8 Special Safety Considerations

This section will address the following safety considerations: potential for metabolic drug-drug interactions, pharmacokinetics in special populations, and abuse and overdose potential.

8.1 Potential for Metabolic Drug-Drug Interaction

The potential for drug-drug interaction with Ome has been extensively studied. In performing *in vivo* drug-drug interaction studies with Ome, the experimental conditions were optimized to detect a drug-drug interaction if one existed. For example, the dosing of the two drugs was timed to obtain the maximum plasma concentrations of each drug to coincide, thereby maximizing the exposure of the liver enzymes at one particular time point and accordingly maximizing the possibility of revealing any sign of competitive inhibition. The highest recommended dose of Ome was used in most cases, again to maximize the possibility of detecting a drug-drug interaction (Table 8.1).

As previously mentioned, Ome is metabolized by two different cytochrome P450 (CYP) isoforms, CYP2C19 (responsible for about 80% of the total metabolism) and CYP3A4.[21] Interactions reported in pharmacologic studies are rare and not clinically relevant, and appear only for drugs metabolized by CYP2C19, since the affinity of Ome to that enzyme is about ten-fold higher than for CYP3A4.

Intravenous diazepam, which is a CYP2C19 substrate, showed a 25% inhibition in metabolism with a 1-week 20 mg Ome treatment in normal metabolizers, but not in "slow" metabolizers.[23] This interaction was only detected when diazepam levels were decreased to about 25% of maximum, 12 hours after diazepam administration.

Minor metabolic pathways for phenytoin, R-warfarin, and tolbutamide are also mediated by CYP2C19. Ome has a minor effect on these compounds, evaluated in a series of studies. Although slight metabolic drug-drug interactions have been identified, the clinical significance is minimal and does not require intervention.

In studies that looked primarily at 20–40 mg Ome, Ome has not been shown to interact with clarithromycin[22,34-36], cyclosporine[21], erythromycin[22], estradiol[21], lidocaine[21], nifedipine[21], or quinidine[21], all of which are mainly metabolized by CYP3A4 (Rx labeling indicates an interaction between Ome and clarithromycin). Since plasma levels in "slow" metabolizers after 20 mg Ome are, on average, only two-fold higher than after 40 mg Ome in normal metabolizers, the potential for drug-drug interactions at the CYP3A4 level, even in "slow" metabolizers, is negligible at 20 mg Ome.[37] Other studies indicate that Ome, in daily doses of 20 to 40 mg Ome, has no influence on any other relevant CYP isoforms with no demonstrated metabolic interaction with drugs metabolized by CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, naproxen), CYP2D6 (metoprolol, propranolol) or CYP2E1 (ethanol).[21] Studies with food, antacids, and H_2RAs show negligible influence on Ome absorption.[21,24,25,38]

TABLE 8.1
SUMMARY TABLE OF DRUG-DRUG INTERACTION STUDIES WITH OMEPRAZOLE VERSUS DIAZEPAM, PHENYTOIN, WARFARIN, AND CLARITHROMYCIN

Drug	Study population (#)	Drug dose (mg)	Oral omeprazole dose (mg)	Change in CL (%)	Change in AUC (%)	Change in C_{ss} (%)	Reference
Diazepam	Healthy subjects (n=8)	0.1/kg (iv)	40 x 7 days***	-54	—	—	39,40
Diazepam	Healthy subjects (n=12)	0.1/kg (iv)	20 x 7 days***	-27	—	—	41,42
Diazepam	Healthy subjects (n=10)	0.1/kg (iv)	20 x 7 days***	-26****	—	—	23,43
Phenytoin	Healthy subjects (n=8)	250 (iv)	40 x 7 days***	-15	—	—	40,44
Phenytoin	Healthy subjects (n=10)	300	40 x 7 days***	—	+19	—	45,46
Phenytoin	Healthy subjects (n=18)	4.5/kg	40 x 3 days***	—	NC	—	47
Phenytoin	Epileptic patients (n=8)	ss	20 x 21 days	—	—	NC	48,49
Warfarin - R Warfarin - S	Healthy subjects (n=21)	4.7*	20 x 14 days	—	—	+12 NC	50,51
Warfarin - R Warfarin - S	Anticoag. Patients (n=28)	ss	20 x 21 days	—	—	+9.5 NC	52,53
Clarithromycin	Healthy subjects (n=20)	500 tid**	40 x 6 days	—	+15	—	34
Clarithromycin	Healthy subjects (n=16)	250 bid**	20 bid x 7 days	—	NC	—	35
Clarithromycin	Healthy subjects (n=16)	500 bid**	20 bid x 7 days	—	NC	—	36

* 2 weeks' dosing; ** 1 week's dosing; *** dosed throughout the blood sampling period; ****no effect in slow metabolizers
ss = patients at steady state on continuous treatment; NC = not changed; - = not evaluated
CL = clearance; AUC = area under the plasma concentration versus time curve; C_{ss} = trough concentration at steady state; iv = intravenously; tid = three times daily; bid = twice daily

8.1.1 Effect of Decreased Gastric Acidity on Absorption of Drugs

As with all anti-secretory drugs, Ome may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability. Absorption of drugs that have a pH-dependent absorption were tested with Ome 20 mg in daily doses. The absorption of amoxicillin, bacampacillin, and ethanol were unaltered.[21,22] A slight but not clinically relevant increase in absorption was noted for digoxin and nifedipine.[21] However, one study demonstrated that absorption of ketoconazole was decreased by 80% when administered 6 to 8 hours after a 60 mg dose of Ome.[54] In another study, the absorption of itraconazole was decreased by 64% if administered after 2 weeks of treatment with Ome 40 mg daily.[55]

8.2 Pharmacokinetics in Special Subpopulations

In a study of 8 patients with varying degrees of hepatic impairment, the AUC of Ome 40 mg was seven-fold higher and the plasma $t_{½}$ was about 4 times longer in this population than in healthy individuals (Table 8.2).[56] Similar results were obtained in a second study of patients with hepatic cirrhosis.[57] The pharmacokinetics of Ome in patients with varying degrees of renal impairment were shown to be comparable to those reported in healthy individuals.

TABLE 8.2
PHARMACOKINETIC PARAMETER VALUES FOLLOWING ADMINISTRATION OF OMEPRAZOLE IN DIFFERENT SUBPOPULATIONS — ADJUSTED TO A 40 MG ORAL DOSE (FOR AUC, C_{MAX}, AND F) AND A 20 MG INTRAVENOUS DOSE (FOR $t_{½}$ AND CL)

Parameter	Young Healthy (n=18)[a]	Elderly Healthy (n=14)[a]	Renally Impaired (n=12)[b]	Hepatically Impaired (n=8)[c]	Slow Metabolizers (n=4)[d]
AUC (μmol*h/L)	4.0	8.8	2.4	29	18
C_{max} (μmol/L)	3.3	5.7	3.2	8.4	4.8
F	0.56	0.76	0.70	0.98	—
$t_{1/2}$ (h)	0.7	1.0	0.6	2.8	2.1
CL (L/min)	0.59	0.25	0.56	0.07	—

[a] Data from Reference[58]; [b] Data from Reference[59];
[c] Data from Reference[56]; [d] Data from Reference[23]
Slow metabolizers = lack the CYP2C19 enzyme AUC = area under the plasma concentration versus time curve;
C_{max} = maximum plasma concentration; F = absolute bioavailability; $t_{½}$ = plasma elimination half-life; h = hours;
CL = systemic clearance

In the elderly, hepatic and renal functions can be somewhat decreased as a result of the aging process. A study in which elderly patients (average age 76 years) received single doses of Ome 40 mg orally and Ome 20 mg intravenously showed the mean plasma $t_{1/2}$ was slightly longer and the AUC two-fold higher compared to young individuals.[58]

As previously described, 80% of Ome metabolism occurs at the CYP2C19 isoform. Metabolism can still occur in individuals who lack this enzyme, but at a slower rate. These individuals are referred to as "slow" metabolizers.[23] The incidence of "slow" metabolizers

among Caucasians is about 3%, and in the Asian population is about 15%. The "slow" metabolizers obtain higher plasma levels and AUC of Ome than normal healthy patients, but due to the rapid elimination relative to the dosing interval, no drug accumulation is seen. The increase in plasma concentrations observed during repeated dosing in ordinary metabolizers is not seen in "slow" metabolizers.

8.3 Abuse/Overdose

8.3.1 Summary of AstraZeneca, LP Post-marketing Surveillance Data

Omeprazole does not appear to have abuse potential nor is there any evidence that it potentiates the effects of substances of abuse. Reports of overdose are rare and have been readily managed. There were few medically significant outcomes. The reason Ome is not a drug associated with many cases of abuse is probably due to the lack of pharmacological effects associated with abuse potential.

Information on omeprazole overdosage in the approved labeling for PRILOSEC® Delayed Release Capsules is based on data from 6 overdose cases and the following statement is represented in the current package insert for Prilosec:

> "Rare reports have been received of overdosage with omeprazole. Doses ranged from 320 mg to 900 mg (16–45 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, and dry mouth. Symptoms were transient, and no serious clinical outcome has been reported. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not dialyzable. In the event of overdosage, treatment should be symptomatic and supportive."[60]

As of 30-Jun-98 there were a total of 21 overdose cases reported either in the literature or directly to the Sponsor via the collection of world-wide post-marketing surveillance data. Three of the 21 cases were cases that involved subjects in clinical trials. These 21 cases represent over 10 years of post-marketing surveillance and approximately 300 million patient treatments. The 15 cases collected after the labeling statement noted above have been reported either in the literature or directly to the Sponsor via the collection of worldwide post-marketing surveillance data. Nine of these 15 cases involve ingestion of omeprazole with at least one other drug, while 6 represent overdosage with only omeprazole. Two deaths are noted among these 15 cases and both of these deaths occurred in subjects who ingested more than one drug product. One subject had a history of bi-polar disorder and multiple previous hospital admissions for drug-related suicide attempts. She overdosed with an unknown amount of omeprazole and sertraline. The subject was placed on a respirator, developed Adult Respiratory Distress Syndrome, a pneumothorax, and subsequently arrested and died. The second suicide death occurred with unknown amounts of omeprazole, diltiazem, and doxepin. This case was published in an annual report from the AAPCC and the cause of death was not noted.

There is a report of a pharmacist who dispensed omeprazole inappropriately and the subject took 20 mg omeprazole every 4 hours for 2 months. The subject was subsequently admitted to the hospital with atrial fibrillation and recovered with "permanent disability."

From a review of omeprazole overdose cases, the most common clinical features observed include nausea, vomiting, flushing, tachycardia, confusion, drowsiness, and headache.

There is no evidence to suggest that omeprazole has any potential for abuse from either clinical trials or post-marketing surveillance data. Omeprazole is not scheduled under the Controlled Substances Act.

8.3.2 Summary of American Association of Poison Control Center (AAPCC)

A summary of the number of AAPCC reports involving the drug omeprazole or H_2RAs without concomitant medications is provided in the following table (Table 8.3).

For omeprazole, the total number of reports was greater in 1996 than in 1995 and this was also observed for H_2RAs. The larger number of cases for H_2RAs is likely due to the inclusion of multiple drugs under this heading (famotidine, cimetidine, ranitidine, nizatidine) and because these drugs are sold as both R_x and OTC. The percentage of total reports as sorted by gender, age, reason for exposure, and by medical outcome were similar for both omeprazole and H_2RAs. In general there were slightly more females than males and the largest age category was children less than 6 years of age.

TABLE 8.3
AAPCC TOXIC EXPOSURE SURVEILLANCE SYSTEM (TESS)
DEMOGRAPHIC SUMMARY
OMEPRAZOLE AND H_2RAS
(WITHOUT CONCOMITANT MEDICATIONS)[a]
1995 AND 1996

	OMEPRAZOLE (WITHOUT CONCOMITANT DRUGS)		H_2RAS (WITHOUT CONCOMITANT DRUGS)	
	1995	**1996**	**1995**	**1996**
Total Number of Reports	248	931	3,472	4,351
Gender				
Male	46%	47%	46%	46%
Female	54%	52%	54%	53%
Age (Years)				
< 6	66%	63%	49%	53%
6 to 12	1%	2%	4%	4%
13 to 19	2%	3%	8%	6%
20 to 59	17%	20%	25%	23%
> 59	6%	7%	9%	9%
Reason for Exposure				
Unintentional	85%	90%	79%	84%
Intentional	6%	6%	14%	10%
Adverse Reaction	9%	4%	7%	6%
Medical Outcome				
No Effect	37%	39%	34%	33%
Minor Effect	3%	3%	8%	6%
Moderate Effect	0%	1%	2%	2%
Major Effect	1%	0%	<1%	0%
Not Followed	56%	55%	50%	53%

[a] AAPCC Summary Report for 1995 and 1996 adapted from NDA 21-229 summary tables in Appendix 2, Tables 2A–2D, 3A–3B, 4A–4D and 8A–8D. Definitions of various categories are given in the text.

The majority of cases in the omeprazole TESS database (Table 8.3) were classified as "unintentional by reason of exposure." "Unintentional" is defined by the AAPCC as either general (most unintentional exposures in children captured here), therapeutic error (wrong dose, incorrect route of administration, administration of a wrong substance, etc.), misuse (unintentional improper or incorrect use), or other/unknown. The majority of omeprazole cases classified as "unintentional" involved children under 6 years of age.

There were significantly fewer cases reported as "intentional by reason of exposure". Cases classified by the AAPCC as "intentional" include suspected suicidal cases, misuse resulting from intentional improper or incorrect use for reasons other than pursuit of a psychotropic effect, and abuse. A breakdown of the omeprazole alone cases in the "intentional" category for the years 1995 and 1996 combined (71 total cases) represent 57 suspected suicide, 9 misuse, 1 abuse, and 4 unknown. Because of the few cases in the "intentional" category, these data support the conclusion that omeprazole is unlikely to be a drug with potential for abuse.

With respect to medical outcome classifications (See Table 8.3**)** there were very few omeprazole cases falling into the 3 categories of "moderate" (0%–1% of cases), "major" (0%–1% of cases) or "unable to follow — potentially toxic" effects (2% of cases). There were no deaths. The majority of outcomes were classified as "no effect" (37%–39% of cases), "minor effect" (3% of cases), "not followed — judged as non-toxic exposure" (28%–29%), and "not followed — minimal clinical effects possible" (25%). The totals for the latter 4 categories represent 94% of the omeprazole cases. These four categories combined can be considered as representing the total number of outcomes which were not medically significant. Thus, the majority of medical outcomes for omeprazole can be considered as not medically significant. The profile is similar for H_2RAs.

In 1995, there were no deaths, there was one case classified as "major effect," and 6 cases classified as "unable to follow — potentially toxic exposure". The case classified as "major effect" involved an elderly female, age 71 years, with the reason classified as "adverse drug reaction" and the reported clinical effects of tremor (related) and miscellaneous-other (related). Likewise, for 1996, there were no deaths.

For the 21 omeprazole cases in 1996 classified as "unable to follow — potentially toxic," there were 4 cases classified as "accidental general". There were 11 cases classified as "intentional, suspected suicides". There were 2 cases classified as "accidental therapeutic error." There was 1 case involving "accidental misuse", 1 case of "adverse drug reaction", 1 case classified as "intentional, unknown", and 1 case classified as "intentional misuse". In summary, with respect to medical outcome classifications, there were very few cases falling into the 3 categories of "moderate," "major," or "unable to follow — potentially toxic" effects. The majority of outcomes were found in 4 categories ("no effect," "minor effect," "not followed — judged as non-toxic exposure," and "not followed — minimal clinical effects possible") which can be considered as outcomes which are not medically significant.

Clinical effects judged to be related to omeprazole, based on cases without concomitant medications, are difficult to interpret since there is very little information available in the

AAPCC database regarding doses involved in cases. There are a variety of reported effects associated with these overdose cases ranging from tachycardia (5) in the cardiovascular system, dermal effects (1 edema, 2 hives/welts, 3 pruritus, and 2 rash), typical gastrointestinal side effects (7 abdominal pain, 1 constipation, 1 dehydration, 3 diarrhea, 9 nausea, 2 oral irritation, and 9 vomiting), neurologic effects (5 agitated/irritable, 1 confusion, 4 dizziness/vertigo, 9 drowsiness/lethargy, 3 headache, 1 tremor, and 1 report of seizures classified as "status" with no details available), 1 report of urinary retention, 1 dyspnea, 2 reports of diaphoresis, 1 report of fever/hyperthemia, and a total of 12 other effects not specified. Details of these events were not available at the time of this review; however, the types of reported effects along with the medical outcome information suggests that there are very few events which resulted in effects which can be considered as medically significant. This provides reassurance of omeprazole's safety for potential accidental and intentional exposures.

The majority of exposures to omeprazole alone were managed in a non-health care facility (82%–85%) or treated in a health care facility and released (8%–9%). By combining the numbers in these 2 categories, one can see that for omeprazole only, over 92% of cases were either treated in a non-medical facility or were treated in a health care facility and released.