12 Omeprazole – Selected Adverse Events

12.1 Introduction

The AstraZeneca LP post-marketing surveillance database is called SafeTNet. SafeTNet contains:

- all non-serious post-marketing adverse events reported in the US
- all serious post-marketing adverse events reported worldwide
- all serious clinical trial (Investigational) adverse events reported worldwide

These reports come from a variety of sources, such as healthcare professionals, physicians, clinical trial investigators, consumers, government agencies, and the literature. Within SafeTNet, one or more AEs occurring in a patient that are associated medically and/or temporally are grouped together in a single case, each case has a unique PSE ID (Product Safety and Epidemiology) identification number. Adverse event data is coded into SafeTNet using an AstraZeneca LP Dictionary (a modified version of WHOART). Adverse event information is summarized for labeling reviews, serious, proactive/reactive evaluation, and/ or issues under surveillance.

All worldwide serious clinical and serious post-marketing adverse events that occurred through 30-Jun-98 (where an oral formulation of omeprazole was used) were identified and reviewed to verify cases of the following selected adverse events:

- Angioedema and Anaphylaxis
- Hepatic Function
- Visual Disturbances

In preparing these three summaries, each case was reviewed by a physician at AstraZeneca LP and assigned a rating to stratify cases based on available documentation and possible causes. The case ratings are as follows:

A. A well-documented case with no other explanation identified
B. A well-documented case with more than one possible explanation or suggestive contributing factor
C. A case with evidence of the reported adverse event but, insufficient information is available to determine causality
D. A case with no documented evidence of the reported adverse event

12.2 Anaphylaxis and Angioedema

12.2.1 Introduction

Anaphylaxis and angioedema are serious and potentially life-threatening hypersensitivity reactions that can occur with virtually all classes of drugs, including antisecretory therapy and currently available over-the-counter (OTC) medications. The currently approved labeling for PRILOSEC® (omeprazole) includes angioedema occurring in <1% of patients in clinical trials and rare cases of anaphylaxis with omeprazole.[60] This summary provides a review of all cases of anaphylaxis and angioedema and other severe allergic-type reactions reported in patients receiving omeprazole.

12.2.2 Reactions to Pharmacologic Agents

Anaphylaxis is a reaction occurring in a hypersensitive individual in response to a sensitizing antigen. Anaphylactic (IgE-mediated) and anaphylactoid (non-IgE-mediated) reactions encompass a spectrum of pathologic responses, which range from mild localized reactions to severe systemic reactions culminating in anaphylactic shock and death. The penicillins are frequent causes of anaphylaxis and are responsible for between 400 and 800 deaths annually in the US.[169] Other frequent causes of anaphylactic reactions include insect venoms, food-derived antigens, and chemical agents such as radiocontrast dyes. Pharmacologic agents known to cause anaphylactic reactions include immunotherapy, narcotics, local anesthetic agents, muscle relaxants, and nonsteroidal anti-inflammatory drugs. Hypersensitivity-like reactions have also been reported with OTC analgesic products including aspirin and acetaminophen.[170-173]

12.2.3 Nonclinical Experience with Omeprazole

The potential of omeprazole to elicit hypersensitivity reactions has been tested in several animal models. The results from a guinea pig maximization test indicated that omeprazole has the potential to cause contact hypersensitivity, a possibility that was confirmed in an *in vitro* lymphocyte transformation test with cells from human subjects who were occupationally exposed to omeprazole and exhibited signs of contact hypersensitivity. Although this should be considered during the manufacture of omeprazole, little risk for development of contact hypersensitivity from OTC use of the drug should occur since the nature of the formulation will minimize cutaneous contact. No evidence of active systemic anaphylaxis, passive cutaneous anaphylaxis or release of anaphylactic mediators in response to sensitization with omeprazole was observed. Thus, the results from nonclinical models of hypersensitization do not indicate a potential risk from the OTC use of omeprazole.

12.2.4 Post-Marketing Adverse Events

One-hundred thirty four cases were identified. Eighty-six cases were from post-marketing reports and 48 cases were from clinical trials. The following is a summary of these events by evidence of documentation, using the case rating (A, B, C, or D) algorithm:

OUTCOME	A	B	C	D	TOTAL
FATAL	0	4	3	0	7
NON-FATAL	9	52	42	24	127
TOTAL	**9**	**56**	**45**	**24**	**134**

There were 7 cases with a fatal outcome: four cases from post-marketing reports and 3 cases from clinical trials. Four of these cases were rated "B" and 3 cases were rated "C". In each of these cases, patients had significant, serious, and/or life-threatening Concurrent Conditions/Medical History that could have caused or contributed to the patient's death. In addition, 6 of the 7 patients were receiving multiple concomitant medications that could not be excluded from having a potential causal relationship to the adverse effect.

There were 9 patients with a well-documented case with no other possible explanations identified (Category A). All of these cases were from non-fatal post-marketing reports. Eight of these cases involved a positive re-challenge. There were no fatal outcomes in category "A" cases.

There were 52 "B" cases that included 17 cases from clinical trials and 35 cases from post-marketing reports; 42 "C" cases which included 7 cases from clinical trials and 35 cases from post-marketing reports and 24 "D" cases which included 21 cases from clinical trials and 3 cases from post-marketing reports.

12.2.5 L**iterature Reports**

Several case reports of anaphylaxis or angioedema have appeared in the published literature. All of these cases were entered into the SafeTNet database and are included in this summary.

In addition, the following abstract and international pharmaco-epidemiology data for omeprazole have been reported in the literature:

In a published abstract, Brunner et al.,[174] described five female patients who received omeprazole (20 or 40 mg once daily) and subsequently experienced swelling of the face, hands, and legs 8 to 25 days after the onset of omeprazole therapy. Omeprazole re-challenge was positive in all cases. Two patients also experienced the same reaction to pantoprazole. Edema was reversible within 2-3 days.

12.2.6 Experience in The Netherlands

Van der Klauw et al., analyzed all reports of drug-associated anaphylaxis in the Netherlands over the 20-year period between 1974 and 1994.[175] Only 3 cases of anaphylaxis with omeprazole were reported out of a total of 773 reports of drug-induced anaphylaxis with a causal relationship of certain or probable.

12.2.7 Experience in The UK

A report by the Committee on Safety of Medicines (CSM) of the UK indicated that in 1991, there was only one report to CSM of a patient on omeprazole developing angioedema.[176]

In a post-marketing surveillance program conducted by the Drug Safety Research Unit in the UK, exposure data and physician-reported events with newly marketed drugs was collected.[177] With a total of 77,623 patient-months of omeprazole treatment, the incidence density* of reported edema (unspecified) was 1.3 and the incidence density* of dyspnea was 0.9.

12.2.8 Experience in New Zealand

In New Zealand, the Intensive Medicines Monitoring Programme (IMMP) was established in 1977 to perform adverse event monitoring for certain drugs during the early post-marketing period. Once a drug has been chosen for monitoring, every prescription dispensed in the country is recorded and sent to the IMMP. Adverse events are reported by a combination of spontaneous reporting and systematic prescription follow-up and recorded only once. Events are recorded only if they are new or have worsened since the patient began taking the drug. Omeprazole was selected for monitoring by the IMMP in August 1990 because it was the first agent in a new class of drugs. Between March 1990 and November 1996, there were 8 reports of angioedema/ urticaria to IMMP out of a total of 17,365 patients treated with omeprazole. The adverse event rate for angioedema /urticaria was estimated to be 0.5/1000 patients.[178,179]

12.2.9 Experience in Switzerland

Spontaneously reported adverse drug reaction profiles for the proton pump inhibitor class of agents was compared with the histamine H_2 receptor antagonists by the Swiss Drug Monitoring Center (SANZ).[180] During the monitoring period of 1981-1995 there were 9,720 total reports with the histamine antagonists accounting for 108 reports. Of these 108 reports, 90 with a total of 100 adverse events were classified as related to a histamine antagonist. From 1988 to 1995, the SANZ received 7,119 reports with 65 reports involving the proton pump blockers. Of these reports, 60 with 61 adverse events were related to a proton pump inhibitor. Adverse events during treatment with either histamine antagonists or

* Incidence density (ID) = number of reports of an event during treatment/number of patient months of treatment x 1,000

proton pump inhibitors accounted for 0.9% of all reports and 0.8% of all reports, respectively, during this time period. Hypersensitivity reactions (which were defined as fever, anaphylactic reactions [with/without dyspnea], and allergic reactions) were reported less frequently with the proton pump inhibitors than with the H_2 antagonists.

12.2.10 Summary and Conclusions

Anaphylaxis and angioedema are drug-induced reactions that may occur with all classes of pharmacologic agents. The current approved labeling for PRILOSEC® warns that omeprazole is contraindicated in patients with a known hypersensitivity.[60] With approximately 300 million courses of omeprazole patient treatment worldwide, a total of 134 patients with anaphylaxis, angioedema, or events possibly symptomatic of a severe allergic reaction were reported in the AstraZeneca LP worldwide post-marketing/clinical trial database capturing serious adverse events. A review of the published literature shows that anaphylaxis and angioedema with omeprazole are rare events with frequency similar to other drugs used for treatment of heartburn.

12.3 Hepatic Function

12.3.1 Introduction

Liver injury in patients on omeprazole treatment is infrequent and ranges from asymptomatic transient elevations in liver enzymes to rare cases of fulminant hepatic failure. The most frequently observed evidence of hepatic dysfunction associated with taking omeprazole is the finding of transient elevations in serum transaminase levels. These mild increases, approximately twice the upper limit of normal, in transaminases occur in less than 1% of patients taking omeprazole and the incidence does not increase with long term use.[181-183] This low incidence of hepatotoxicity in patients taking omeprazole has also been documented in long term (up to 6 years) studies by Joelson et al., and Klinkenberg-Knol et al.[183-184] In most cases ALT levels tend to return to normal during therapy.

This summary provides a review of all cases of serious hepatic dysfunction reported in patients receiving omeprazole as well as a review of the literature.

12.3.2 Nonclinical Experience with Omeprazole

The potential of omeprazole to cause adverse effects on the liver was studied in nonclinical toxicology studies. The results indicate that omeprazole possesses little potential to cause hepatotoxicity. Increases in liver weight found in some studies in rats and dogs and the histopathological findings in the rat carcinogenicity study are likely results of the cytochrome P450-inducing properties of omeprazole,[185] and these effects are typical of enzyme inducers.[186,187] Treatment of human subjects with 20 mg omeprazole daily for two weeks does not result in significant hepatic enzyme induction.[188] Regardless, exposure of humans to enzyme inducing drugs, including the OTC sleep aid doxylamine, are not associated with adverse hepatic effects.[186,187,189,190]

Thus, the results of toxicology studies, in which potential effects on the liver were evaluated, do not indicate a potential risk from the OTC use of omeprazole.

12.3.3 Clinical Trial Experience with Omeprazole

Following an assessment of 4 US and 5 Non-US clinical trials:

- The most frequently observed liver function abnormality appeared to be a single mild elevation of SGPT
- The liver function test abnormalities appeared to be infrequent and mild with no definite association to omeprazole dose or duration of therapy

To assess whether identifiable patterns of elevated liver function tests (LFTs) developed in patients on omeprazole therapy, the baseline and treatment alkaline phosphatase, total bilirubin, SGOT, and SGPT laboratory values from 4 US (853 patients) and 5 Non-US (556 patients) clinical trials were reviewed. Of these 9 studies, 892 patients were male and 517 patients were female. While dosages of up to 40 mg daily of omeprazole were used in these studies, patients in one trial were on a regimen of omeprazole 20 mg 3 out of 7 days per week. The duration of therapy ranged from 4 weeks to 15 months.

A panel of at least 3 liver function tests was needed to qualify for evaluation. Patients having a liver function test above the reference range were identified. The abnormal liver function tests were then evaluated.

Liver function test abnormalities were divided into 4 groups and each patient's elevated liver function test panels were evaluated using the following classification:

ETs: Hepatocellular pattern (elevated transaminases)
Ch: Cholestatic pattern (elevated transaminase and alkaline phosphatase and/or bilirubin elevation)
Hep: Hepatitis (transaminases >3x the upper limit of the normal reference range)
SE: Single elevation of one enzyme (alkaline phosphatase, total bilirubin, SGOT, or SGPT) – no specific pattern

The design of 1 trial used during this evaluation required that patients receive two different dosages of omeprazole therapy, 40 mg daily for 4 to 8 weeks followed by 20 mg daily or 20 mg 3 out of 7 days for 6 months, during the trial. The initial blood draw for liver function tests was taken while patients were receiving omeprazole 40 mg daily. Blood for subsequent laboratory tests was drawn while patients were dosing with either omeprazole 20 mg daily or 20 mg 3 out of 7 days. The laboratory results for these patients were then grouped for evaluation per patient per omeprazole dosage. This resulted in several patients' receiving two of the above pattern classifications. To ensure being counted only once, the higher laboratory value and greater number of abnormal liver function tests was chosen and the patient was grouped with that pattern classification..

Of the 853 patients from the 4 US clinical studies, 253 patients had an abnormal liver function test while on omeprazole treatment. The most frequent pattern of abnormal liver function seen was a single elevation (SE) of SGPT: n=66. Other single elevated LFTs included alkaline phosphatase: n=35, total bilirubin: n=17, and SGOT: n=10. Mildly elevated transaminases (ETs) were noted in 31 patients and 5 patients had transaminases elevated (Hep) 3 times the upper limit of the normal reference range (nr).

A cholestatic pattern (Ch) was noted in 15 patients. Abnormal liver function at baseline with subsequent improvement during omeprazole therapy was seen in 72 patients and no follow-up information was available for 2 patients.

Of the 556 patients from the 5 NON-US clinical studies, 177 patients had an abnormal liver function test while on omeprazole treatment. The most frequent pattern of abnormal liver function seen was a single elevation (SE) of SGPT: n=36. Other single elevated LFTs included alkaline phosphatase: n=31, total bilirubin: n=14, and SGOT: n=3. Modestly elevated transaminases (ETs) were noted in 9 patients and 1 patient had transaminases elevated (Hep) 3 times their normal values [SGOT: 139 (nr=0-30) and SGPT: 308 (nr=0-30)/trial I609b, patient 145]. A cholestatic pattern (Ch) was noted in 17 patients. Abnormal liver function at baseline with subsequent improvement during omeprazole therapy was seen in 62 patients and no follow-up information was available for 4 patients.

In summary, the liver function test abnormalities appear to be mild with no specific pattern and no definite association or influence by dose (10 mg to 40 mg) or duration (4 weeks to 12 months) of omeprazole therapy. The most frequently observed liver function abnormality appears to be a single mild transaminase elevation: SGPT.

12.3.4 Post-Marketing Adverse Events

A total of 261 serious (fatal and non-fatal) events of hepatic dysfunction were reported to AstraZeneca LP through the worldwide post-marketing surveillance program. Two hundred sixty cases were from post-marketing reports and 0 cases were from clinical trials.

The following is a summary of these events by evidence of documentation, using the case rating (A, B, C, or D) algorithm:

OUTCOME	A	B	C	D	TOTAL
FATAL	2	19	12	0	33
NON-FATAL	4	114	99	10	227
TOTAL	**6**	**133**	**111**	**10**	**260**

Six cases were attributed to omeprazole use (case rating A). The remaining 255 cases have factors that confound the cases (case rating B, C, or D). A total of 33 serious adverse events of hepatic dysfunction with an outcome of death were reported. Two of these 33 deaths can be attributed directly to omeprazole (case rating A). With the number

of worldwide omeprazole patient treatments approximately 300 million, these 261 serious cases suggest there is no clear association between the use of omeprazole and hepatic function.

12.3.4.1 Serious Fatal Cases of Hepatic Dysfunction

A total of 33 fatal cases involving hepatic dysfunction were reported to AstraZeneca LP. Of these, 20 events occurred in males and 13 events occurred in females. Nineteen cases occurred in patients under 65 years of age (a range of 21 to 64 years of age) and 13 cases occurred in patients aged 65 years or older (a range of 65 to 86 years of age); age was not reported in 1 case. All thirty-three of the cases were from post-marketing reports. Of the total 33 fatal cases, 2 were assigned an A-rating. Of the remaining cases with fatal outcome, 19 were rated "B" and 12 cases were rated "C". In each of these cases, patients had significant, serious, and/or life-threatening concurrent medical conditions that could have caused or contributed to the patient's death.

12.3.4.2 Serious Non-Fatal Cases of Hepatic Dysfunction

A total of 227 cases involving hepatic dysfunction as serious events that did not end in death were reported to AstraZeneca LP. Of these, 116 events occurred in males and 101 events occurred in females; gender was unknown in 10 cases. One hundred thirty nine cases occurred in patients under 65 years of age (a range of 13 months to 64 years of age) and 68 cases occurred in patients 65 years of age or older (a range of 65 to 93); age was not reported in 20 cases. All of the 227 cases were from post-marketing reports and none were from clinical trials.

Of the total 227 non-fatal cases, 4 were attributed directly to omeprazole and were assigned an A-rating. All 4 of these events occurred in males. Three cases occurred in patients under 65 years of age (a range of 30 to 51 years of age) and 1 case occurred in a patient 65 years of age. All 4 cases were from post-marketing reports.

One hundred fourteen, 99, and 10 cases received ratings of B, C, and D, respectively. These cases lacked sufficient information regarding omeprazole dose and/or duration of use, co-existing medical conditions, or concomitant medication use to be attributed directly to omeprazole.

12.3.5 Published Medical Literature

A review of the published literature shows few reports of hepatic dysfunction following omeprazole therapy. The incidence of mild increases in transaminases is less than 1% of patients taking omeprazole and does not increase with long-term use at a higher dosage of omeprazole therapy.

In a trial by Gustafsson et al., 32 patients with duodenal ulceration were randomized to receive 20 mg or 60 mg omeprazole daily for 4 weeks. Ten of the 32 patients had a slight elevation of ALT levels, which occurred in the majority of these patients on day 8. The elevated ALTs did not appear to be dose-related. A return to normal was seen within

2-6 weeks during continued treatement.[191] This high percentage of transiently elevated ALT levels, however, was not seen in a subsequent trial by Loof et al., who evaluated 60 healthy individuals randomized to receive omeprazole 40 mg for 2 weeks or placebo in a double-blind placebo controlled tolerance test.[192] Only one patient on omeprazole and 2 patients on placebo had evidence of elevated ALT levels.

In a long-term trial by Klinkenberg-Knol et al., of patients with refractory reflux esophagitis (n=91) who received omeprazole for up to 5 years, none had evidence of clinically significant hepatotoxicity.[184] No relevant deviations in laboratory tests were noted during treatment. McArthur et al., studied Zollinger-Ellison syndrome patients (n=11) receiving various doses of omeprazole from 20 - 100 mg daily. No significant serum transaminase changes during therapy were observed.[193]

There are rare case reports in the literature of severe hepatic injury in patients taking omeprazole. These cases are entered into the SafeTNet database at AstraZeneca LP. The etiology is not established but is thought to be idiosyncratic.

There are conflicting reports on the incidence of hepatotoxicity following the use of H_2-receptor antagonists. This was addressed in a recently published trial that compared the relative risk of hepatotoxicity in over 100,000 users of famotidine, cimetidine, ranitidine and omeprazole. Medical records from the General Practitioners Research Database were reviewed and included 108,981 patients aged 20 to 74 who received at least 1 prescription for one of these medications over a period from 1990 to 1993, with evidence of acute liver injury. A total of 33 patients had findings of acute liver injury, with 50% listed as hepatocellular injury and 80% of the cases presenting with jaundice. Twelve patients were taking cimetidine, 5 were on ranitidine and 1 patient was on omeprazole. The risk of acute injury using cimetidine was estimated to be 1:5000 with the adjusted relative risk (RR) and 95% confidence interval (CI) of acute liver damage associated with current use of cimetidine compared to non-use was 5.5 (1.9 – 15.90). The RR of omeprazole was estimated to be 2.1 (0.2 – 19.2) and that of ranitidine 1.7 (0.5 – 5.8).[194]

In summary, hepatotoxicity is rare with Ome and the literature suggests that H_2-receptor antagonists and omeprazole have a similar hepatic adverse event profile.[195-197]

12.3.6 Summary

The presented data do not indicate an increased risk of development of hepatic dysfunction in patients treated with omeprazole.

Worldwide patient exposure to omeprazole is approximately 300 million courses of patient treatments. The incidence of hepatic dysfunction in patients receiving omeprazole therapy is low and similar to that of H_2-receptor antagonists ranitidine and cimetidine, which are available for both prescription and over-the-counter use.

In most of the cases presented in this section with hepatic adverse events that were listed as serious, including deaths, other possible causative or contributing factors could be identified.

Based on the relatively rare occurrence of drug-induced hepatic dysfunction, the small number of serious cases found in the post-marketing surveillance database at AstraZeneca LP and the few reports found in published literature, there is no clear association between the use of omeprazole and hepatic dysfunction. With respect to hepatic injury, the availability of omeprazole as an over-the-counter medication for heartburn should pose no greater health risk than other agents currently available for over-the-counter use in the United States.

12.4 Visual Disturbances

12.4.1 Introduction

Evaluations of possible visual disturbances related to the use of parenteral formulations of omeprazole were based on initial concerns expressed by the regulatory authority in Germany. Scientific considerations of these adverse events by AstraZeneca LP (formerly Astra Merck Inc.) and medical reviews of spontaneous reports of visual disturbances formed the basis of several submissions to the FDA under PRILOSEC® NDA 19-810. The content of these submissions, as well as that of a recently filed update of safety information with a proposal for an amendment of the prescribing information for PRILOSEC® [filed 15 Nov. 99 to NDA 19-810] are summarized in this section. The available data do not suggest that there is any medically significant ocular toxicity associated with either short or long-term use of omeprazole in the general population.

12.4.2 Historical Review of Visual Disturbance Considerations for Omeprazole

BGA Findings and Astra Hässle Response

In March 1994, Astra Hässle (Sweden) was requested by the Bundesgesundheitsamt (BGA) to address their concerns about reported cases of visual disturbances associated with the use of omeprazole. Of principal concern to the BGA were several cases of severe visual disturbances, including blindness, reported in severely ill patients receiving an intravenous formulation of omeprazole. The BGA requested comment on 19 adverse event case reports from post-marketing surveillance, 6 of them after administration of intravenous omeprazole and the remaining cases after oral administration. The BGA also suggested a series of prospective toxicological, pharmacological, and clinical studies to further address their concerns.

Astra Hässle, in turn, compiled and submitted a report describing all available information that was relevant to these cases, and included the results of studies and analyses requested by the BGA to address their concerns. This report was submitted to the BGA on 20-Mar-94 and organized into an 8 volume report by Astra Merck that was submitted to FDA on 20-Apr-94.

The nonclinical information in the submission to the BGA consisted of the following: a report of a state-of-the-art computerized electroretinography study in rabbits that had

received injections of high intravenous doses; a report of a study in dogs after intravenous infusion that included ophthalmoscopy, fundus photography and full histologic evaluation, including of the eyes and optic nerves; a review of the ocular findings from 12 previous toxicology studies with omeprazole in mice, rats and dogs and an autoradiographic distribution study in mice; and a report on the histological reevaluation of the eyes from the animals in the two-year carcinogenicity/chronic toxicity study in rats.

The conclusion from this extensive evaluation of nonclinical data was that there was no evidence from any of the studies of any adverse effect of omeprazole on the visual or vascular systems at high concentrations and over long periods, irrespective of the route of administration.

The safety section of the report contained adverse event data from investigational clinical trials, clinical pharmacological studies, and case reports arising during worldwide commercial use. In all, there were no adverse events indicating any causal effect of omeprazole on the visual systems.

In comparative clinical trials, the low frequency and mild nature of adverse events suggested visual disturbance associated with omeprazole was comparable to that with placebo as well as histamine-2 receptor antagonists.

The pharmacological data were from 177 studies involving 1,498 human volunteers and patients, and included patients with hepatic and renal impairment. The frequency and types of adverse events during omeprazole use were comparable to those with placebo, irrespective of dose, route of administration or whether slow or fast metabolizers were considered. No single case of impaired vision was reported in any of the studies, or among the patients with Zollinger-Ellison syndrome who were treated long-term with high doses of omeprazole.

The post-marketed adverse events were evaluated at that time against a background of over 75 million patient treatment courses from which AstraZeneca LP had received notification of a total of 5,942 adverse events reported for 3,937 patients.

A review of all safety data confirmed that there was no evidence for a causal relationship between omeprazole and visual disturbances. In addition to the Astra Hässle assessment of the adverse event reports cited by the BGA, evaluations were also provided by several independent expert ophthalmologists. In the opinion of these experts, there was no conclusive evidence for any causal relationship between omeprazole therapy and visual disturbances.

The adverse event cases cited by the BGA, in addition to the Astra Hässle preclinical and clinical data, were reviewed by an independent Expert Advisory Group composed of 18 leading German and international experts. This group unanimously concluded that there were no data to support a causal role of omeprazole in the cases of visual

disturbance. Based on the preclinical and clinical data, the group dismissed an overall causal relationship to omeprazole.

In summary, Astra Hässle concluded that there was no evidence to suggest a causal relationship between omeprazole and the visual symptoms in the cases cited by the BGA. This was in complete accordance with the unanimous conclusions of a number of independent scientists.

Analysis of the BGA Concern over the Intravenous Injectable Form of Omeprazole

After review of the BGA findings, Astra Merck identified a number of inaccuracies in the conclusions derived from the BGA analysis of adverse event reports of visual disturbances and omeprazole.

Scientifically sound evidence for a causal relationship was lacking mainly because the concept of temporal relationship in cases of optic neuropathy was addressed in an indiscriminate manner. That is, optic neuropathy was observed following hemorrhage and other disorders which result in significant hemodynamic compromise. In this scenario, the precipitating event is commonly followed by a latent period prior to symptomatic presentation. Application of temporal relationships was used in the assessment of these cases without an understanding of the pathophysiologic course of the actual events.

The BGA reported an increase in reporting frequency. This phenomenon was more likely to be an artifact resulting from the publicity that followed the BGA inquiry in addition to related publications that specifically solicited adverse event reports.

Extrapolation of the fact that blurred vision appears in the International Data Sheet for omeprazole by Astra Hässle and therefore is evidence of a causal association between omeprazole and more severe visual disturbances was not logical. Events such as blurred vision occur quite commonly in the general population, the events occurred in uncontrolled situations, and the addition of blurred vision to the international data sheet was simply an attempt to acknowledge the occurrence of the events and not to convey a finding of causal association.

In addition, use of the intravenous injection formulation of drugs in Germany has historically been a cultural preference. The dose of intravenous drug has been much higher in Germany than would be considered medically appropriate in the US environment. The BGA has been concerned about off-label use of omeprazole including dosing in excess of local labeling recommendations (10-20 mg daily), prescription for non-approved indications, and excessive use of the intravenous injection form. It was more likely that these concerns had actually influenced the BGA's action rather than a concern about a relationship between adverse reactions and intravenous omeprazole in critically-ill patients.

European CPMP Response to the BGA's concerns

On 25-Jul-94, the European Committee for Proprietary Medicinal Products (CPMP) discussed concerns about visual impairment that were identified by the BGA. The content of these discussions were included in a submission to the FDA on 4-Aug-94.[a]

In addition to the previously mentioned data evaluations, a presentation of epidemiologic data was discussed. A group associated with the Boston Collaborative Drug Surveillance Programme had retrospectively studied a cohort using the VAMP database in the United Kingdom with the objective to estimate and compare the incidence of serious visual disorders associated with the use of omeprazole and four other ulcer-healing drugs. The source population for the study was derived from 444 practices in England and Wales from almost three years and encompassed almost four million registered individuals. The study cohort included all subjects who received at least one prescription for a histamine-2 receptor antagonist or omeprazole during the study period.

Incidence rates and relative risk estimates for all the study outcomes (visual descriptors) were calculated. The group found no evidence of an increased risk associated with use of omeprazole as compared to non-use, nor was there any difference in risk across the study drugs. It was demonstrated that there were no differences among the frequencies of serious visual disorders during clinical use of omeprazole or histamine-2 receptor antagonists, or with non-use.

Dr. Ralph Edwards of the World Health Organization also conducted an epidemiologic study using the database maintained by the WHO Collaborating Centre for International Drug Monitoring. The study findings did not show an increased risk of visual disturbance with omeprazole exposure.

Subsequent to all discussion, and once all the data were reviewed, the CPMP reached the following conclusions: 1) A causal relationship between the reported reactions and the use of omeprazole has not been established; 2) The preferred route of administration of omeprazole is oral. If this is not possible, then intravenous administration can be used taking into account the different pharmacokinetic profiles of the intravenous (IV) bolus injection and the IV infusion when prescribing the intravenous form; 3) The infusion form should be preferred over the bolus injection form because of the higher plasma concentration peaks and remaining suspicions of adverse events related to special clinical conditions and high doses of the latter; and 4) The summary of product characteristics (SPC) for the intravenous presentations should be adjusted to include the following statement: "Irreversible visual impairment has been reported in isolated cases of critically ill patients who have received omeprazole intravenous injection, especially at high doses, but no causal relationship has been established."

[a] The findings of this report were included in the following submission to the FDA on 4-Aug-94: NDA 19-810 General Correspondence, which provided an update of the activities of the BGA and CPMP to that point in time. The reader is directed to those sections addressing the visual system.

Despite the firm conclusions drawn by the CPMP regarding the lack of evidence for a causal association, the BGA elected to take unilateral action with regard to marketing of omeprazole within their national jurisdiction and gave notice to Astra's German subsidiary of the suspension of the registration for the injectable bolus formulation of omeprazole. This action was not supported by any of the other Member States.

FDA Response to BGA's Findings and Astra Hässle and Astra Merck Reviews

In August 1994, the FDA Division of Epidemiology and Surveillance, Postmarketing Safety Branch, compiled their review of the visual disturbance issue based on the report they received from Astra Merck in April 1994. In addition to the three adverse event data sets evaluated in that report, this review also included a set of reports from the FDA spontaneous reporting system (SRS) through May 1994. However, it should be noted that the SRS set was not corrected for duplications. The cases were individually reviewed, and it was determined that assessment of causality was not possible because of the limited amount of information provided in many of the cases. Missing data included the lack of ophthalmologic examination results, concomitant administration of multiple drugs in some cases, the presence of confounding factors such as concurrent illnesses or conditions, and the lack of a potential mechanism to explain a possible ocular toxicity. The conclusion of this review was that if a relationship existed between omeprazole and these ocular events, the currently available information from the SRS cases suggests that the overall nature of such events is non-serious, of short-term onset and is reversible, although three of the patients reported permanent vision loss.

Review of the Published Literature

The published medical literature includes letters, case reports and small case series concerning visual disturbances associated with the use of omeprazole. These anecdotal data are balanced by published rebuttals and review articles, and pharmacoepidemiology studies.

Several anecdotal reports of visual disturbances associated with the use of omeprazole have been published as editorial correspondence, case reports, or small case series. These cases have been captured in SafeTNet and described in regulatory submissions to the FDA (see above) or reflect similar visual aberrations described in cases reported in these submissions. Some of this literature reflects the concerns raised by the BGA on this issue.[198-202] The concern of the German regulatory authority was mainly over case reports of visual disturbances related to anterior ischemic optic neuropathy with the use of omeprazole, but this suspected drug-event association was not scientifically validated. A significant body of literature exists in which this condition is described in association with a variety of medical conditions.[203-212] Several additional references to medical news articles and editorials describing the BGA inquiry and subsequent deliberations by other expert panels are not included because these do not contribute any additional information to the historical review presented earlier in this section.

The following types of visual disturbances were reported: anterior ischemic optic neuropathy[213-214] perception of color changes or decreased visual acuity[215] blurred vision[214-218] and transient blindness in association with seizures.[219-220] Rebuttal correspondence and review articles reported on the absence of scientific data to implicate omeprazole as a cause of the described visual disturbances.[221-226]

12.4.3 Nonclinical Pharmacodynamic and Toxicology Studies

The potential of omeprazole to adversely affect the visual system has been evaluated extensively in nonclinical pharmacodynamic and toxicology studies. Compelling molecular biological evidence has clearly shown that the gastric H^+,K^+-ATPase is not expressed in the human eye.[227] Immunological results from animal studies also strongly suggest that the gastric proton pump is not found in the eye; however, binding of antibodies to the gastric H^+,K^+-ATPase in the rabbit and bovine eye may indicate the presence of a closely related protein or cross reactivity with one of the ocular Na^+,K^+-ATPases.[227,228] Even if the gastric proton pump was present in the eye, the local pH is not sufficiently low to concentrate and activate omeprazole. No evidence of adverse effects on ocular structure or function have been observed in extensive pharmacodynamic and toxicological studies in animals, including ones which involved high doses and/or long-term exposure. Thus, the results from nonclinical studies regarding the eye do not indicate a risk from the over-the-counter (OTC) use of omeprazole.

Visual disturbances during clinical trials have been rarely observed. For example, in a multicenter clinical trial of 674 patients with dyspepsia, one vision adverse event was reported in each of the omeprazole 10 and 20 mg treatment arms, and three such events were reported in the antacid/alginate treatment arm.[229]

Four independent pharmacoepidemiology studies have been published. In a prescription-event monitoring study of 16,204 patients treated with omeprazole, during the first year following market authorization in the UK, no “signal” of visual disturbances was detected when compared to the pattern of adverse events observed with four other drugs (cisapride, misoprostol, famotidine, and nizatidine) used for similar indications.[230] In an independent analysis of adverse event data from 42 countries contained in the WHO international adverse event database regarding visual disorders associated with the use of omeprazole, it was concluded that the increased rate of reports from Germany was possibly explained by solicited reporting artifact.[231] A retrospective cohort study was conducted using the General Practitioner’s Research Database in the UK, of which 94,063 individuals formed the study population. The findings showed no increased risk for inflammatory or vascular disorders of the eye associated with omeprazole when compared to that with four other anti-ulcer drugs (ranitidine, cimetidine, famotidine, and nizatidine).[232,233] The ocular safety of omeprazole and six histamine-2 receptor antagonists (cimetidine, famotidine, niperotidine, nizatidine, ranitidine, and roxatidine) was also demonstrated in a similarly designed study conducted in Italy using a large, automated regional database sourced by hospital patient records and outpatient prescriptions for a total of 71,108 study patients.[234]

12.4.4 Visual Disturbance Adverse Event Analysis

The AstraZeneca LP (AZLP) post-marketing safety surveillance database is called SafeTNet. SafeTNet includes serious adverse events reported worldwide and non-serious adverse events reported only in the United States (US). However, in 1994, reports of visual AEs received by Astra from Germany (both serious and non-serious) were included in the SafeTNet database and reported to FDA. Therefore, in this report, non-serious adverse events represent those reported in the US as spontaneous postmarketing reports, cases of nonserious AEs reported from Germany in 1994, and some nonserious adverse events that may have accompanied reports of serious AEs from overseas.

A search of SafeTNet was conducted between the time frame of 1988 through April 1999. The serious and non-serious adverse events for both oral and intravenous formulations of omeprazole were sought according to their categorization under all preferred terms related to disturbed visual function, ocular structural pathology, or non-visual ocular symptoms. Therefore, preferred terms of several WHOART body system categories (e.g., vision disorders, central nervous system, psychiatric disorders, and others) were used to search the adverse event database to ensure capture of all ocular events. This comprehensive medical review focused on adverse events categorized both broadly (symptomatology versus structural pathology) and specifically under 41 different preferred terms. Specific features of individual adverse event reports that suggest or refute possible relatedness to the use of omeprazole were sought [filed 15 Nov. 99 to NDA 19-810].

A total of 479 adverse events pertaining to visual disturbance were identified. Three hundred and eighty-nine patients contributed to these 479 ocular adverse events. Although only one eye-related adverse event was reported per patient for the majority of patients, there were up to six adverse events for a single patient in several reports. Medical review of all 479 adverse events led to classification of these events into one of three general categories. These categories include events with 1) symptoms of visual dysfunction without objective ophthalmologic diagnoses, 2) a specific diagnosis of ocular pathology, or 3) ocular symptoms unrelated to any disturbances of vision.

Adverse events were subsequently grouped into those related to symptoms of visual dysfunction and all other events. The organization of adverse events divides the entire group of 479 adverse events approximately in half for each of the two categories. Although a due diligence review was performed on all events categorized according to preferred terms, the grouping of events into these two major categories facilitated consideration of adverse events, across preferred terms, which might be thought to be associated with the use of omeprazole. A total of 235 adverse events related to symptoms of visual dysfunction were categorized according to 11 select preferred terms (Table 12.1). A total of 244 adverse events related to structural abnormalities of the eye or other non-visual ocular symptoms were categorized according to 30 select preferred terms (Table 12.2).

TABLE 12.1
AZLP SAFETNET DATABASE SERIOUS AND NON SERIOUS POST-MARKETING REPORTS
SUMMARY OF ADVERSE EVENTS BY PREFERRED TERM
VISION DISORDERS BODY SYSTEM AND EYE EVENTS IN OTHER BODY SYSTEMS
SYMPTOMS OF VISUAL DYSFUNCTION

PREFERRED TERM	TOTAL EVENTS	SERIOUSNESS		ROUTE	
		SERIOUS	NON-SERIOUS	PARENTERAL	OTHER[a]
Accommodation Abnormal	3	0	3	0	3
Blindness	18	16	2	7	11
Blindness Transient	5	3	2	0	5
Chromatopsia	1	0	1[b]	0	1
Diplopia	21	7	14	0	21
Myopia	2	0	2	0	2
Optic Atrophy	13	13	0	5	8
Optic Neuropathy	9	9[c]	0	2	7
Papilledema	6	5	1	1[d]	5
Vision Abnormal	141	39[e]	102	14	127
Vision Disorders NOS	16	2	14	0	16
TABLE TOTALS	235	94	141	29	206

[a] Oral form, combination of parenteral and oral forms, or unknown (but presumed oral form)

[b] Although the case summary report indicates the event is serious, sponsor review of available information leads to categorization of the case as non-serious.

[c] One report of the AE, optic neuropathy, was reported as Serious = unknown; however, sponsor medical review determined event to be medically significant. For the purposes of this cumulative review, this case is included in the total of serious AEs.

[d] One report of the AE, papilledema, occurred while patient was taking parenteral formulation of omeprazole. Oral omeprazole was administered subsequent to the onset of the AE.

[e] Four reports of the AE, vision abnormal, were reported as Serious = unknown; however, they were also reported as medically significant. At the time the AEs were reported (1995), medical significance was not part of the definition of a serious AE. For the purposes of this cumulative review, these cases are included in the total of serious AEs.

TABLE 12.2
AZLP SAFETNET DATABASE SERIOUS AND NON SERIOUS POST-MARKETING REPORTS
SUMMARY OF ADVERSE EVENTS BY PREFERRED TERM
VISION DISORDERS BODY SYSTEM AND EYE EVENTS IN OTHER BODY SYSTEMS
RELATED TO STRUCTURAL ABNORMALITIES OR OTHER NON-VISION SYMPTOMS
(PAGE 1 OF 2)

PREFERRED TERM	TOTAL EVENTS	SERIOUSNESS		ROUTE	
		SERIOUS	NON-SERIOUS	PARENTERAL	OTHER*
Amaurosis Fugax	1	1	0	0	1
Blepharitis	1	0	1	0	1
Cataract	21	13	8	2	19
Conjunctivitis	34	4	30	0	34
Corneal Ulceration	3	2	1	0	3
Eye Abnormality	24	8	16	1	23
Eye Pain	10	1	9	0	10
Eye Symptoms NOS	4	0	4	0	4
Glaucoma	15	4	11	0	15
Hallucination	65	34	31	0	65
Hemorrhage Ant Chamber Eye	3	1	2	0	3
Iridocyclitis	1	1	0	0	1
Iritis	1	0	1	0	1
Lacrimal Duct Obstruction	1	1	0	0	1
Lacrimal Gland Disorder	1	0	1	0	1
Lacrimation Abnormal	5	1	4	0	5
Macula Lutea Degeneration	1	0	1	0	1
Mydriasis	4	1	3	1	3
Photophobia	2	1	1	0	2
Pupillary Reflex Impaired	1	1	0	1	0

* Oral form, combination of parenteral and oral form, or unknown (but presumed oral form)

TABLE 12.2 (CONT.)
AZLP SAFETNET DATABASE SERIOUS AND NON SERIOUS POST-MARKETING REPORTS
SUMMARY OF ADVERSE EVENTS BY PREFERRED TERM
VISION DISORDERS BODY SYSTEM AND EYE EVENTS IN OTHER BODY SYSTEMS
RELATED TO STRUCTURAL ABNORMALITIES OR OTHER NON-VISION SYMPTOMS
(PAGE 2 OF 2)

PREFERRED TERM	TOTAL EVENTS	SERIOUSNESS		ROUTE	
		SERIOUS	NON-SERIOUS	PARENTERAL	OTHER*
Retinal Artery Occlusion	1	1	0	0	1
Retinal Detachment	5	4	1	0	5
Retinal Disorder	12	6	6	1	11
Retinal Hemorrhage	4	4	0	1	3
Retinitis	2	2	0	0	2
Scleral Bleeding	1	0	1	0	1
Strabismus	2	2	0	0	2
Twitching	8	0	8	0	8
Visual Field Defect	10	6	4	1	9
Vitreous Floaters	1	0	1	0	1
TABLE TOTALS	*244*	*99*	*145*	*8*	*236*

* Oral form, combination of parenteral and oral form, or unknown (but presumed oral form)

12.4.5 Visual Disturbances — Summary

Relatively few reports of ocular adverse events have been received following approval of omeprazole, for which surveillance has encompassed 10 years. This is despite the fact that a variety of symptoms of visual dysfunction, ocular structural pathology, and non-visual ocular symptoms are quite common in the general population. With the exception of the reports of patients who experienced nonspecific ocular symptoms that are often self-limited, relatively mild, and interpreted medically as either "blurred vision" or "eye irritation," there is no evidence of an increased risk of specific ophthalmologic diseases in patients who are treated with omeprazole.

The adverse event data do not establish a safety signal nor suggest an increased risk of specific ophthalmologic disease associated with short or long-term use of omeprazole in the general population.

In summary, information available in the published literature is consistent with data that were presented in the regulatory submissions discussed above. Although there are reports of individual cases of visual disturbances associated with the use of omeprazole, pharmacoepidemiologic investigations do not reveal an increased rate of such adverse reactions for omeprazole when compared to that of other antisecretory medications.