and 44 years old and the expected background rate of anencephaly in the US (0.36 per 1,000 births), it does not appear that there is an excess of this defect in omeprazole users. Likewise, since major defects affect approximately 3%-4% of live born infants, there does not appear to be excessive drug-related teratogenic effects associated with this drug (Ray Alderfer, MD, MPH, MO, Epidemiology Branch, HFD-733). Attached to these findings are a number of epidemiologic studies which have revealed no increased risk to the fetuses of pregnant omeprazole users. Based on these observations the sponsor has submitted a separate labeling supplement to the prescription formulation NDA (NDA 19-810/S-058) to support a change in the pregnancy category

assignment for omeprazole from 'C' to 'B'. To further explore safety issues associated with pregnancy for OTC omeprazole a series of reviews will be submitted by the Division of Epidemiology and Surveillance. Based on the accumulated experience, to date there does not appear to be a significant teratogenic effect associated with omeprazole. The implications of fetal exposure to the drug for long-term post-natal development and risk for the development of diseases in later life has not been fully addressed. Such questions can only be addressed by properly designed prospective or nested control cohort studies. The sponsor has proposed the following wording in labeling for OTC omeprazole use: 'If pregnant or breastfeeding ask a health professional before use. May cause damage to your unborn or nursing child.' This wording does not address the scenario in which an individual becomes pregnant while using omeprazole. In the OTC arena a labeled warning to avoid pregnancy is does not provide a sufficient 'safety net' to prevent exposure to drugs which are toxic to human fetuses. An adequate safety profile of omeprazole in pregnancy is mandatory to ensure adequate protection of the American consumer. In this respect, if omeprazole is not eligible for a Category 'B' status because of significant safety concerns for the unborn fetus, it would be difficult to justify its approval for OTC use.

## **B. Adverse events associated with long-term administration of omeprazole (more than 4 weeks total use)**

Safety issues linked to Long-term treatment with omeprazole (greater than 4 weeks, either continuous or intermittent administration) that have been identified include:

- Potential of omeprazole to mask underlying diseases including Barrett's esophagus, dysplasia and esophageal and gastric adenocarcinoma
- serum gastrin levels and ECL changes
- fundic gland polyps
- colorectal adenomatous polyps and adenocarcinoma
- atrophic gastritis, progression to intestinal metaplasia, dysplasia and gastric adenocarcinoma. Data addressing the safety profiles and risk of gastrointestinal cancer have been presented.
- Genotoxic potential of omeprazole
- Potential of omeprazole to induce rebound of gastric acid secretion.

Most of these sections will include an overview of the clinical studies, postmarketing experience and reviews of the relevant worldwide literature.

### **Masking of Disease**

Concern has been raised about the potential of omeprazole to mask symptoms of serious diseases which include Barrett's esophagus with dysplasia, esophageal carcinoma and gastric malignancy. As described above, amongst the cases of gastric adenocarcinoma linked to omeprazole treatment that have been reported voluntarily in the post-marketing phase to the SafeTNet databank there are a few cases in which treatment with the PPI led to a substantial delay of a number of months in the performance of diagnostic endoscopy. The sponsor has correctly pointed out in the NDA submission that in the context of chronic heartburn associated with GERD the presence of '*alarm symptoms*' necessitate immediate referral to a physician for endoscopic diagnosis. These symptoms include:

- Dysphagia and odynophagia
- Symptoms that are persistent, even during treatment
- Hematemesis, melena, rectal bleeding or anemia
- Weight loss and/or anorexia

The absence of such an instruction in the proposed OTC labeling is a matter of concern, since it has been established that

- a significant percentage of study subjects enrolled in the 'actual use' studies that have been performed who have self-medicated in order to prevent heartburn have not followed the instruction not to exceed 10 continuous days of treatment with omeprazole

- the pharmacokinetic/pharmacodynamic characteristics of omeprazole which are characterized by an approximately two day delay from the beginning of treatment until maximal acid suppression is reached and a relatively long duration of action make this drug an attractive choice for chronic or intermittent therapy for extended periods of time to prevent recurrent symptoms.

For these reasons, it is especially important to ensure that patients with chronic symptoms who will self-medicate for heartburn with agents that are available over-the-counter will be appropriately warned when empirical treatment in the absence of physician referral and diagnostic testing is inappropriate. The sponsor has correctly pointed out that in a large undifferentiated population of individuals who suffer from reflux symptoms or postprandial heartburn endoscopic studies reveal that most have negligible or benign and medically trivial mucosal changes, on endoscopic examination. Nonetheless, as alluded to in the introduction, a significant number of individuals with chronic heartburn have Barrett's esophagus or advanced stages of erosive esophagitis linked to significant potential to develop strictures in the absence of aggressive medical therapy. In addition, rarely individuals harbor dysplasia and/or adenocarcinomas.

Certain medically significant complications of GERD can only be diagnosed by endoscopic evaluation. Patient history plays an important role in the decision making process for triage by health care providers of patients. Important features that would be considered include the duration of heartburn symptoms and the presence/absence of accompanying symptoms.

According to current standards of medical practice in the United States and guidelines of the American College of Gastroenterology, patients with Barrett's esophagus should undergo regular endoscopic surveillance for the detection of dysplastic and/or pre-malignant changes. It needs to be emphasized that Barrett's esophagus or stricture, significant complications of GERD that require medical attention, are not necessarily related to the severity or frequency of heartburn. In the case of Barrett's esophagus, the frequency and severity of reflux symptoms among patients with this disorder compared to patients with uncomplicated nonerosive GERD are similar. Thus, both the qualitative and quantitative aspects of heartburn cannot differentiate between patients with this metaplastic and potentially premalignant condition and many patients with GERD.

In one study, 178 subjects with at least three months of frequent heartburn relieved by antacids who had symptoms for at least 4 of 7 days during the week prior to the study, were screened by upper endoscopy. After exclusion of 13 of these patients because of other baseline gastrointestinal diseases that included mucosal dysplasia, columnar metaplasia of the esophageal epithelium, adenocarcinoma and peptic ulcer disease, and ten other subjects because of ineligibility criteria. Of the remaining 155 subjects that were analyzed, 93% of the subjects rated their heartburn as moderate to severe, although less than half recorded daily heartburn. In the study, endoscopic evaluation revealed that 31% had mild esophagitis; however, 16% had more severe erosive esophagitis which in some cases included stricture. Importantly, 6% of the study subjects had non-dysplastic Barrett's esophagus; moreover, two subjects were excluded at the outset because of dysplastic mucosal changes. Because patients had heartburn for an average duration of 11 years it was concluded that:

.. 'chronic heartburn can reflect a wide range of diagnostic findings including important underlying pathological features and they warrant a full medical examination to detect such abnormal conditions and to permit selection of appropriate therapy'.

"long-term heartburn may warrant full medical examination to exclude important underlying pathological conditions and select appropriate treatment. The results of the current study and long-term users of antacids show that heartburn and other GERD symptoms may not be the trivial problem suggested by some consumer advertising. Physicians should understand that frequent and persistent GERD symptoms might reflect important gastrointestinal pathologic features"...

However, it was also concluded that:

'most individuals with occasional mild heartburn can be adequately and safely treated with life style modifications and OTC medications including antacids and low dose H<sub>2</sub> receptor antagonists'..



Recently, the 'GERD Management Group', a multidisciplinary team of physicians in family practice, general internal medicine, gastroenterology, and gastrointestinal surgery developed a consensus approach on the optimal medical management of GERD. In the algorithm of patient management that they have proposed empiric therapy for symptoms that are typical of GERD is recommended as follows:

- OTC antacids/low dose H-2 receptor antagonists in conjunction with life-style modifications are deemed appropriate as modalities of empirical treatment in the absence of a definitive endoscopic diagnosis
- With symptomatic relief, the initial empiric treatment regimen should be continued for 4-6 weeks, before a trial off medication
- Should symptoms recur, retreatment with the previous regimen should be instituted
- If symptoms persist after 4-6 weeks, higher doses of H-2 receptor antagonists or a PPI should be administered for up to an additional 6 weeks
- After this 'step-up' phase of treatment, a 'step-down' phase to the earlier regimen of low-dose H-2 receptor antagonists/antacids, etc. should be instituted. If symptoms recur, referral for endoscopy to make a definitive diagnosis and evaluate for GERD complications is indicated
- At any phase of treatment, including when heartburn first appears, if symptoms are atypical or suggest a serious non-GERD diagnosis prompt referral to a physician for diagnostic evaluation that usually includes endoscopy is appropriate.
- Upon endoscopic evaluation, a number of treatment options are available, depending on the lesions that are found. In the case of symptomatic non-erosive GERD and erosive esophagitis PPIs are often prescribed for maintenance treatment. In recalcitrant cases, anti-reflux surgery can be considered

In summary, although empiric therapy with pharmacological agents which suppress acid in the gastric lumen is a recognized element in the management of patients with GERD, proper triage of certain individuals for prompt endoscopic evaluation and appropriate medical followup is required. One reason for immediate referral is the presence of 'alert symptoms'. This standard of care must be taken into account during adjudication of the suitability of PPIs in the OTC market if it is determined that patients with GERD will be among those who will self-medicate for heartburn.

Although people with these medically significant lesions that require early recognition and/or management by a physician represent a minority of undifferentiated patients with heartburn, the prospect that they would not be 'gated out' from the OTC check-out line at the pharmacy presents a disturbing scenario. The 'minimalist' OTC labeling that has been proposed for omeprazole does not bear adequate warnings for the identification of individuals at high risk for advanced lesions. In the current submission, the sponsor has strongly agreed with the need to recognize 'alarm symptoms' and has made the following statement:

... 'In order to avoid the risk of possible complications that may occur with long-standing and persistent heartburn, consumers should be made aware of the indications, dosage and duration of therapy of over-the-counter heartburn medications they intend to use. In addition, they should have a clear understanding of when to seek medical attention. This information should be clearly labeled with explicit instructions that are understandable by all potential users. The proposed labeling for over-the-counter omeprazole does instruct users to seek medical advice if they need to take the medication as directed continuously for more than 10 days... The label will also clearly highlight alarm symptoms that the presence of any of these additional symptoms must warrant prompt medical attention before continuing self-treatment' ...

The statements by the sponsor correctly express one of the most significant caveats concerning the appropriate use of any empiric therapy for chronic heartburn. Unfortunately, the proposed labeling does not contain substantial information about the 'alarm symptoms' nor does it define in a specific way an appropriate endpoint of chronic self-medication. The phrase 'continuously for more than 10 days'.. is ambiguous and may infer to some consumers the notion that chronic treatment is acceptable if subjects take a 10 day one-day 'holiday' from self-administration of omeprazole.

Consideration should be given to modify the proposed labeling to recommend individuals who suffer from chronic heartburn to self-administer omeprazole for a maximum period of 4-6 weeks in an OTC setting, if diagnostic endoscopy has not yet been performed. In conjunction with the formulation of clear instructions that define which individuals should immediately seek referral to a health care provider the sponsor should provide adequate efficacy information and new actual use studies to determine that there is strict adherence to the labeling.

### **Hypergastrinemia, ECL cell hyperplasia and Atrophic Gastritis**

Because of growth promoting effects of omeprazole on the gastrointestinal mucosa, concern has been raised about the carcinogenic potential of long term administration of this drug to patients. Specifically, the Agency has sought to exclude pathophysiologic processes related to carcinogenesis in humans exposed to omeprazole for more than 1 year.

- First, there is a significant incidence of carcinoid (ECL cell) tumors of the stomach induced by long-term treatment of rats. In the oxyntic mucosa of adult humans and in all animal species tested, ECL hyperplasia is frequently induced by omeprazole. This phenomenon has been linked to the trophic effects of increased levels of circulating gastrin (endocrinological effects) that occur as a result of the suppression of acid secretion by the drug. In addition to endocrine, paracrine and even autocrine effects of gastrin have been postulated. Nonetheless, unlike the rat, there is no compelling evidence that drug-related ECL hyperplasia progresses to carcinoid tumors in adult humans.
- In addition, concern has been raised about the trophic effect of omeprazole induced hypergastrinemia on nongastric mucosa. In particular, attention has been directed to effects of omeprazole on epithelial cells in various organs. In cell culture, gastrin exerts trophic effects on non-ECL gastrointestinal cells (including colonocytes).

The chronicity and recurrence of symptoms which is characteristic of many heartburn sufferers and the demonstration of the frequent extension of continuous omeprazole usage beyond the labeled limit of 10 days that was observed in the 'actual use' OTC studies (see above and review by MO in the OTC division) strongly suggest that a significant percentage of patients will self medicate on a chronic intermittent or continuous basis, irrespective of labeling instructions. It is critical that this prediction be taken into account in the formulation of a safety profile analysis of omeprazole usage in an OTC setting. A number of physiological consequences emanate from the chronic usage of omeprazole. One of these is the heightened secretion of gastrin as a consequence of long-term PPI therapy. Circulating gastrin released by G cells from the stomach antrum has trophic effects, on enterochromaffin like (ECL) cells which secrete histamine, parietal cells which secrete acid, and other epithelial cells in the gastrointestinal tract. Gastrin release is controlled by a negative feedback mechanism that is sensitive to acid levels in the stomach. The extent of release of this hormone depends on a number of factors which include the size of the G cell mass, the degree and duration of acid suppression, the presence/absence of food in the stomach and the degree of antral distension. Due to the long duration of action of omeprazole and the profound suppression of acid secretion which occurs in many individuals treated with daily 20 mg doses, a two to fourfold rise in serum gastrin levels often occurs. In addition, there is a subset of individuals in which serum gastrin levels rise well above the upper limit of normal to levels greater than 400 pg/ml (ref of normal upper limit). Many patients with profound rises of serum gastrin levels while on omeprazole treatment are H. pylori positive and manifest histopathological features consistent with chronic corpus atrophic gastritis. It is likely that in the face of reduced parietal cell function caused by H. Pylori in some individuals who are colonized with the organism, the degree of acid suppression induced by omeprazole is more pronounced than in non-infected individuals. H. Pylori infected individuals may be particularly susceptible to develop exaggerated secretion of gastrin during treatment with PPIs. As described above, gastrin release is stimulated by the suppression of acid. In this respect, exaggerated gastrin responses observed in some subjects treated with agents that suppress acid secretion is not limited to the pharmacological class of PPIs. High dose frequently administered H<sub>2</sub>-blockers have also been shown to induce increased serum gastrin levels. However, because of the reversible nature of H<sub>2</sub> receptor blockade by these agents, low dose H<sub>2</sub>-receptor antagonists administered once or twice a day, which are currently approved for OTC marketing, generally are not associated with this phenomenon. In contrast, because of their long duration of action and potency full-dose PPIs that are indicated for the treatment of active ulcer disease (eg omeprazole 20 mg qd) induces

elevated serum gastrin levels in some individuals. Concerns raised about the potential of high circulating levels of gastrin to induce tumors have been raised emanate from the following observations:

- ECL cell carcinoids develop both in male and female rats treated for 24 months with daily doses of omeprazole, in a dose-related matter.
- In studies involving more than 200 patients serum gastrin levels increased during the first 1-2 weeks of once daily administration of therapeutic dosages of omeprazole, in parallel with inhibition of acid secretion. Immediate increases of serum gastrin levels induced by 20 mg doses of omeprazole were higher than those induced by full doses of H<sub>2</sub>-receptor antagonists that are indicated in the treatment of peptic ulcer disease, (range increases were 1.3 - 3.6 fold vs 1.1 - 1.8 fold, respectively). Gastrin values returned to pretreatment levels usually within 1-2 wks after discontinuation of therapy.
- Gastric carcinoids are also linked to two conditions associated with chronically elevated serum gastrin levels. These include Zollinger-Ellison Syndrome (ZES) which is a component of Multiple Endocrine Neoplasia I (MEN-1) and gastric body predominant chronic atrophic gastritis (CAG). Carcinoid tumors associated with elevated serum gastrin levels are not as invasive as those that develop in the presence of normal serum gastrin levels and normal oxyntic gastric mucosa. Generally, their growth is hormone-dependent and they are amenable to treatment by local excision. Although many patients on long-term PPI therapy manifest a 2-4 fold increase in gastrin levels there are a small number of individuals who develop greater than 4-fold increases in serum concentrations of the hormone, above baseline. Although elevated serum gastrin levels have been associated ECL cell hyperplasia in humans, currently there is little empirical evidence that they induce carcinoids or other malignancies.
- It has been postulated that raised serum gastrin levels may be risk factor for the development of colorectal adenocarcinoma. Studies examining serum gastrin levels in patients with colorectal adenomas and adenocarcinomas, compared to individuals without these lesions, have produced conflicting findings (Insert references). These investigations are limited because of their retrospective, case control study designs. In some of the studies, mean serum concentrations were elevated only in a small subset of patients with colorectal neoplasms. The mixed results of the studies suggest that it will be necessary to perform trials with prospective study designs to definitively determine whether there is a causal link between elevations of serum gastrin and these lesions, particularly since patients with pernicious anemia, post-truncal vagotomy and/or gastric surgery, CAG or ZES who have longstanding hypergastrinemia have not been observed to have an increased risk to develop colorectal cancer.

Numerous reports in the literature have demonstrated an association between the use of omeprazole and fundic gland polyps. Although the pathogenesis of these benign lesions is unknown they have negligible malignant potential. Histopathologically, they are comprised of hyperplastic gastric epithelial cells and cystic glandular structures. Because parietal cells bear gastrin receptors, it is likely that omeprazole-stimulated increases in serum gastrin concentrations lead to parietal cell hypertrophy.

- A possible carcinogenic mechanism that has been proposed is that omeprazole administration may cause a tumor enhancing effect in patients who are infected with *H. pylori*. The organism has been found to play an etiological role in the pathogenesis of a number of conditions in the stomach. These include chronic atrophic gastritis, which when associated with intestinal metaplasia (types II and III), is considered to be precursor lesions in a multiple step neoplastic process that leads to gastric adenocarcinoma. *H. Pylori* stimulates gastrin release by the antral 'G' cells. This may occur because the organism induces a reduction in somatostatin secretion by 'D' cells. In the presence of *H. pylori* infection, proton pump inhibitors have been found to accentuate inflammation of the oxyntic (corpus) mucosa. A question has been raised as to whether drug-linked accentuation of the inflammatory process and an increase in gastrin stimulation may promote the risk for progression to Types II and III intestinal metaplasia, and eventually dysplasia and adenocarcinoma.

It is estimated that 1% of individuals with *H. Pylori* induced chronic gastritis will eventually develop gastric adenocarcinoma. Since the organism is classified as a Group I carcinogen by the World Health Organization, concern has been raised whether PPI treatment promotes dysplastic transition of the infected gastric mucosa. A study by Kuippers et al concluded that long-term treatment with omeprazole hastened

the development of atrophic gastritis in H. Pylori positive patients. This investigation was limited since it was not a randomized, controlled trial and the two cohorts that were compared were from different countries and were characterized by mean ages which were nine years apart. Other published trials in patients with atrophic gastritis prior to pharmacological acid suppression who were then placed on long-term omeprazole treatment for up to 8 years have not revealed progression of the inflammatory process. In two studies which reported an increase in the prevalence of atrophic gastritis in individuals treated with omeprazole, the H. Pylori status of patients was not consistently determined. Thus, it can be concluded that even if omeprazole causes histopathologic progression to intestinal metaplasia not associated with dysplastic changes (Type I) in the stomach, there is no convincing evidence that a causal relationship exists between administration of the PPI and further progression to Types II and III intestinal metaplasia, associated with dysplasia or adenocarcinoma. Acceleration of atrophic gastritis in H. Pylori positive individuals treated long-term with PPIs was addressed by a FDA Advisory Panel (GI Drugs Advisory Committee Meeting held on Nov 4, 1996). After a discussion surrounding the data which was available at that time the committee concluded that there was not convincing documentation of an increase in atrophic gastritis or intestinal metaplasia in patients on prolonged PPI therapy to warrant a recommendation that H. Pylori infection should be eradicated prior to prescribing long-term PPI therapy. Because of lingering uncertainty, the FDA requested an update of information from the sponsor that was submitted on June 17, 1999 (NDA 19-810; Prescription formulation of omeprazole for GERD etc.). The update included clinical study data, an updated review of the medical literature and an analysis of the world-wide safety database (SafeTNet) through December 31, 1998. This submission has been reviewed separately (NDA 19-810/S061; MO reviewer Mark Avigan, MD CM). Information from that submission has been incorporated into the analysis discussed below.

### **Long-term Clinical Trials**

The sponsor has provided information gathered from 2 US and 4 non-US trials encompassing approximately 1,100 patients treated with study medication for time periods ranging between 2 and 14 years.

In this database more than half the patients were treated in an open-label fashion. Conditions that were being treated included Barrett's esophagus, severe and recurrent erosive or ulcerative esophagitis and severe peptic ulcer disease, patient populations with conditions which are distinct from those who have been proposed for OTC market. Findings of these trials included the following:

- Only a minority of patients developed serum gastrin concentrations exceeding 400 pg/ml. When categorized by H. Pylori status serum gastrin levels over 400 pg/ml were observed only in H. Pylori positive individuals.
- Greater increases in serum gastrin concentrations were noted in the omeprazole treated group compared to the group treated with ranitidine.

These findings are demonstrated in Trial 016 as follows:

- After 24 months between 51% and 69% of patients treated with omeprazole 40 mgs qd for 12 months followed by 20 mgs qd for 12 months manifested increases in serum gastrin concentrations of more than 40 pg/ml. In contrast, between 18% and 28% of patients treated with ranitidine 300 mg bid for 24 months. At the end of treatment the highest serum gastrin concentrations were observed in 3 patients (7%) in the omeprazole-treated group. These patients manifest gastrin levels ranging from 250 pg/ml to less than 400 pg/ml.
- In trial 017 median gastrin concentrations increased moderately with omeprazole treatment (3 open-label phases - 20 mg qd for 4 weeks; followed by 20mg or 10 mg od for 1 year; followed by 20mg or 10 mg od for 1 year). Few patients developed serum gastrin concentrations in excess of 150% of the upper limit of normal.
- In trial I-665 (omeprazole 40 mgs bid vs ranitidine 150 mgs bid; followed by open-label omeprazole 40 mgs bid) serum gastrin levels of greater than 400 pg/ml occurred in patients who were H. Pylori positive.
- In trial I-635 patients in the omeprazole treatment group (vs the anti-reflux surgery group) had greater increases in serum gastrin concentrations. These rarely exceeded 100 pmol/l.

- In trial I-548/614 two H. Pylori positive patients developed marked increases in serum gastrin concentrations between baseline and year 5 measurements (430 pg/ml to 6,320 pg/ml and 173 pg/ml to 9,650 pg/ml). In conjunction with H. Pylori infection these individuals developed severe chronic corpus atrophic gastritis

In summary the presence infection has been observed to accentuate rises in omeprazole-induced serum gastrin concentrations. In some 'outlier' individuals rises in gastrin levels induced by omeprazole 20 mg per day are pronounced reflecting H. Pylori associated reduction in parietal cell function. The trophic effects of longstanding hypergastrinemia on ECL like cells and other gut epithelial cells (eg colonocytes) are not fully known. With the information at hand it is not possible to absolutely exclude the possibility that this mechanism may promote malignancy in some individuals. Whether omeprazole plays a role in promoting transition from early to late stages of gastritis or dysplasia/malignancy is not clear. Further prospective and/or nested cohort studies are necessary to answer this question.

#### **ECL cell changes evaluated during long-term clinical trials of omeprazole in adults**

It is well established that omeprazole and other PPIs induce the benign hyperplasia of ECL cells. A review of the clinical trials has established that omeprazole treatment for 24 months or longer was associated with the induction of simple, linear or micronodular forms of hyperplasia. No cases of dysplasia or carcinoid tumors were observed, with one exception. In trial 017, one case of carcinoid was reported during the study period. This was analyzed to be a preexisting condition (examine study).

#### **Colonic epithelial cell changes evaluated during long-term clinical trials of omeprazole in adults**

In Trial 016 (treatment duration - 24 months) with colonoscopic assessment of colorectal polyps greater than 3mm in diameter at baseline and after treatment, no substantial differences in polyp numbers between the omeprazole and ranitidine treatment groups were observed. Similarly, there were no meaningful differences between the treatment groups when patients were stratified at baseline according to polyp numbers and then grouped according to the number of polyps that were identified at the end of treatment (After the two year treatment phase, when patients were grouped according to the polyp histopathologic type, no meaningful differences were discerned between the omeprazole and ranitidine treatment groups

#### **Fundic gland polyps during long-term clinical trials of omeprazole in adults**

Clinical studies to investigate the relationship between fundic gland polyps and treatment with omeprazole have not been provided. However information has been accumulated from the post-marketing databank and literature (see below).

#### **Atrophic gastritis and gastric cancer risk evaluated during long-term clinical trials of omeprazole in adults**

As alluded to above, advanced atrophic gastritis with intestinal metaplasia is associated with an increased risk for adenocarcinoma. Controversy exists whether H. Pylori infection hastens the development of this lesion, best characterized by true gland atrophy in the corpus of the stomach. In the six long-term clinical studies, described above, there were no patients who developed gastric dysplasia or adenocarcinoma. In study 017, at baseline, only four patients developed histopathologic characteristics of atrophic gastritis. After two years of omeprazole treatment (10 mg or 20 mg daily doses) the number of patients with atrophic gastritis increased to 13. No case of intestinal metaplasia or dysplasia were recorded. In Trial I-665, after 24 months of treatment, 3 patients who were administered omeprazole and one who was administered ranitidine developed moderate atrophy of the corpus mucosa. All of these patients were H. Pylori positive. In Trial I-635, as in the other studies, corpus gastritis activity was confined to patients who were H. Pylori positive. In the study the administration of omeprazole did not impact on the degree or rate of mucosal atrophy compared to treatment with surgery alone. In Trial I-548/614 an annualized incidence rate of mucosal atrophy was observed to be 4.0% in H. Pylori positive patients and 0.7% in H. Pylori negative patients. Similar to the results listed above, in Trial I-565 there was little apparent change in the activity of corpus gastritis in patients who were H. Pylori negative, irrespective of treatment with omeprazole. However, in the H. Pylori positive group there was an increase in the severity of gastric mucosal atrophy noted in some patients. No patients developed mucosal dysplasia or adenocarcinoma. From this relatively small patient database, it is apparent the predominant factor that impacts on the evolution of corpus gastritis to atrophy is the presence of H. Pylori infection. The evidence suggests that long-term treatment with

omeprazole does not slow this process. On the other hand, there is little evidence to support the contention that omeprazole treatment hastens the process that leads to atrophy, dysplasia or adenocarcinoma. It is important to exclude this possibility since if omeprazole treatment augmented the risk of H. Pylori infected individuals to develop adenocarcinoma, then a strong case could be made that eradication of the organism with combination antibiotic therapy should precede long-term treatment with PPIs. Further controlled studies to definitively answer this question are still needed.

#### **Neoplastic and hyperplastic changes of gut mucosal cells associated with omeprazole reported during post-marketing safety surveillance**

In another submission, which was reviewed separately (sponsor's response to the Agency's communication regarding an earlier pediatric written request; submitted August 4, 1999) the sponsor has catalogued adverse events reported to the Worldwide Adverse Event Database (SafeTNet). Amongst the list of events were reports of ECL cell hyperplasia and other gastro-intestinal epithelial cell abnormalities linked to use of the drug through June 30, 1998.

Of 22 reports of ECL cell hyperplasia, 10 were not attributable to underlying gastrinomas, pernicious anemia or atrophic gastritis. In addition, of 21 reports of gastric or duodenal carcinoids, 6 could not be attributed to gastrinoma or pernicious anemia. From this information, it is not possible to fully exclude a potential for drug-induced chronic hypergastrinemia to induce carcinoid tumors in a small percentage of omeprazole treated patients. The true incidence of such an association appears to be very small.

Of a total of 73 reports of benign gastric or duodenal polyps there were 3 reports of duodenal adenomatous polyps. Adenomatous polyps of the stomach and duodenum are neoplastic and have the potential to progress to malignancy. Of concern is the relative rarity of spontaneous duodenal adenomas in the absence of Familial Adenomatous Polyposis/Gardner's Syndrome. In the post-marketing surveillance of omeprazole there have been a total of 38 reports of definite or possible colorectal carcinomas and 49 cases of gastric adenocarcinomas. A detailed characterization of these cases was not initially presented by the sponsor. To further characterize these omeprazole-associated cases of neoplasia obtained from the post-marketing database, the agency requested that the sponsor submit detailed case narratives (see below).

To address concerns raised about the carcinogenic potential of omeprazole in humans, the Agency issued an Information Request Letter to the sponsor on 12/14/99 requesting the following documents:

- Case report forms for patients enrolled in Study 016 who developed skin cancer or other neoplasms
- Case report forms for patients enrolled in Study 016 who developed gastrointestinal polyps with inclusion of histopathologic information as well as a description of their site, size, number, and distribution
- Case report forms for patients who had gastrointestinal carcinoids, adenomas, or carcinomas from four long-term treatment trials that include: a) Study I-665 ('Effects of elimination of gastro-esophageal reflux by omeprazole on parameters of premalignant change and dedifferentiation'), b) Study I-635 ('Omeprazole versus anti-reflux surgery in the long-term management of peptic esophagitis—a Scandinavian comparative multicenter study'), c) Study I-548/614 ('The compassionate use of omeprazole in patients with peptic ulcer disease or severe erosive esophagitis, not responding to treatment with histamine-2 receptor antagonists and ineligible for surgical treatment'), and d) Study I-565 ('Efficacy and safety of omeprazole in long-term treatment of patients with peptic ulcer or esophagitis resistant to treatment with ranitidine')
- Adverse reaction reports from post-marketing surveillance for gastrointestinal carcinoids, adenomas, or carcinomas (all segments of the gastrointestinal tract)

From the information that has been provided it is apparent that 7 patients enrolled in Study 016 developed malignant neoplasms, including 5 in the omeprazole treatment arm and 2 in the ranitidine treatment arm. In the omeprazole treatment arm, the cases included 2 basal cell and 1 undefined cancer of the skin, 1 prostate cancer and 1 breast cancer. In the ranitidine treatment arm, the cases included 1 adenocarcinoma of the lung and 1 basal cell cancer. From this small series, it is not possible to attribute causality to the use of drug. In the same study, colonoscopic surveillance revealed colonic polyps in 30 patients in the

omeprazole treatment arm and 26 patients in the ranitidine treatment arm. Of the total number of subjects who were surveillanced at the end of the study, there was an almost identical number in each group who developed histopathologically proven adenomas (7 in the omeprazole treatment arm and 10 in the ranitidine treatment arm). In addition, there were no apparent differences in the incidence and rate of growth (size) of colonic polyps in the two study arms.

A composite of the submitted post-marketing surveillance adverse reaction reports of gastrointestinal neoplasms in patients being treated with omeprazole includes the following:

- 32 cases of carcinoid tumors of the stomach and/or duodenum. Of these, based on information that has been provided, at least 13 were not attributed to the presence of gastrinoma(s) due to ZE or MEN syndromes or other conditions. Of the carcinoids not attributable to gastrinomas, 9 were gastric and 4 duodenal. These numbers are higher than those tabulated in a separate document that the sponsor has submitted seeking approval for an omeprazole formulation OTC (NDA 21-229, Integrated Summary of Safety Data, 8.8.5, p. 66 & 114) which reports only 8 gastric carcinoids and 1 duodenal carcinoid in the total world-wide non-serious adverse event counts. The sponsor should be asked to explain these discrepancies.
- 29 cases of gastric adenomas.
- 3 cases of duodenal adenomas. None of these patients was reported to have a hereditary polyposis syndrome and all were medicated with omeprazole for 7 months or longer.
- 22 cases of colonic adenomas.
- 12 cases of esophageal carcinoma, many who had underlying risk factors such as Barrett's esophagus.
- 49 cases of adenocarcinoma of the stomach. In at least 4 of these cases, omeprazole therapy caused masking of symptoms and/or temporary healing of the gastric mucosa with a 1 to 12 month delay in the diagnosis of malignancy.
- 1 case of duodenal adenocarcinoma.
- 31 cases of carcinoma of the colon.
- 18 cases of GI anatomic site not specified.

The sponsor has provided some safety information concerning the long-term use of omeprazole. Safety data from a two-year study (Study 016) of patients with Barrett's esophagus treated either with omeprazole or an H<sub>2</sub> antagonist were analyzed. As an outcome of this analysis the sponsor has concluded that there are "no significant differences between treatment groups observed in the development of ECL cell hyperplasia, corpus atrophic, gastritis, corpus intestinal metaplasia or colon polyps exceeding 3 mm in diameter." It is apparent that the sponsor's submission is characterized by significant limitations with regards to the Agency's strong interest to ensure the safety of long-term usage of Omeprazole. These limitations include the following:

- The submitted study was small. Of a total of 57 patients randomized to receive omeprazole only 46 completed the two year study. This small N- value precludes a comprehensive safety analysis and detection of adverse events which may not be very common.
- Patients in Study 016 were tracked for only two years. Because of the potential for a lag in drug-related effects associated with omeprazole, results of the study do not preclude long-term growth related effects of omeprazole in the G.I. tract and other organs.
- The sponsor has not submitted information about the safety of omeprazole usage beyond two years.
- The comparative study, which the sponsor has presented, pertains only to patients with Barrett's esophagus. This patient population is distinct and may manifest different responses to long-term omeprazole administration than the much larger group of patients who are being treated with this drug for GERD not necessarily associated with metaplastic changes of the esophagus.

As stated above, there are three areas of concern that have been raised by the Agency concerning the potential tumorigenic effects of omeprazole in patients. First, ECL cell hyperplasia that is associated with omeprazole-induced hypergastrinemia may progress to carcinoid tumors, or other G.I. tumors. Second, the genotoxic effects that have been observed by *in vitro* testing of omeprazole may be associated with carcinogenic effects in multiple tissues which are not necessarily confined to the

gastrointestinal tract. Third, combined effects of omeprazole with comorbid conditions such as *H. Pylori* infection and atrophic gastritis may be linked to significant safety effects.

In a separate submission submitted in response to a request for information from the agency sent recently (see above) the sponsor has provided information on post-marketing safety surveillance of patients treated with the drug. Of concern is the accrual of 32 reports of gastric/duodenal carcinoids, 13 of which lacked evidence of conditions linked to gastrinoma or pernicious anemia. In addition, the sponsor has reported three cases of duodenal adenomatous polyps not linked to heredity polyposis syndromes, a relatively rare condition. From this experience it is clear that further tracking of mucosal neoplastic lesions in the post-marketing phase is crucial in order to exclude a causal link between neoplasia and omeprazole.

The delay in diagnosis of gastric malignancy attributable to omeprazole treatment in a small group of patients (4/49 reported cases). Analysis of the submitted narratives suggests that the delay was due to temporary alleviation of symptoms or endoscopic findings showing improvement of malignant lesions or synchronous nonmalignant lesions. In some cases, a diagnosis of malignancy was made 10 months or longer after the beginning of symptoms.

In extrapolating whether omeprazole-linked malignancy to an OTC population poses a significant risk, a number of important limitations must be addressed. These include:

- Limitations of detecting omeprazole-linked malignancy in a large population by volunteer reporting
- The prediction that there is a long lag phase between drug exposure and malignancy
- High background rates of certain GI malignancies (eg colorectal and pancreatic Ca) that would 'drown out' weak signals
- Lack of prospective or nested cohort studies to track patients who have been treated with omeprazole over a long period of time
- Lack of definition of groups that may be especially vulnerable to the carcinogenic effects of omeprazole. Such subsets of consumers may be diluted by individuals who are not at increased risk for malignancy when exposed to the drug. The sponsor has provided information obtained from long-term clinical trials in which adult patients were treated with omeprazole between 2 and 14 years. Analysis of results of these studies revealed that there is no evidence of progression of ECL cell hyperplasia to severe grades of ECL cell pathology. This experience is corroborated by the lack of a significant number of adverse case reports of carcinoid tumors in patients treated with omeprazole. Although very reassuring, the aforementioned data do not preclude the possibility that the susceptibility for ECL cellular transformation and tumor progression is different susceptible individuals. Such a difference(s) could occur as a result of developmentally modulated biological characteristics such as altered ratios of undifferentiated (precursor) cells in organs during the growth phase of development. In addition, after a putatively rare drug-induced perturbation of target cells, the emergence of carcinoid tumors probably requires other superimposed genetic 'hits'. This process is predicted to be time dependent and requires a long latency (years) until a malignant neoplasm would form. Analogously, in the case of sporadic colon cancer in adults, such time dependent accrual of multiple growth selective genetic 'hits' in target colonocytes is well characterized. Because of the short duration and the relatively small number of pediatric patients that were studied by the sponsor, it is not possible to exclude that in a large pediatric population treated with omeprazole (short-term and/or maintenance treatment), a time-linked association with carcinoid tumors will emerge. For this reason, the absence of a pattern of adverse reports of carcinoid tumors in patients treated with omeprazole does not preclude a long-term carcinogenic effect of the drug in some individuals. In addition, the absence of a comprehensive long-term follow-up of all members of defined study groups of patients taking omeprazole underscores the limitations of the world-wide voluntary side-effect reporting system (SafeTNet) that has been instituted by the sponsor. Because of sporadic/voluntary/ spontaneous reporting by only a small percentage of individuals treated with the drug, results of adverse side-effects may be misleading.



## Rebound of Gastric Acid Secretion

Acid rebound is defined as an increase in gastric acid secretion (basal and/or stimulated) above pretreatment levels after discontinuation of anti-secretory therapy. Mechanisms associated with rebound include increases in serum gastrin concentrations and increased sensitivity to histamine (eg upregulation of H-2 receptors). Factors that lead to acid rebound following anti-secretory therapy are linked to the pharmacologically induced degree and duration of acid suppression. In addition, H. Pylori infection may augment acid rebound (ref 2). The sponsor has cited 9 clinical studies that measure the potential for acid rebound after discontinuation of omeprazole treatment (duration of treatment up to 3 months).

The results of these studies are mixed. In many of the studies in which the treatment phase was two weeks or less acid rebound was not observed, after discontinuation of omeprazole. In contrast, in a study by Waldam et al (insert ref Waldam, 1996), after a 90 day treatment period with omeprazole 40 mg daily, there was a significant rise in basal acid output in 3/8 patients, 14 days after discontinuation of omeprazole. This rise may be interpreted to reflect an increase in size and number of ECL cells, a consequence of the effects of longstanding anti-secretory treatment. Consistent with this interpretation was the observed increase in serum chromogranin A. Administration of omeprazole 40 mgs daily for eight weeks in healthy patients was linked to an increase of maximal acid output measured at 6 and 16 days post-treatment. This increase correlated with individual rises in serum gastrin concentrations during omeprazole treatment, suggesting that there is a trophic effect on parietal cells. In a study by Fischer et al, both omeprazole 20 mg daily and ranitidine 150 mg bid (the recommended treatment dose for peptic ulcers which is double the labeled limit for OTC use) were associated with increases in basal acid secretion 3 days post-treatment. After long-term treatment with omeprazole, Weinstein et al observed that patients with Barrett's esophagus developed a significant increase in pentagastrin stimulated acid secretion which returned to normal 3 months after cessation of therapy.

From a clinical perspective, despite the fact that most patients with GERD-related reflux esophagitis heal during treatment with omeprazole, there is a high recurrence rate, both of symptoms and inflammatory disease, within a short time after cessation of therapy. In one study, almost all patients with severe esophagitis healed during the treatment phase. Nonetheless, within 30 weeks of discontinuation of PPI therapy, more than 80% recurred. This finding is consistent with the concept that irrespective of the degree of inflammation, the underlying pathophysiological predisposition to develop esophagitis remains.

From these data the following can be concluded:

- Omeprazole associated acid rebound is reflected both by increases in basal and pentagastrin stimulated acid secretion. This effect is variable and may be linked to the extent of acid suppression as well as duration of treatment.
- Acid rebound occurs following treatment with H-2 receptor antagonists at doses which are recommended for the treatment of peptic ulcers.
- Acid rebound is self-limited after discontinuation of treatment with omeprazole.
- No information is available to determine whether acid rebound plays a role in patterns of self-medication by OTC subjects.
- H. Pylori may influence in variable ways the development of acid rebound after cessation of omeprazole treatment.
- Pronounced acid rebound in a subset of susceptible individuals in the population at large cannot be excluded. Such a phenomenon would not necessarily be detected in studies which enroll small numbers of test subjects.

## Genotoxic Potential of Omeprazole

A cause for concern about the carcinogenic potential of omeprazole in humans is that based on the results of *in vitro* and *in vivo* testing, the agent and its S-enantiomer, H 199/18, which is a component of the formulation in Prilosec, may be genotoxic in a number of cell lineages, not limited to the GI tract. Although results of mutagenicity testing using the Ames Salmonella typhimurium test have been consistently negative, both *in vivo* and *in vitro* exposure of mouse cells to the agent has been tied to clastogenic effects. Positive testing has been observed in a bone marrow micronucleus assay and

chromosome aberration has been noted in peripheral human lymphocytes exposed *in vivo* and *in vitro* to the agent, respectively. The question whether omeprazole is genotoxic in humans has been raised by a report of increased sister chromatid exchanges (SCEs) in peripheral lymphocytes obtained from subjects treated with omeprazole (C. Thompson et al. *Comparative effects of omeprazole, cimetidine and ranitidine on sister chromatid exchange frequencies in lymphocytes of healthy human subjects*. *Gastroenterology* 102[4, part 2]: A177, 1991). This finding has not been reported elsewhere in the medical literature. With regards to carcinogenesis in humans, the clinical significance of the limited range of positive testing of omeprazole has not been addressed. Furthermore, whether genotoxic effects of this agent on target cells that emanate from a variety of lineages has a greater impact on enhancing the risk for carcinogenicity in pediatric patients in comparison to adult patients is unknown.

There is a substantial body of information regarding the testing of omeprazole and its S- enantiomer H199/18 (which is a component of the racemic mixture contained in Prilosec) for genotoxicity. Results of these studies can be summarized as follows:

- Ames Salmonella typhirium, assay – Omeprazole and H 199/18 were not mutagenic in this assay.
- *In vitro* chromosomal aberration assay – In limited concentration ranges omeprazole and H 199/18 induced a significant number of chromosomal aberrations in human lymphocytes. In the case of omeprazole, a statistically significant increase was noted at a concentration of 345.4 mg/L when compared to the solvent alone control. H 199/18 was clastogenic at concentrations of 0.56 mM or higher.
- No significant increases in chromosomal aberrations were noted in mouse bone marrow cells after administration of omeprazole to Crl:CD-1 mice (110, 367 and 1,100 mg/kg) by oral gavage.
- H 199/18 was not clastogenic in two *in vivo* cytogenetic assays, a bone marrow micronucleus test and a rat bone marrow chromosome aberration test, even at toxic doses that caused deaths in some animals.

The genotoxic effects that have been observed in some *in vitro* tests of omeprazole may reflect carcinogenic properties of the systemically circulating agent on susceptible cells which need not be confirmed to the gastrointestinal tract. Susceptibility of cells to omeprazole or H 199/18 genotoxicity may be related not only to parameters of drug exposure alone, but also to growth related phases of target cells that are modulated during development. Third, although omeprazole may not be carcinogenic to gastric epithelium alone, a combined additive or synergistic effect, to form tumors, linked with the metaplastic and/or dysplastic associated changes that are known to be caused by *H. Pylori* infection in some patients must be ruled out.

The sponsor has provided information regarding *in vitro* and *in vivo* testing of omeprazole and H 199/18 for genotoxicity. Omeprazole is in a class of benzimidazole proton pump inhibitors. In a milieu of a low pH these pro-drugs are converted to a highly unstable DNA-reactive sulfenimide metabolite. Extensive testing of omeprazole in rodents has revealed that it does not induce the formation of neoplasms other than carcinoid tumors in rats. Omeprazole and H 199/18 are not mutagenic in the Ames Salmonella typhirium assay. This reduces the likelihood that there is a *high* risk that these agents are hazardous in humans. In the face of inconsistently positive results yielded by the testing of omeprazole and H 199/18 in chromosomal aberration assays, it is not possible to exclude the possibility of genotoxicity in humans with an associated (possible *low*) risk of carcinogenicity. Therefore, the clinical relevance of the observation that omeprazole and H 199/18 are clastogenic *in vitro* is elusive. Even if these agents were carcinogenic in humans, with the information that is currently available and taking into account the limited predictive value of the assays that have been performed, it would not be possible to quantify a risk in patients being administered the drug, determine which organ systems would be vulnerable to tumor formation or assess a differential risk in certain patients (eg adolescents). Thus, a global assessment of the risk of carcinogenicity in susceptible patients cannot be determined by the battery of genotoxic testing that has been performed. Based on the information that the sponsor has provided it cannot be definitely determined that omeprazole does not have a carcinogenic potential in some individuals. However, its track record in adult patients until now suggests that the risk in the population as a whole may be low or negligible.

## C. Conclusions

The sponsor is seeking approval for approval of omeprazole magnesium 20 mg for the treatment or prevention of occasional episodic heartburn. This condition is distinct from chronic heartburn linked to GERD. In assessing the safety profile of omeprazole for an OTC setting in the US it is important to determine whether both of these conditions will be treated. If individuals with GERD will comprise a significant element of the self-medicating population, because of the high recurrence rate of symptoms after cessation of anti-heartburn treatment, a high likelihood that some consumers will use the product either chronically or intermittently must be taken into account in a safety analysis. In addition, the development of an OTC indication of self-medication for individuals with GERD must take into account the need to avoid a substantial delay in diagnosis or pharmacological masking of significant complications that require timely recognition and care by a physician.

Occasional episodic heartburn is effectively managed by self-administration of agents which have a rapid onset and relatively short-lasting duration of action. The fact that maximal suppression of gastric acid secretion is only achieved after 2 or 3 days of daily treatment with omeprazole and that after each dose, there is a long duration of acid suppression suggests that this drug is very suitable for heartburn prevention rather than for the immediate relief of occasional episodic symptoms by the administration of a single tablet. Actual use studies were characterized by recruitment of many individuals who suffer from chronic heartburn symptoms consistent with GERD. The studies demonstrated that a large percentage of people who were self medicated with omeprazole to prevent heartburn used the drug for more than 10 days continuously. This observation is consistent with the prediction that in addition to short-term users some consumers will use the drug, either chronically or intermittently.

An analysis of adverse events associated with short-term drug exposure (less than 4 weeks) has revealed that Omeprazole can be linked to the following:

- A range of liver toxicities in small percentage of patients. The toxicity is usually mild, idiosyncratic, self-limited and is reversed upon drug withdrawal. However, the drug causes significant hepatocellular necrosis in some individuals and has been linked to a few deaths. Although rare, causality of significant hepatocellular damage has been confirmed in some cases by dechallenge/rechallenge with omeprazole.
- Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome. Although very rare, some cases have been linked to death
- Agranulocytosis and other disorders of marrow suppression. These are a rare events which usually, although not always, are reversible upon drug withdrawal
- Anaphylaxis/Angioedema. In some cases of immediate hypersensitivity with symptoms of urticaria, wheezing, rash, swelling, etc clear causality with omeprazole has been proven by successful dechallenge and rechallenge with the drug. The incidence of hypersensitivity responses is high enough to have been detected in clinical trials and be as high as 0.5 per 1000 users of omeprazole

*Adequate labeling that warn consumers about these rare side-effects is necessary.*

#### **Special populations in which OTC omeprazole has been linked to important concerns**

- Pediatric subjects. Currently, omeprazole is not approved for prescription use in adolescents. The numbers of clinical study subjects in this age group and the numbers of AEs reported in the post-marketing database are too small to determine whether adolescents have differential susceptibilities to develop rare toxic events linked to omeprazole. For this reason, *the lower age limit for OTC use of omeprazole should be 18.*
- Pregnancy. Currently, Omeprazole is categorized as a 'Class C' drug because of fetal toxicity in an animal model. On the other hand, off-label use in humans has not demonstrated omeprazole-linked loss of fertility or teratogenicity. *In the future, the sponsor should develop registries to study the outcomes of pregnancy in users of omeprazole. If omeprazole cannot pass muster for a Category 'B' status it is difficult to justify its approval for OTC use.*

- Drug-drug interactions. In conjunction <sup>w/</sup> affects on absorption of anti-fungal drugs omeprazole has the potential to reduce clearance of drugs that are metabolized by CYP2C19 such as diazepam, phenytoin, R-warfarin and tolbutamide. In the case of diazepam, an omeprazole-induced reduction of 25% may be clinically significant in individuals who are particularly susceptible, such as those with liver disease. *Because of the absence of a learned intermediary, labeling should indicate the possibility of drug-drug interactions to protect individuals treated with multiple drugs who may develop drug toxicity due to exaggerated drug-drug interactions.*

An analysis of adverse events associated with long-term drug exposure (more than 4 weeks) has revealed that Omeprazole can be linked to the following:

- Masking of disease. *Adequate consideration by the Advisory Committee whether GERD/chronic heartburn can be treated safely and effectively in an OTC setting with omeprazole for a maximum of 4-6 weeks, if diagnostic endoscopy has not yet been performed. To ensure that individuals with GERD will be triaged appropriately, labeling that lists 'alert symptoms' that require immediate physician referral should be instituted. The sponsor should be asked to provide adequate studies that treatment of chronic heartburn with omeprazole-mg is effective and actual use studies that demonstrate that there is strict adherence to the labeling.*
- Prolonged hypergastrinemia and Genotoxic Potential of Omeprazole. Hypergastrinemic responses to omeprazole may be more pronounced in some people such as those with H. Pylori infection or 'slow metabolizers'. Although in the general undifferentiated population of the US there is no clear tumor association with omeprazole, the possibility ~~of~~ that there are oncogenic effects in susceptible groups who are exposed to omeprazole for very long periods of time has not been ruled out. *Phase IV studies to investigate the incidence of GI adenocarcinomas and other malignancies using long-term, prospective or nested control cohort study designs of large numbers of exposed individuals should be established.*
- Rebound of Acid Secretion. *To adjudicate whether the acid rebound phenomenon associated with cessation of omeprazole treatment is clinically meaningful, studies to determine AEs at the time of cessation of treatment and the rate of reinstatement of acid suppression therapy (within 1 month after completion of a course of treatment) should be provided by sponsor.*

*Mark D. [Signature]*  
9/18/00

*Noted. September 18, 2000*

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